Annual Meeting & Best of ASCO®

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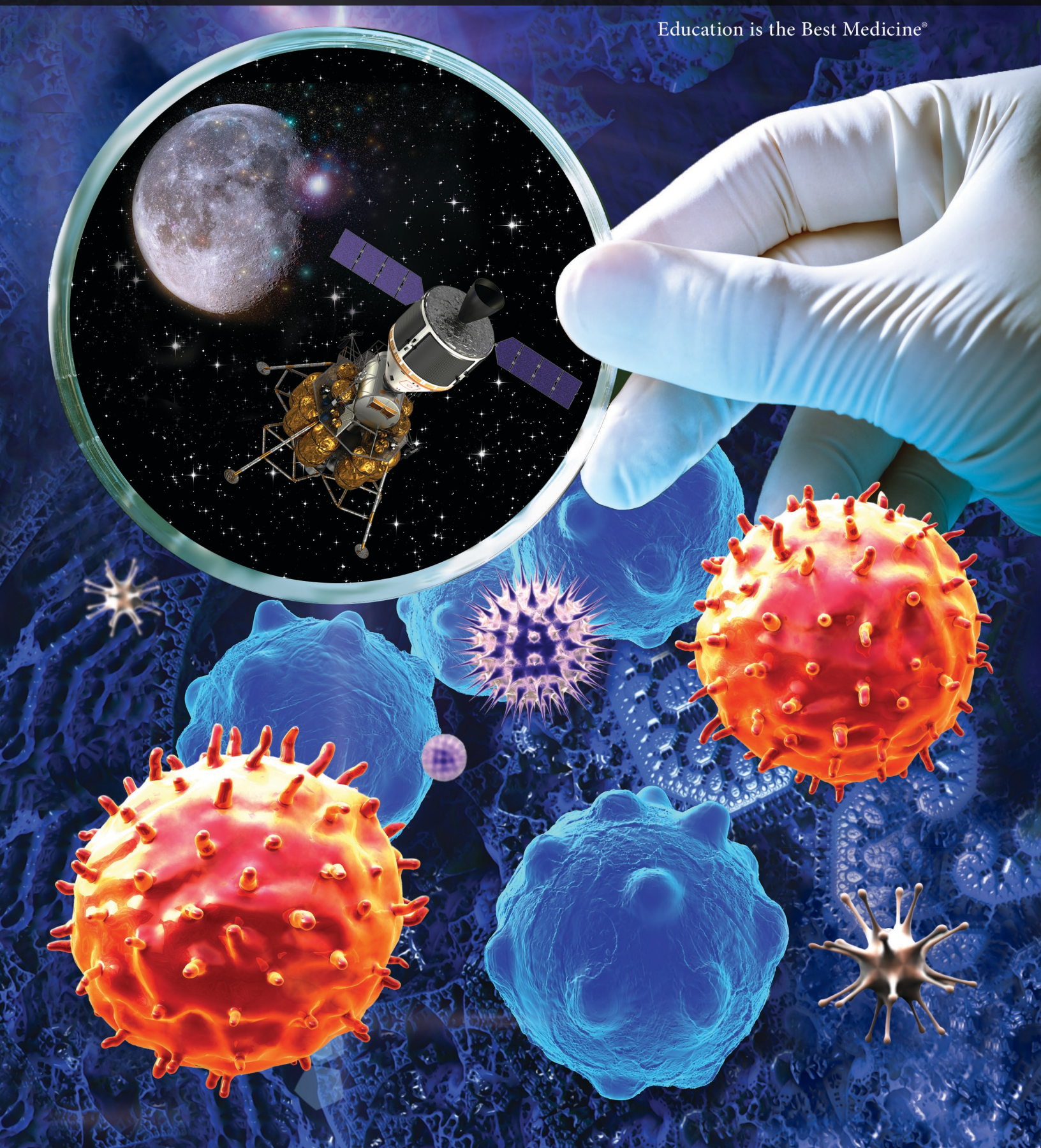
GASCO™

September 9 - 10, 2016
Atlanta, Georgia
Westin Hotel, Buckhead

Education is the Best Medicine®



An Invitation from GASCO's President

On behalf of The Board of Directors of the Georgia Society of Clinical Oncology (GASCO), I invite you to attend GASCO's 2016 Annual Meeting and Officially Licensed Best of ASCO® program scheduled for September 9 - 10, 2016. Our program committee has put together an exceptional and relevant agenda with CEUs available through Augusta University.**

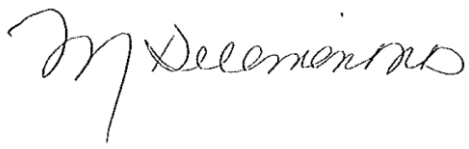
This year GASCO's Program Co-chairs are Dr. Rodolfo Bordoni and Dr. Melissa Dillmon, who have brought together a very distinguished faculty. Please review the complete agenda that follows. Registration is free for GASCO members, hematology/oncology Fellows and medical students.

On Friday, September 9th, we continue the very highly rated Clinical Think Tank sessions and begin the Best of ASCO® summaries. After the President's Reception, we invite you to stay for a dinner presentation on biologic therapies and the role of biosimilars in oncology.

On Saturday we continue the Best of ASCO® discussions but we are very excited to add the first annual Dr. Thomas E. Seay Memorial Lecture - "Personalized Medicine for Localized Pancreatic Cancer," presented by Douglas B. Evans, M.D., Chair of the Department of Surgery at The Medical College of Wisconsin. We have also invited ASCO's Chief Executive Officer, Dr. Clifford Hudis, to provide a timely policy update from the ASCO headquarters and Capitol Hill. The leadership of Cancer Patient Navigators of Georgia have planned a Friday educational track for clinical and non-clinical cancer patient navigators.

The Georgia Cancer Care Community has a great story of accomplishment! Please join us to hear the clinical presentations and network with your colleagues.

Best Wishes,



Melissa Dillmon, M.D., President
Georgia Society of Clinical Oncology

2016 Annual Meeting & Best Of ASCO® Program Committee and Faculty

Program Planning Committee

Melissa Dillmon, M.D.
GASCO President
The Harbin Clinic

Rodolfo Bordoni, M.D.
Program Chairman
Georgia Cancer Specialists

Faculty

Catherine M. Broome, M.D.
Associate Professor, Div. of Hematology and Oncology, Georgetown University

Bassel El Rayes, M.D.
Professor & *Vice Chair for Clinical Research, Director, GI Oncology Program, Emory Winship Cancer Institute*

Douglas B. Evans, M.D.
Donald C. Ausman Family Foundation Professor of Surgery and Chair of the Department of Surgery at The Medical College of Wisconsin

Daniel J. George, M.D.
Director, Section of Genitourinary Medical Oncology, Duke University Medical Center

Faculty (cont.)

Sharad Ghamande, M.D.
Director, Gynecology Oncology, Augusta University Cancer Canter

Clifford Hudis, M.D.
Chief Executive Officer, American Society of Clinical Oncology, Chief of Breast Medicine Service, Memorial Sloan Kettering Cancer Center

Edward Li, Pharm D., MPH, BCOP
Associate Professor, Depart Pharmacy Practice, University of New England College of Pharmacy

Sagar Lonial, M.D.
Professor and Chair of Hematology and Medical Oncology, Emory Winship Cancer Institute

Thom R. Mitchell, M.D.
Senior Contractor Medical Director, Cahaba GBA, LLC

Robert Motzer, M.D.
Memorial Sloan Kettering Cancer Center

Suresh Ramalingham, M.D.
Chief of Medical Oncology, Emory Winship Cancer Institute

Ruth O'Regan, M.D.
Division Head, Hematology/Oncology, and Associate Director of Faculty Development & Education, U of Wisconsin Carbone Cancer Center

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Medical College of Georgia at Augusta University and the Georgia Society of Clinical Oncology. The Medical College of Georgia at Augusta University is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation

The Medical College of Georgia at Augusta University designates this live activity for a maximum of 11.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CEUs

This activity includes 11.25 hours of instruction and attendance at the entire activity is approved by Augusta University for a maximum of 1.125 Continuing Education Credit Units. *Presentations noted with * are jointly provided by the France Foundation.

Friday, September 9, 2016 **– General Session** **GASCO Best of ASCO® Program -** ***Clinical Track***	
8:30-9:00AM	Registration & Continental Breakfast for NCORP Participants
9:00-11:30AM	Georgia NCORP Briefing for Investigators - Investigators of the Georgia NCORP Network will review network progress to date and plans for it's ongoing efforts. *Sponsored by GASCO and Georgia CORE*
11:00-12:15PM	Registration & Exhibits Open
11:00-12:00PM	Light Lunch Buffet
12:00-12:10PM	Welcome and Opening Remarks **-** Dr. Melissa Dillmon, *GASCO President*
12:10-1:10PM	Think Tank in Genitourinary Malignancies – Prostate Cancer Management & Best of ASCO - Daniel J. George, M.D., *Director Section of Genitourinary Medical Oncology, Duke University Medical Center*
1:10-2:00PM	Think Tank in Genitourinary Malignancies - Renal Cell Carcinoma Management: Present and future **-** Robert Motzer, M.D., *Memorial Sloan Kettering Cancer Center*
2:00-2:30PM	Networking Break and Exhibitors
2:30-3:15PM	Review of Best of ASCO® Renal Cell Cancer Abstracts **-** Robert Motzer, M.D., *Memorial Sloan Kettering Cancer Center*
3:15-4:15PM	Hematology Think Tank: Diagnosis & Management of Thrombotic Microangiopathy **-** Catherine M. Broome, M.D., *Associate Professor, Div. of Hematology and Oncology, Georgetown University*
4:15-5:15PM	ASCO Policy Update **-** Clifford Hudis, M.D., *Chief Executive Officer, American Society of Clinical Oncology, Chief of Breast Medicine Service, Memorial Sloan Kettering Cancer Center*
5:15PM	President's Reception: Faculty and All Meeting Participants
6:00 PM	Dinner
6:00-7:00PM	Biologic Therapies and the Role of Biosimilars in Oncology **-** Edward Li, Pharm D., MPH, BCOP - *Associate Professor, Depart Pharmacy Practice, University of New England College of Pharmacy*
7:00PM	Adjourn *(Note: GASCO Board Meeting Follows)*

Saturday, September 10, 2016 **GASCO Best of ASCO® Program** - ***Clinical Track***	
7:00-8:00AM	Breakfast & Registration – Exhibits Open
8:00-8:05AM	Welcome & Introductions – Melissa Dillmon, M.D., *GASCO President*
8:05-9:05AM	Review of Best of ASCO® Lung Cancer Abstracts – Suresh Ramalingham, M.D., *Chief of Medical Oncology, Emory Winship Cancer Institute*
9:15-10:15AM	Review of Best of ASCO® Gastroenterology Cancer Abstracts – Bassel El Rayes, M.D. - *Professor* & *Vice Chair for Clinical Research, Director, GI Oncology Program, Emory Winship Cancer Institute*
10:15-10:45AM	Break – Exhibit Area
10:45-11:45AM	Medicare Policy Update - Thom R. Mitchell, M.D., *Senior Contractor Medical Director, Cahaba GBA, LLC*
11:45-1:00PM	Lunch & Keynote Presentation: Dr. Thomas E. Seay Memorial Lecture - "Personalized Medicine for Localized Pancreatic Cancer." - Douglas B. Evans, M.D., *Donald C. Ausman Family Foundation Professor of Surgery and Chair of the Department of Surgery at The Medical College of Wisconsin*
1:00-2:00PM	Review of Best of ASCO® Multiple Myeloma Abstracts – Sagar Lonial, M.D., *Professor and Chair of Hematology and Medical Oncology Emory Winship Cancer Institute*
2:00-2:15PM	Break
2:15-3:15PM	Review of Best of ASCO® Gynecological Cancer Abstracts Sharad Ghamande, M.D., *Director, Gynecology Oncology, Augusta University Cancer Center*
3:15-4:15PM	Review of Best of ASCO® Breast Cancer Abstracts Ruth O'Regan, M.D., *Division Head, Hematology/Oncology, and Associate Director of Faculty Development & Education, U of Wisconsin Carbone Cancer Center.*
4:15 PM	Closing Remarks & Adjourn Melissa Dillmon, M.D., *GASCO President* & Grant Lewis, M.D – *President Elect*

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Publication Information: In our continuing effort to provide conference attendees with a permanent copy of the information discussed at this meeting, a summary and/or presentation have been requested from the speakers at this meeting. While every effort has been made to secure this information, in some cases these requests are not fulfilled by a speaker for a variety of reasons. We appreciate your understanding in our quest to provide you with the most updated and complete information possible, and are confident that you will have an enjoyable and educational experience.

American Society of Clinical Oncology

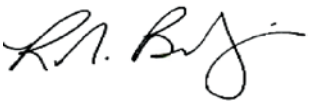
August 11, 2016

The American Society of Clinical Oncology (ASCO®) is pleased to announce an agreement with the Georgia Society of Clinical Oncology to hold an official Best of ASCO® meeting in Atlanta, Georgia, September 9-10, 2016. This premier event will highlight abstracts and educational updates from the 2016 ASCO Annual Meeting, the world's largest gathering of physicians, researchers, and others engaged in the study and practice of oncology.

Many summary events is held after the Annual Meeting, but only a select few are organized in connection with ASCO and reliably deserve the title "Best of ASCO" for their objectivity in content selection. These official Best of ASCO meetings present the top abstracts from a pool of more than 4,000 rated by a panel of ASCO experts. The Georgia Society of Clinical Oncology has created a custom program that promises to meet the needs of members of the oncology care team.

ASCO would like to take this opportunity to encourage you to support official Best of ASCO meetings, including the one being held in Atlanta, Georgia in 2016. Best of ASCO meetings are an excellent way to support local physicians with the latest science and education.

Sincerely,



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BEST of ASCO®

GENITOURINARY MALIGNANCIES: PROSTATE CANCER MANAGEMENT

DANIEL J. GEORGE, M.D.

Daniel J. George, M.D.
Duke University Medical Center

Daniel J. George, MD, has been the director of the section of genitourinary medical oncology at Duke University Medical Center since 2003.

His research focuses on growth factor-targeted drug development in the areas of prostate and kidney cancer. He has also participated in several trials on these subjects, using small molecule inhibitors of specific growth factors against vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) pathways.
George's research has demonstrated that blood levels of VEGF in advanced prostate cancer patients can have independent prognostic significance. His studies also include novel assessment of blood flow in renal cell carcinoma and growth factors as prognostic markers, molecular targets, and surrogate measures of response in prostate cancer.
A member of the GU correlative science subcommittee in the Cancer and Leukemia Group B (CALGB), George was recently appointed medical director of cancer clinical research at Duke and CALGB cadre leader for RCC.

George has the principal investigator for Duke on the Department of Defense Prostate Cancer Clinical Trials Consortium Grant since 2006, which focuses on early-phase drug development in prostate cancer. He has led several multi-center clinical trials involving VEGF-targeted agents through this mechanism.

George attended Duke University School of Medicine and completed his training in internal medicine and medical oncology at Johns Hopkins Hospital. He spent five years at the Dana-Farber Cancer Institute in the Lank Center for Genitourinary Oncology as Assistant Professor of Medicine at Harvard Medical School.

GENITOURINARY (PROSTATE) CANCER

Abstract: 5006 (166318)

Title: Cabazitaxel vs docetaxel in chemotherapy-naive (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA).

Authors: A. Oliver Sartor, Stephane Oudard, Lisa Sengelov, Gedske Daugaard, Fred Saad, Steinbjoern Hansen, Marie Hjelm-Eriksson, Jacek Jassem, Antoine Thiery-Vuillemin, Orazio Caffo, Daniel E. Castellano, Paul N. Mainwaring, John P Bernard, Liji Shen, Mustapha Chadjaa, Karim Fizazi; Tulane University, New Orleans, LA; Department of Medical Oncology, Hôpital Européen Georges Pompidou, Paris, France; Department of Oncology, Herlev, Denmark; Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; University of Montreal, Montreal, QC; ODENSE UNIVERSITY HOSPITAL, Odense, Denmark; Department of Oncology, Karolinska Institute, Stockholm, Sweden; Medical University of Gdansk, Gdansk, Poland; Jean Minjoz Hospital, Besançon, France; Medical Oncology, Santa Chiara Hospital, Trento, Trento, Italy; Hospital Universitario 12 de Octubre, Madrid, Spain; ICON Cancer Care, South Brisbane, Australia; Sanofi, Cambridge, MA; Sanofi, Bridgewater, NJ; Sanofi, Paris, France; Institut Gustave Roussy, University of Paris Sud, Villejuif, France

Background: The Phase III TROPIC study (NCT00417079) reported significant improvement in overall survival (OS) for cabazitaxel 25 mg/m^{2}IV Q3W plus prednisone 10 mg PO QD (P) vs. mitoxantrone plus P in mCRPC pts previously treated with a docetaxel (D)-containing regimen. The FIRSTANA study examined if cabazitaxel 20 mg/m^2 (C20) or 25 mg/m^2 (C25) IV Q3W plus P is superior to docetaxel 75 mg/m^2 (D75) IV Q3W plus P in terms of OS in CN mCRPC pts. **Methods:** In this multinational, open label phase III study, mCRPC pts, ECOG PS 0-2, who had progressed after castration were randomized 1:1:1 to C20, C25 or D75 IV Q3W plus P. The primary endpoint was OS. Key secondary endpoints were safety, progression free survival (PFS), tumor PFS, tumor response (RECIST 1.1), PSA response, PSA PFS, pain response, pain PFS, time to skeletal-related events (SRE) and health-related quality of life (HRQOL). **Results:** Between May 2011 and April 2013, 1168 pts were randomized (C20=391, C25=389, D75=388). Baseline demographics and disease characteristics were similar across cohorts. The median number of treatment cycles was 9 for all dose groups. In the ITT analysis, median OS was 24.5 months for C20, 25.2 months for C25 and 24.3 months for D75. HR for C20 vs. D75 was 1.009 (0.85 to 1.197, p=0.9967) and for C25 vs. D75 was 0.97 (0.819 to 1.16, p=0.7574), indicating that C20 and C25 were not superior to D75 in terms of OS. PFS was 4.4 months for C20, 5.1 months for C25 and 5.3 months for D75 (NS). Tumor responses were superior in C25 (41.6%) compared to D75 (30.9%), p=0.0370. Other secondary endpoints did not significantly differ across dose groups. Adverse events (AEs) grade 3-4 were 41.2% in C20, 60.1% in C25 and 46.0% in D75; pts discontinuing treatment due to an AE were 25.2% in C20, 31.7% in C25 and 33.9% in D75. Febrile neutropenia, diarrhea and hematuria were more frequent in C25; peripheral neuropathy, peripheral edema, alopecia and nail disorders were more frequent in D75. **Conclusions:** C20 and C25 did not demonstrate superiority for OS compared to D75 in CN mCRPC

pts. Among secondary endpoints only tumor responses were significantly superior for C25. AEs were less frequent in C20 for most categories.

GENITOURINARY (PROSTATE) CANCER

Abstract: 5008 (169889)

Title: Phase III non-inferiority study of cabazitaxel (C) 20 mg/m^2 (C20) versus 25 mg/m^2 (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D).

Authors: Johann S. De Bono, Anne-Claire Hardy-Bessard, Choung-Soo Kim, Lajos Geczi, Daniel Ford, Loic Mourey, Joan Carles, Phillip Parente, Albert Font, Gabriel Kacso, Mustapha Chadjaa, Wenping Zhang, François Ravez, Mario A. Eisenberger; The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; Centre Armoricain d'Oncologie, Cario, Plérin, France; Asan Medicine Center, Seoul, South Korea; National Institute of Oncology, Budapest, Hungary; City Hospital, Cancer Centre Queen Elizabeth Hospital, Birmingham, United Kingdom; Institut Claudius Regaud, IUCT-O, Toulouse, France; Vall d'Hebron University Hospital, Barcelona, Spain; Eastern Health Clinical School, Monash University, Melbourne, Australia; Institut Català d'Oncologia, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; Amethyst Radiotherapy Center, Cluj, Romania; Sanofi, Paris, France; Sanofi, Bridgewater, NJ; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: The Phase III TROPIC study (NCT00417079) reported a significant improvement in overall survival (OS) for C plus prednisone (P) (25 mg/m^{2}once every 3 weeks plus 10 mg orally once daily) versus mitoxantrone plus P (Hazard Ratio [HR] 0.70; P < 0.0001) in pts with mCRPC previously treated with D. This PROSELICA study (NCT01308580) was designed to determine the relative efficacy and safety profile of C20 plus P compared with C25 plus P. **Methods:** In this randomized, open-label, multinational phase III study, pts with mCRPC and ECOG performance status 0–2, who progressed after treatment with D, were stratified (ECOG, RECIST, region) and randomized 1:1 to C20 or C25. To show that C20 could preserve ≥ 50% of the efficacy benefit showed by C25 in TROPIC, the HR of C20 vs C25 for the primary endpoint OS could not exceed 1.214 under 1-sided 98.89% confidence level adjusted after interim analyses. Secondary endpoints included progression free survival (PFS), safety, PSA, pain and tumor responses and quality of life. **Results:** From April 2011 to December 2013, 1200 pts were randomized (C20 n = 598; C25 n = 602). Patient characteristics were similar for C20 and C25. Median number of C cycles was 6 for C20 and 7 for C25. The median survival of C20 and C25 did not differ significantly and the HR boundaries (99% confidence level) were within the non-inferiority margins assumptions, therefore meeting the study's non-inferiority endpoint. PSA and RECIST response rates were higher in C25 (see Table). Grade 3–4 adverse events: 39.7% C20; 54.5% C25. Grade 4 laboratory neutropenia: 21.3% C20; 48.6% C25. Neutropenic sepsis/infection: 2.2% C20; 6.1% C25. **Conclusions:** In pts with mCRPC progressing after treatment with D, C20 demonstrates non-inferiority for OS compared with C25 and an improved overall safety profile.

GENITOURINARY (PROSTATE) CANCER

Abstract: 5001 (166934)

Title: A randomized phase III trial between adjuvant docetaxel and surveillance after radical prostatectomy for high risk prostate cancer: Results of SPCG12.

Authors: Goran Ahlgren, Per Flodgren, Teuvo L. J. Tammela, Pirkko Kellokumpu-Lehtinen, Michael Borre, Anders Angelsen, Jon Reidar Iversen, Asgerdur Sverrisdottir, Eirikur Jonsson, Lisa Sengelov, Scandinavian Prostate Cancer Group; Department of Urology, Skane University Hospital, Lund University, Malmö, Sweden; Skane University Hospital, Lund, Sweden; Tampere University Hospital, Department of Urology, Tampere, Finland; Department of Oncology, Tampere University Hospital, Tampere, Finland; Department of Urology, Aarhus University Hospital, Skejby Sygehus, Aarhus, Denmark; Norwegian University of Science and Technology, Trondheim, Norway; Department of Oncology, Oslo, Norway; Department of Oncology, Reykjavik, Iceland; Landspitali Unversity Hospital, Reykjavik, Iceland; Department of Oncology, KAS Herlev, Herlev, Denmark

Background: Docetaxel has proved to prolong survival in advanced castrate resistant prostate cancer (PCa) and we therefore started this trial to evaluate if six courses of docetaxel improves biochemical disease free survival (BDFS) after radical prostatectomy for high risk PCa. **Methods:** A total of 459 patients were randomised in 2005-2010 in this multinational openlabeled phase III study, to receive either 6 cycles of adjuvant docetaxel 75mg/m2 q 3 weeks (Arm A) or Surveillance (Arm B). Primary end-point was a rising PSA >0.5ng/ml. High risk prostate cancer was defined as pT2 with a positive margin if Gleasonscore (GS) 4+3 or higher, pT3b >GS 3+4, any lymph node positive disease with >GS 3+4, patients were followed for 5 years with PSA every 3 months. The study was powered to show a 15% difference at 5 years follow up. **Results:** All six cycles were completed by 79.1% of the patients. Salvage radiotherapy before the primary end-point was reached was given to 8% in Arm A and 10% in Arm B. Mean age was 62.2 years, mean baseline PSA 0.156, 83.7% had pT3 disease and 37.5% had GS 8-10 at randomisation. Of the 308 patients that had a lymph node dissection, 55 (17.5%) had metastasis. Median follow up was 56.8 months. The endpoint was reached in 43.2% of patients; 47.9% in Arm A and 38.9% in Arm B. In a Kaplan-Meier analysis there was no significant difference between the BDFS curves (p=0.078), but the curve of Arm A crossed the curve of Arm B at 15 months and it was parallel at a 10% lower level beyond 24 months. There were 6 deaths from prostate cancer in Arm A and only 3 in Arm B. Febrile neutropenia occurred in 18.7% of the patients in Arm A. No deaths were related to treatment. In a Cox multivariate analysis excluding lymph node status, GS (p<0.001), pT-stage (p=0.002) and positive surgical margin (p=0.009) were significant predictors of progression while randomisation arm (p=0.09) did not reach significance. **Conclusions:** Adjuvant docetaxel without hormonal therapy did not improve BDFS after radical prostatectomy for high risk prostate cancer. Instead, docetaxel as monotherapy seems to generate a more rapid biochemical progression in a subgroup of patients. Further analysis of this subgroup is warranted.

GENITOURINARY (PROSTATE) CANCER

Abstract: 5003 (165234)

Title: A randomized trial of a shorter radiation fractionation schedule for the treatment of localized prostate cancer.

Authors: Charles N Catton, Himu Lukka, Jim A. Julian, Chu-Shu Gu, Jarad Martin, Stéphane Supiot, Peter W. M. Chung, Glenn Bauman, Jean-Paul Bahary, Shahida Ahmed, Patrick Cheung, Keen Hun Tai, Jackson Wu, Matthew Parliament, Mark Norman Levine; Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON; Juravinski Cancer Centre, Hamilton, ON; Ontario Clinical Oncology Group, McMaster University, Hamilton, ON; Oncology Research Australia, Toowoomba, Australia; Institut de Cancérologie de l'Ouest René Gauducheau, Nantes Saint Herblain, France; London Regional Cancer Program, London, ON; CHUM- Hopital Notre-Dame, Montreal, QC; CancerCare Manitoba, Winnipeg, CANADA; Sunnybrook Health Sciences Centre, Toronto, ON; Peter MacCallum Cancer Centre, East Melbourne, Australia; Tom Baker Cancer Centre, Calgary, AB; Cross Cancer Institute, Edmonton, AB; McMaster University, Hamilton, ON

Background: Men with localized prostate cancer (PC) are often treated with high dose radiotherapy (RT) over 8-9 weeks. The α-β ratio which describes the dose-response of tumors and normal tissues to fractionated RT is low for PC. Hence, hypofractionation RT may be more efficacious in PC. **Objective:**To determine whether an 8-week course of escalated dose conformal RT can be compressed safely, and with similar efficacy into a 4-week course in intermediate risk PC. **Methods:** Men with intermediate risk PC (T1-2 Gleason 6 and PSA 10-20 ng/ml or T2b-c Gleason 6 and PSA < 20 ng/ml or T1-2 Gleason 7 and PSA < 20 ng/ml) were randomized to conventional (CON) RT, 78Gy in 39 fractions over 8 weeks or hypofractionated (HYP) RT, 60Gy in 20 fractions over 4 weeks, without hormone therapy. RT was planned to respect predefined dose constraints to a risk-adapted volume that included prostate +/- base of seminal vesicles. Daily image guidance was mandated and RT plans underwent real-time central review. The primary outcome is biochemical-clinical failure (BCF) defined by any of: PSA failure (nadir+2), hormonal intervention, clinical local or distant failure, or death. The trial was designed to show that the 5-year BCF of the HYP RT regimen is no higher than CON RT by up to 7.5% (hazard ratio [HR] up to 1.32) with 85% power and one-sided α = 5%. Acute and late GU/GI toxicity were assessed using RTOG criteria. **Results:**Between 2006 and 2011, 1,206 men from 27 sites in Canada, Australia and France were allocated to HYP RT (608) or CON RT (598). Mean age was 71 (48-88) years. Baseline characteristics were similar between arms. Median follow-up is 6.0 years. To date, 164 patients receiving HYP RT experienced a BCF event compared to 173 in the CON RT group. The BCF event rate at 5 years in both arms was 21%. The observed HR is 0.96 with 90% CI, 0.80 to 1.15. Overall 75 patients have died in each group. GU/GI toxicity grade > 3 was comparable in the acute period; however, late toxicity favored the HYPO RT arm: 3.5% vs. 5.4%, diff = -1.9%, 95% CI, - 4.3 to 0.43%. **Conclusion:** The HYP RT regimen was not inferior to conventional RT with no increase in acute or late toxicity. Thus, it is a consideration for men with intermediate risk PC. (ClinicalTrials.gov Identifier: NCT00304759).

GENITOURINARY (PROSTATE) CANCER

Abstract: 5004 (171187)

Title: Quality of life (QOL) analysis from CHAARTED: Chemohormonal androgen ablation randomized trial in prostate cancer (E3805).

Authors: Linda J. Patrick-Miller, Yu-Hui Chen, Michael Anthony Carducci, David Cella, Robert S. DiPaola, Benjamin Adam Gartrell, Glenn Liu, David Frazier Jarrard, Alicia Katherine Morgans, Yu-Ning Wong, Christopher Sweeney; The University of Chicago Medical Center, Chicago, IL; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Northwestern University, Feinberg School of Medicine, Chicago, IL; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Albert Einstein College of Medicine, Bronx, NY; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Wisconsin Hosp and Clinics, Madison, WI; Vanderbilt University Medical Center, Nashville, TN; Fox Chase Cancer Center, Philadelphia, PA; Dana-Farber Cancer Institute, Harvard Cancer Center, Boston, MA

Background: Androgen deprivation therapy plus docetaxel (ADT+D) for metastatic hormone sensitive prostate cancer (mHSPC) improves overall survival over ADT. However, docetaxel's adverse event profile that can diminish QOL **Methods:** Patients were randomized to ADT+D (6 cycles) or ADT. QOL instruments including Functional Assessment of Cancer Therapy-Prostate (FACT-P), FACT-Taxane, FACIT-Fatigue, and Brief Pain Inventory (BPI) were collected at baseline, 3, 6, 9 & 12 months (mo) post randomization. Wilcoxon signed rank tests examined change over time. Mixed effect models compared QOL between arms at each time point. **Results:** 790 patients were randomized to ADT+D (N = 397) or ADT alone (N = 393) and completed QOL assessments (90% baseline; 84% 3 mo; 74% 9 mo; 69% 12 mo). ADT+D patients reported significant decline in FACT-P at 3 mo ($p < .001$), but did not differ significantly from baseline to 12 mo ($p = .38$). ADT+D was associated with significantly worse FACT-P scores at 3 mo ($p = 0.02$), yet significantly better scores at 12 mo ($p = .04$). ADT+D patients reported significantly worse FACIT-F scores at 3 mo ($p < .001$). ADT+D and ADT patients both reported significantly worse follow-up FACT-Taxane scores at all time points ($P < .001$) and significantly worse BPI scores at 9 and 12 mo ($p < .05$). BPI scores did not differ significantly between arms over time. **Conclusions:** Although ADT+D is associated with decreased QOL at 3 mo, 12 mo QOL was better for ADT+D than ADT patients. While both ADT+D and ADT patients report some increased symptoms over time, this study suggests that ADT+D not only provides a survival benefit, but also preserves a better QOL for mHSPC longer than ADT alone. [caption] Mixed effects model FACT-P total score[1]. [/caption]

THINK TANK IN GENITOURINARY MALGINANCIES RENAL CELL CARCINOMA

Robert Motzer, M.D.

Robert Motzer, M.D.
Memorial Sloan Kettering Cancer Center

Dr. Motzer is a board-certified medical oncologist who is dedicated to improving the lives of patients with genitourinary tumors. His primary area of expertise is kidney cancer (renal cell carcinoma) and testicular cancer (germ-cell tumor). For more than 25 years, Dr. Motzer has used his skills as a clinician to provide high-quality and compassionate care for cancer patients at Memorial Sloan Kettering.

In addition to providing patients with the highest standard of medical care, Dr. Motzer has led more than 50 clinical trials in patients with kidney cancer and testicular cancer, including national and international multicenter clinical trials. His research has helped to identify five targeted drugs — sunitinib (Sutent®), pazopanib (Votrient®), axitinib (Inlyta®), temsirolimus (Torisel®), and everolimus (Afinitor®) — as effective treatments for patients with advanced kidney cancer. Also, Dr. Motzer has developed a system to aid in the prediction of treatment outcomes for patients taking medications for advanced kidney cancer; this ("MSKCC") risk system is widely applied by physicians internationally to direct the care of patients. In the area of testicular cancer, his patient care and research efforts focus on developing better treatments for patients with difficult-to-treat tumors.

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RENAL CELL CARCINOMA

Robert Motzer, M.D.

GENITOURINARY (NONPROSTATE) CANCER

Abstract: 4506 (167275)

Title: Overall survival (OS) in METEOR, a randomized phase 3 trial of cabozantinib (Cabo) versus everolimus (Eve) in patients (pts) with advanced renal cell carcinoma (RCC).

Authors: Toni K. Choueiri, Thomas Powles, Bernard J. Escudier, Nizar M. Tannir, Paul Mainwaring, Brian I. Rini, Hans J. Hammers, Frede Donskov, Bruce J. Roth, Katriina Peltola, Jae-Lyun Lee, Daniel Yick Chin Heng, Manuela Schmidinger, Dana T. Aftab, Colin Hessel, Christian Scheffold, Gisela Schwab, Sumanta K. Pal, Thomas E. Hutson, Robert J. Motzer; Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Institut Gustave-Roussy, Villejuif, France; The University of Texas MD Anderson Cancer Center, Houston, TX; HOCA @ Mater, South Brisbane, Australia; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Aarhus University Hospital, Aarhus, Denmark; Washington University School of Medicine, St. Louis, MO; Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Tom Baker Cancer Center, University of Calgary, Calgary, AB; Medical University of Vienna, Vienna, Austria; Exelixis, Inc., South San Francisco, CA; Exelixis, Inc., South San Francisco, CA; City of Hope, Duarte, CA; Texas Oncology, Dallas, TX; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cabo is an inhibitor of tyrosine kinases including MET, VEGF receptors, and AXL, which are oncogenic drivers in RCC. In the METEOR trial (NCT01865747), Cabo showed a statistically significant improvement in progression-free survival (PFS, the primary endpoint) compared with Eve in pts with previously treated RCC (median of 7.4 vs 3.8 mo; HR=0.58, 95% CI 0.45–0.75; *P* <0.001) and improved the objective response rate (Choueiri NEJM 2015). The safety profile of Cabo was acceptable and similar to other VEGFR TKIs in this population. Interim analysis of the secondary endpoint of OS with a minimum follow-up of 6 mo revealed a favorable trend for Cabo vs Eve (HR=0.67, 95% CI 0.51–0.89; P=0.005). Here we present the final OS results, arising from a second interim analysis. **Methods:** Pts with measurable clear cell RCC, KPS ≥70, and ≥1 prior VEGFR TKI were randomized 1:1 to Cabo (60 mg qd) or Eve (10 mg qd) stratified by MSKCC risk group and number of prior VEGFR TKIs (1 or ≥2). The study was designed to detect a HR for OS of 0.75 (80% power, 2-sided α=0.04). **Results:** From Aug 2013–Nov 2014, 658 pts were randomized. As of 31 Dec 2015, with a minimum follow-up of 13 mo, 320 deaths were recorded (140 for Cabo and 180 for Eve). 74 (22%) pts remained on therapy in the Cabo arm vs 25 (8%) pts in the Eve arm. The secondary endpoint of improved OS for Cabo-treated pts was met. The median OS was 21.4 mo for Cabo vs 16.5 mo for Eve, with a 33% reduction in the rate of death (HR 0.67, 95% CI 0.53 to 0.83, P=0.0003). Landmark estimates of survival at 18 mo were 58% in the Cabo arm vs 47% of the Eve arm. OS benefit with Cabo was consistently observed across all prespecified subgroups including MSKCC risk group, number and type of prior VEGFR TKIs, prior anti-PD-1/PD-L1 treatment, location and extent of tumor metastases, and tumor MET expression level. SAEs were consistent with the safety profile previously reported. **Conclusions:** Cabo is the only agent to demonstrate a significant benefit in OS, PFS, and ORR in a Phase 3 trial in previously treated pts with advanced RCC. Cabo is an important new treatment option for these patients.

GENITOURINARY (NONPROSTATE) CANCER

Abstract: 4507

Title: Long-term overall survival (OS) with nivolumab in previously treated patients with advanced renal cell carcinoma (aRCC) from phase I and II studies

Author(s): David F. McDermott, Robert J. Motzer, Michael B. Atkins, Elizabeth R. Plimack, Mario Sznol, Saby George, Charles G. Drake, Brian I. Rini, Toni K. Choueiri, Timothy Kuzel, Jeffrey Alan Sosman, David C. Smith, Ulka N. Vaishampayan, John D. Powderly, Suzanne Louise Topalian, Huanyu Zhao, Ian M. Waxman, Hans J. Hammers; Beth Israel Deaconess Medical Center, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Lombardi Comprehensive Cancer Center, Washington, DC; Fox Chase Cancer Center, Philadelphia, PA; Yale School of Medicine and Smilow Cancer Center, Yale-New Haven Hospital, New Haven, CT; Roswell Park Cancer Institute, Buffalo, NY; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; Northwestern University Feinberg School of Medicine, Chicago, IL; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Karmanos Cancer Institute, Detroit, MI; Carolina BioOncology Institute, Huntersville, NC; Bristol-Myers Sqiubb, Princeton, NJ; Bristol-Myers Squibb, Princeton, NJ

Background: Nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, was recently approved by the FDA for patients with clear-cell aRCC previously treated with anti-angiogenic therapy based on results from the phase III CheckMate 025 study, which showed significantly longer median OS for nivolumab vs everolimus (25.0 vs 19.6 months; $P = 0.002$) with a minimum follow-up of 14 months (Motzer et al, *N Engl J Med* 2015;373:1803–13). Because of the early survival benefit seen in the phase III study, there is increased interest in the potential for nivolumab to provide long-term OS. Here, we report long-term OS results from phase I and II nivolumab studies. **Methods:** Patients with Eastern Cooperative Oncology Group performance status ≤2 and prior systemic treatment with 1–5 regimens received nivolumab (1 or 10 mg/kg) every 2 weeks in a phase I open-label study (NCT00730639; McDermott et al, *J Clin Oncol* 2015;33:2013–20). Patients with Karnofsky performance status ≥70% and prior treatment with 1–3 regimens in the metastatic setting received nivolumab (0.3, 2, or 10 mg/kg) every 3 weeks in a phase II randomized study (NCT01354431; Motzer et al, *J Clin Oncol* 2015;33:1430–37). In both studies, OS was estimated by the Kaplan–Meier method. **Results:** 34 patients with aRCC were treated in the phase I study. At a minimum follow-up of 50.5 months, objective response rate (ORR) was 29% and the median duration of response was 12.9 months. The 3- and 5-year OS rates were 41% and 34%. 167 patients with aRCC were treated in the phase II study. At a minimum follow-up of 38 months, ORR was 21% and the median duration of response was 22 months. The 3-year OS rate was 35%. Additional data will be presented including 4-year OS rate from the phase II study and long-term OS by subgroups. **Conclusions:** With about one-third of patients treated with nivolumab alive at 5 years in the phase I study and 3 years in the phase II study, this is the longest follow-up reported to date with any anti-PD-1/PD-L1 agent in aRCC. Potential predictors of long-term survival with nivolumab in this previously treated population are being explored.

GENITOURNIARY (NONPROSTATE) CANCER

Abstract: 544

Title: First-line sunitinib versus pazopanib in metastatic renal cell carcinoma (mRCC): Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

Author(s): Jose Manuel Ruiz Morales, J Connor Wells, Frede Donskov, Georg A. Bjarnason, Jae-Lyun Lee, Jennifer J. Knox, Benoit Beuselinck, Ulka N. Vaishampayan, James Brugarolas, Reuben James Broom, Aristotelis Bamias, Takeshi Yuasa, Sandhya Srinivas, D. Scott Ernst, Carmel Jo Pezaro, Lori Wood, Christian K. Kollmannsberger, Brian I. Rini, Toni K. Choueiri, Daniel Yick Chin Heng; Tom Baker Cancer Centre - University of Calgary, Calgary, AB, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; Karmanos Cancer Institute, Wayne State University, Detroit, MI; The University of Texas Southwestern Medical Center, Dallas, TX; Auckland City Hospital, Auckland, New Zealand; Dept of Clinical Therapeutics, University of Athens, Athens, Greece; Department of Urology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Stanford University Medical Center, Stanford, CA; London Regional Cancer Centre, London, ON, Canada; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; BC Cancer Agency, Vancouver Cancer Centre, Vancouver, BC, Canada; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Dana-Farber Cancer Institute, Boston, MA; Tom Baker Cancer Center, University of Calgary, Calgary, AB, Canada.

Background: Sunitinib (SU) and Pazopanib (PZ) have been compared head-to-head in the first-line phase III COMPARZ study in metastatic renal cell carcinoma (mRCC). We compared SU versus PZ, to confirm outcomes and subsequent second-line therapy efficacy in a population-based setting.**Methods:** We used the IMDC to assess overall survival (OS), progression-free survival (PFS), response rate (RR) and performed proportional hazard regression adjusting for IMDC prognostic groups. Second-line OS2 and PFS2 were also evaluated. **Results:** We obtained data from 3,606 patients with mRCC treated with either first line SU (n=3226) or PZ (n=380) with an overall median follow-up of 43.5 months (m) (CI95% 41.4 – 46.4). IMDC risk group distribution for favorable prognosis was 440 (17.3%) for SU vs 72 (25%) for PZ, intermediate prognosis 1414 (55.6%) for SU vs 153 (53%) for PZ, poor prognosis 689 (27.1%) for SU vs 62 (22%) for PZ, p= 0.0027. We found no difference between SU vs. PZ for OS (20.1 [CI95% 18.76-21.42] vs. 23.68 m [CI95% 19.54 - 28.81] p=0.19), PFS (7.22 [CI95% 6.76 - 7.78] vs. 6.83 m [CI95% 5.58 - 8.27] p=0.49). The RR was similar in both groups (Table 1). Adjusted HR for OS and PFS were 0.952 (CI95% 0.788 – 1.150 p=0.61) and 1.052 (CI95% 0.908 – 1.220 p = 0.49), respectively. We also found no difference in any second-line treatment between either post-SU vs. post-PZ groups for OS2 (12.88 [CI95% 11.89 – 14.19] vs. 12.91 m [CI95% 10.3 – 19.1] p=0.47) and PFS2 (3.67 [CI95% 3.38 – 3.87] vs. 4.53 m [CI95% 3.08 – 5.35] p=0.4). There was no statistical difference in OS2 and PFS2 if everolimus was used after SU or PZ (p = 0.33 and p = 0.41, respectively) or if axitinib was used after SU or PZ (p = 0.73 and p = 0.72, respectively). **Conclusions:** We confirmed in real world practice, that SU and PZ have similar efficacy in the first-line setting for mRCC and do not affect outcomes with subsequent second-line treatment.

GENITOURINARY (NONPROSTATE) CANCER

Abstract: 4509

Title: Treatment beyond progression with nivolumab (nivo) in patients (pts) withadvanced renal cell carcinoma (aRCC) in the phase III CheckMate 025 study

Author(s): Bernard J. Escudier, Robert J. Motzer, Padmanee Sharma, John Wagstaff, Elizabeth R. Plimack, Hans J. Hammers, Frede Donskov, Howard Gurney, Jeffrey Alan Sosman, Pawel Zalewski, Ulrika Harmenberg, David F. McDermott, Toni K. Choueiri, Martin Eduardo Richardet, Yoshihiko Tomita, Alain Ravaud, Justin Doan, Huanyu Zhao, Helene Hardy, Saby George; Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France; Memorial Sloan Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; South West Wales Cancer Institute, Swansea, United Kingdom; Fox Chase Cancer Center, Philadelphia, PA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Aarhus University Hospital, Aarhus, Denmark; Westmead Hospital, Westmead, Australia; Vanderbilt-Ingram Cancer Center, Nashville, TN; Lakeridge Health, Oshawa, ON, Canada; Karolinska University Hospital, Stockholm, Sweden; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; Oncology Institute of Cordoba, Cordoba, Argentina; Niigata University School of Medicine, Niigata, Japan; Hôpital Saint-André, CHU de Bordeaux, Bordeaux, France; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Sqiubb, Princeton, NJ; Bristol-Myers Squibb, Lawrenceville, NJ; Roswell Park Cancer Institute, Buffalo, NY

Background: Immunotherapy response patterns differ from traditional therapies, and pts may benefit from treatment after initial RECIST progression (*CCR* 2009;15:7412–20). We investigated pts treated beyond progression (TBP) with nivo in study CheckMate 025—nivo vs everolimus (eve) in previously treated pts with aRCC (NCT01668784). **Methods:**Treatment beyond progression was allowed in pts who had investigator-assessed clinical benefit and tolerated study drug. Pts TBP continued to receive nivo ≥4 wk after first RECIST version 1.1–defined progression to account for any delayed scan results; pts not TBP (NTBP) discontinued treatment after first progression. Pts without progression were excluded from this analysis. **Results:** Of 406 nivo pts treated, 38% were TBP; 36% were NTBP (of 397 eve pts treated, 17% were TBP; 36% were NTBP—current analysis for nivo only). Baseline characteristics were generally similar except for higher Karnofsky performance status (KPS) ≥90 with TBP vs NTBP (72% vs 62%) and less bulky tumor burden (18% vs 26%). Median overall duration of treatment (DOT) was 8.8 (TBP) and 2.3 mo (NTBP). From randomization to progression, objective response rate was 20% and 14%; median time to response was 1.9 and 3.7 mo; duration of response was 5.6 and 7.0 mo for TBP and NTBP pts, respectively. Treatment-related adverse events occurred in 71% of pts TBP and 70% of pts NTBP before first progression. Characteristics at first progression are shown (Table). Median DOT after first progression was 3.4 mo. Of 140 pts TBP with tumor measurements before and after progression, 14% had ≥30% tumor burden reduction from first progression. Median overall survival was 28.1 (TBP) vs 15.0 mo (NTBP);$P<0.001$.**Conclusions:** Treatment beyond progression with nivo can be associated with tumor shrinkage after progression. Evaluating disease characteristics at first progression may facilitate decision making to continue nivo treatment beyond progression.

GENITOURINARY (NONPROSTATE) CANCER
Abstract: 4549

Title: Quality of life (QoL) and overall survival (OS) in patients (pts) with advanced clear-cell renal cell carcinoma(aRCC) treated with nivolumab (NIVI) vs. everolimus (EVE) in the phase III CheckMate 025 study

Author(s): David Cella, Viktor Gruenwald, Paul D. Nathan, Justin Doan, Homa Dastani, Fiona Taylor, Bryan Bennett, Michael DeRosa, Scott Berry, Kristine Broglio, Elmer Berghorn, Robert J. Motzer; Northwestern University, Feinberg School of Medicine, Chicago, IL; Medical School of Hannover, Hannover, Germany; Mount Vernon Cancer Centre, Northwood, Middlesex, United Kingdom; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Squibb, Princeton, NJ; Adelphi Values, Boston, MA; Adelphi Values, Bollington, United Kingdom; Berry Consultants, LLC, Austin, TX; Memorial Sloan Kettering Cancer Center, New York, NY

Background: In the CheckMate 025 study (NCT01668784), pts treated with nivo had an OS benefit vs eve (hazard ratio=0.73; 98.5% CI, 0.57 to 0.93), and median scores on the Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms (FKSI-DRS) scale increased from baseline (BL) and were significantly (P<0.05) improved with nivo vs eve through week 104 (*NEJM* 2015;373:1803–13). Here we present a full analysis of QoL in relation to OS. **Methods:** QoL was measured by the kidney-specific FKSI-DRS questionnaire at BL and every 4 weeks. Chi-square analyses were used to assess differences in the proportion of pts who experienced meaningful improvement (2-point change) with nivo vs eve. OS was assessed by subgroups of pts with FKSI-DRS improvement (≥2-point increase), no change (<2-point increase or decrease), and deterioration (≥2-point decrease) at week 8 using the Kaplan–Meier method. **Results:** BL QoL was collected for 86% of all randomized pts; 361/410 (nivo) and 343/411 (eve). Over the course of the study, 55% of pts experienced meaningful DRS improvement with nivo vs 37% with eve (P<0.001). Median (95% CI) time to improvement in DRS occurred at 4.7 (3.7–7.5) months with nivo and was not estimable (NE) with eve due to the limited number of pts who experienced improvement. Association of change in QoL at week 8 and OS is shown in the table. Results using the EQ-5D questionnaire of general health status will be presented.**Conclusions:** In this global study of pts with aRCC, treatment with nivo vs eve resulted in a significantly greater proportion of pts experiencing meaningful QoL improvement, and improvement or no change in QoL at 8 weeks was associated with an OS benefit with nivo vs eve. These results suggest that the assessment of QoL may be helpful for evaluating the extent of OS benefit in clinical practice.

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HEMATOLOGY: DIAGNOSIS & MANAGEMENT OF THROMBOTIC MICROANGIOPATHY

CATHERINE M. BROOME, M.D.

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

Thrombotic Microangiopathy: Where Are We Today?

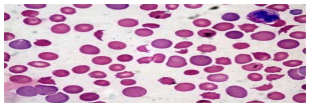
PATIENT CARE
RESEARCH
EDUCATION
COMMUNITY

Catherine Broome MD
Associate Professor of Medicine

http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

Thrombotic Microangiopathy

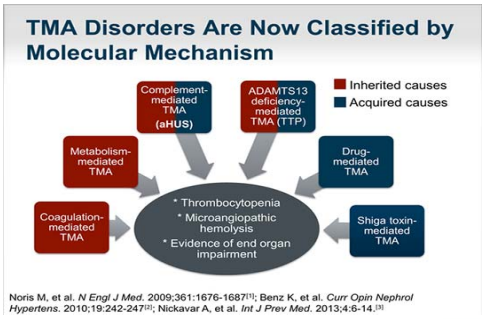
- DEFINED AS:
- Thrombocytopenia (think about defining as you would in HIT)
- Microangiopathic hemolysis (elevated LDH, decreased haptoglobin, smear review)
- Evidence of end organ impairment (renal, neurologic, cardiac, hepatic, GI, skin)



Thrombotic Microangiopathy

- Despite differing underlying causes once TMA develops the patients look very similar from a clinical and laboratory perspective
- It does not matter which door you use to enter the "room" once you are there the room looks the same
- Our challenge is to look back and try to accurately ascertain which door was used to get into the "room"

TMA



Noris M, et al. *N Engl J Med.* 2009;361:1676-1687[1]; Benz K, et al. *Curr Opin Nephrol Hypertens.* 2010;19:242-247[2]; Nickavar A, et al. *Int J Prev Med.* 2013;4:6-14.[3]

Differential Diagnosis of Thrombotic Microangiopathy Based on Pathophysiologic Cause

- HEREDITARY DISORDERS

Name	Cause	Clinical
ADAMSTS13 deficiency mediated TMA (aka TTP)	Homozygous or compound heterozygous ADAMSTS13 mutations	Usually presents in children, acute renal injury uncommon, patients with heterozygous mutations asymptomatic
Complement mediated TMA	Mutations in CFH, CFI, CFB, C3, CD46 and other genes resulting in uncontrolled activation of the alternative pathway of complement	Presents in adults and children, renal injury common, patients with heterozygous mutations may be symptomatic
Metabolism –mediated TMA	Homozygous mutations in MMACHC	Initial presentation usually in children less than 1 year of age, has been reported in one young adult with HTN and renal disease
Coagulation-mediated TMA	Homozygous mutations in DGKE, PLG and THBD	Presents with acute renal injury in children les than 1 year of age

Differential Diagnosis of Thrombotic Microangiopathy Based on Pathophysiologic Cause

- ACQUIRED DISORDERS

Name	Cause	Clinical
ADAMSTS13 deficiency(aka TTP)	Autoantibody inhibition of ADAMSTS13 activity	Uncommon in children, acute renal injury is uncommon
Shiga toxin-mediated TMA(aka ST-HUS)	Infection with shiga toxin producing strain of E. coli or Shigella	More common in young children, acute renal injury is common, most cases are sporadic, outbreaks can occur
Drug-mediated TMA-not dose related	????	Sudden onset of severe symptoms often with severe acute kidney injury
Drug-mediated TMA-toxic dose related	Multiple mechanisms depending on drug ????????	Gradual onset of renal failure occurs over months
Complement mediated TMA	Antibody inhibition of complement factor H activity, other ??	Acute renal injury in children and adults

TMA

Working Classification of TMA

Hereditary	• TTP[ADAMTS13 def] • Complement defects TMA[H,I,B,C3,CD46] • Metabolic defect [Vit B12] • Coag.defects [Dgk E]
Acquired	• Shiga Toxin • Drugs [Immune,Toxic Dose] • Complement [Acq.antibody inh. Factor H]

Terms such as Atypical HUS, Idiopathic HUS are being replaced

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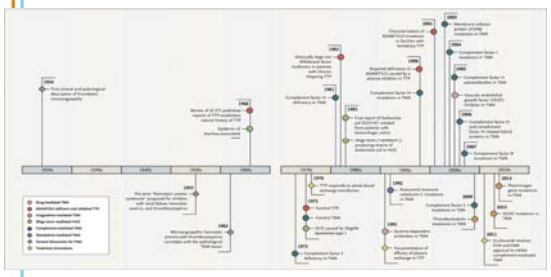
Timeline in TMA



George JN, Nester CM. N Engl J Med 2014;371:654-666.

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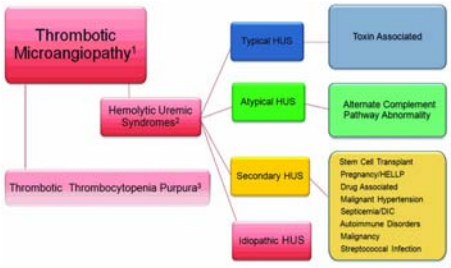
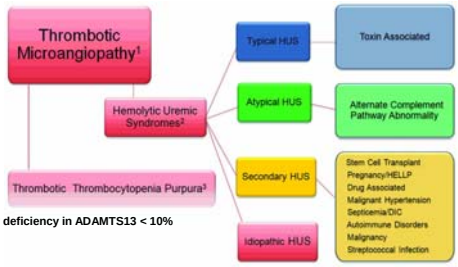
TMA related disorders



Nester et al. Hematology 2012

TMA related disorders



** deficiency in ADAMTS13 < 10%

Nester et al. Hematology 2012

Thrombotic Thrombocytopenic Purpura(TTP)

- **First presumed case described in a 16 yo girl by Moschcowitz in 1924**
- **Clinical Pentad:**
  fever
  altered mental status
  thrombocytopenia
  microangiopathic anemia
  renal insufficiency
- **Very poor outcomes from 1924-1991 with mortality as high as 90%**
- **Can be hereditary(Upshaw –Schulman Syndrome) or acquired**
- **Incidence of acquired TTP higher in adults (2.9 cases per 1 million per year) compared to children (0.1 cases per million per year)**
- **Increased frequency of acquired TTP associated with age (18-50 years), female sex, black race.**

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Thrombotic Thrombocytopenic Purpura(TTP)

- 1982-large multimers of von Willebrand factor were observed in patients with “relapsing” TTP
- 1991-plasma exchange therapy(PEX) was shown to reduce mortality in patients with TTP from 90% to 28%
- 1996-discovery of a von Willebrand factor cleaving protease eventually termed ADAMTS13
- 1998-association between an acquired antibody directed against ADAMTS13 and clinical TTP led to the addition of steroids to the treatment regimen of plasma exchange
- 1997-Rituxan approved by FDA for treatment of NHL
- 2002-widespread off label use of rituxamab for the treatment of TTP
- 2013-SEVERE deficiency of ADAMTS 13(less than 5-10% activity) required to generate VWF mediated TMA or TTP

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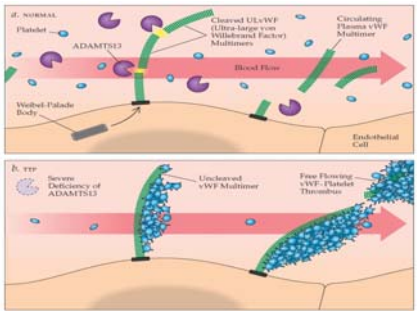
Thrombotic Thrombocytopenic Purpura



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TTP Treatment

Treatment of TTP

- Urgent plasmapheresis (plasma exchange)
  - Plasma Infusion : Infusion of FFP 30 cc/kg/day until ready for plasma exchange (serves as emergency initial measure in those who do not have immediate access to Plasma exchange)
  - Daily plasma exchange with either FFP or cryopoor FFP (45 to 55 cc/kg/day)
- Steroids (Prednisone 1 mg/kg/day) (may help by suppressing anti-ADAMTS13 antibodies).
- Red Blood Cell transfusions if needed
- Platelet transfusion may worsen the disease and are avoided. Used only if absolutely necessary (in very rare cases, where severe bleeding is encountered)
- Refractory TTP : In patients with worsening disease despite daily plasma exchange + Steroids → Increase plasmpheresis to twice daily exchange.
- Poorly responsive or Recurrent TTP → Add Immunosuppressive therapy -Add Rituximab or Cyclosporine

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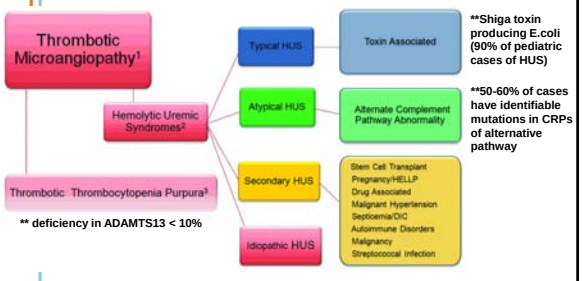
TMA related disorders



**Shiga toxin producing E.coli (90% of pediatric cases of HUS)

**50-60% of cases have identifiable mutations in CRPs of alternative pathway

Nester et al. Hematology 2012

TMA related disorders

** deficiency in ADAMTS13 < 10%

**Shiga toxin producing E.coli (90% of pediatric cases of HUS)

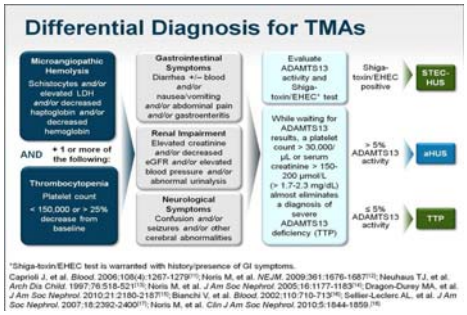
**50-60% of cases have identifiable mutations in CRPs of alternative pathway

**Drugs: CNI, ticlopidine, clopidogrel, simvastatin, interferon, quinine

**Autoimmune: SLE, APS, Scleroderma

Nester et al. Hematology 2012

TMA



Caprioli J. et al. *Blood*. 2006;108(4):1267-1279[11]; Noris M. et al. *NEJM*. 2009;361:1676-1687[12]; Neuhaus TJ. et al. *Arch Dis Child*. 1997;76:518-521[13]; Noris M. et al. *J Am Soc Nephrol*. 2005;16:1177-1183[14]; Dragon-Durey MA. et al. *J Am Soc Nephrol*. 2010;21:2180-2187[15]; Bianchi V. et al. *Blood*. 2002;110:710-713[16]; Sellier-Leclerc AL. et al. *J Am Soc Nephrol*. 2007;18:2392-2400[17]; Noris M. et al. *Clin J Am Soc Nephrol*. 2010;5:1844-1859.[18]

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What is Complement Mediated TMA(aHUS)?

- Life-threatening, chronic disease characterized by TMA and shown to be pathologically caused by dysregulation in the alternative complement pathway
- Onset:
  - Childhood: 42%
  - Adulthood: 58%
- Prognosis:
  - Overall ESRD or death in first year: 33-40%
  - Disease recurrence in renal transplant: 50%

Fremeaux-Bacchi V et al. Clin J Am Soc Nephrol. 2013
Noris et al. NEJM 2009

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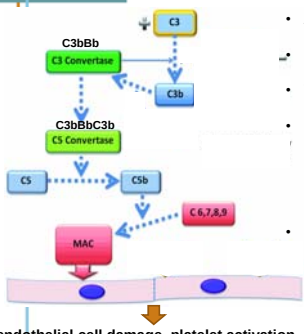
Alternative Pathway of Complement Activation

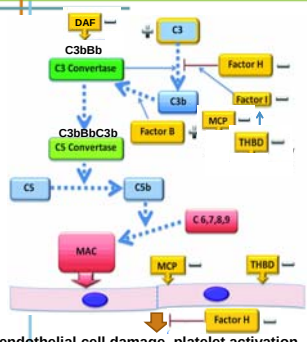


- Arm of our innate immune system
- Constitutively active
- Tight control of the AP is required
- C3 convertase (C3bBb)→
  - C3a: recruitment of pro-inflammatory cells
  - C3b: forms C3 convertase, positive feedback on AP
- C5 convertase (C3bBbC3b)
  - C5a: recruitment of pro-inflammatory cells
  - C5b: sequential assembly of C5b and C6-C9 to form MAC

endothelial cell damage, platelet activation, and thrombus formation

Walport et al. NEJM 2001
Nester, and Thomas. Hematology 2012

Alternative Pathway of Complement Activation



endothelial cell damage, platelet activation, and thrombus formation

Key Regulators of Alternative Complement Pathway

+ C3
- Factor H
- Factor I
+ Factor B
- Thrombomodulin (THBD)
- Membrane co-factor protein
- Decay accelerating factor (DAF/CD55)

Walport et al. NEJM 2001
Nester, and Thomas. Hematology 2012

Definition of aHUS Agreed to by Regulatory Authorities

Signs and symptoms of complement-mediated TMA

- Decreased platelet count
- Evidence of microangiopathic hemolysis
- Evidence of organ impairment/damage

Differentiate from other TMA diseases

- ADAMTS13 activity >5% → excludes severe ADAMTS13 deficiency (congenital or acquired TTP) as cause of TMA
- Absence of positive STEC test → excludes STEC as sole cause of TMA

No requirement for identified complement gene mutation

- Genetic mutation cannot be identified in 30% to 50% of patients with aHUS

Diagnosis of aHUS: Challenges

- aHUS or complement mediated TMA can manifest with early signs and symptoms that are non-specific
- Clinical presentation can be very similar to other systemic thrombotic microangiopathies (TMA)
- Historically there was limited interest to differentiate aHUS from severe ADAMTS13 deficiency(TTP) as no specific management for aHUS existed
- Often presents in patients with other complement amplifying conditions
- aHUS is a rare disease and thus unfamiliar to many
- Remains a clinical diagnosis

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No Role for Complement Level Testing in the Diagnosis of aHUS

- Complement and soluble complement regulatory protein levels in plasma or serum are unreliable in the diagnosis of aHUS
- Majority of aHUS patients have normal levels of complement
  - Serum C3 – normal in 80% of aHUS patients
  - Complement Factor H (CFH) protein levels – normal in 87% of aHUS patients with CFH mutation

References: 1. Davin et al. *Am J Kid Dis.* 2010;55(4):708-777. 2. Noris et al. *JASN.* 2005;16(5):1177-1183. 3. Dragon-Durey et al. *J Am Soc Nephrol.* 2010;21(12):2180-2187. 4. Sellier-Leclerc AL. *JASN.* 2007;18:2392-2400. 5. Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859. 6. Tsai H-M. *Int J Hematol.* 2010;91:1-19. 7. Lamelle et al. *Haematologica.* 2008;93(2):172-177. 8. Barbot et al. *Brit J Haem.* 2001;113(3):649.

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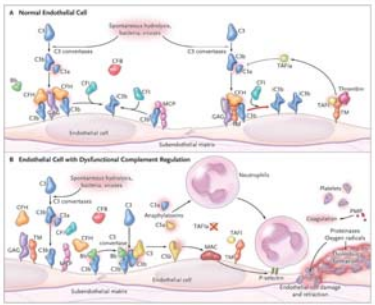
Model of Atypical Hemolytic Uremic Syndrome or the Mechanisms Leading from Impaired Regulation of the Alternative Pathway to Thrombotic Microangiopathy.



Atypical Hemolytic–Uremic Syndrome Marina Noris, Ph.D., and Giuseppe Remuzzi, M.D. N Engl J Med 2009; 361:1676-1687October 22, 2009

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aHUS: More than a Renal Disease

System	Signs/Symptoms	Percent of Patients N=30
Renal	Kidney impairment	90%
Cardiovascular	Cardiomyopathy, myocardial infarction, transient ischemic attacks, pulmonary embolism, and cardiac arrest	50%
Gastrointestinal	Diarrhea, vomiting, constipation	73%
Neurologic	Headache, seizures, migraine, epilepsy and facial paralysis	53%
Pulmonary	Asthma, pneumonia and respiratory failure	50%
aHUS complications in >1 system		100%

12 (40%) of the 30 aHUS patients experienced manifestations of TMA beyond the kidney

. Muus P et al. Historical evidence of systemic multiorgan complications in atypical hemolytic uremic syndrome. Presented at EHA 2015.

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Other Findings May Increase the Index of Suspicion for aHUS

Family History[1-3]	• 20-30% of patients with aHUS report a positive family history • Due to incomplete penetrance, patients may still inherit a genetic basis for aHUS in the absence of positive family history	Eg, ✓ Family history of unexplained renal failure ✓ Family history of cardiovascular disease due to unknown causes
Past Medical History[1,3-5]	• History of signs or symptoms consistent with previous manifestations of TMA • Patients may initially present without thrombocytopenia, anemia or renal injury	Eg, ✓ Malignant hypertension ✓ Unexplained stroke or MI ✓ Preeclampsia/HELLP with renal involvement persisting after pregnancy
Complement Levels[1,2,6]	• Low C3 and normal C4 levels suggests alternative pathway activation • However, the majority of patients with aHUS have normal complement levels	✓ Low complement levels may be observed in some patients ✓ Up to 80% of patients with aHUS have normal C3 levels
Biopsy[6,7]	• While not required for diagnosis, renal biopsy may be useful to confirm TMA lesions in some patients	✓ Histological evidence of renal TMA ✓ Deposits of terminal complement in microvessels

HELLP, hemolysis, elevated liver enzymes, low platelets.

1. Loirat C, et al. *Pediatr Nephrol.* 2016;31(1):15-39. **2.** Loirat C, Fremeaux-Bacchi V. *Orphanet J Rare Dis.* 2011;6:60. **3.** Lhotta K, et al. *Clin J Am Soc Nephrol.* 2009;4(8):1356-1362. **4.** Barbour T, et al. *Nephrol Dial Transplant.* 2012;27(7):2673-2685. **5.** Tsai HM. *Transfus Med Rev.* 2014;28(4):187-197. **6.** Laurence J. *Clin Adv Hematol Oncol.* 2013;40(10 Suppl 17):1-12. **7.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447.

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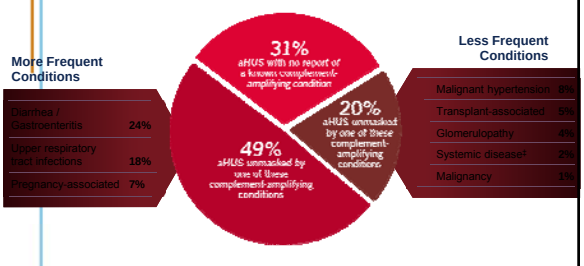
69% of Patients With aHUS Showed Their First Clinical Manifestation While Experiencing One of the Following Complement-Amplifying Conditions (N=191*)[1]



*Patients with non-familial aHUS. ‡E.g., Systemic Lupus Erythematosus and Scleroderma.

1. Noris M, Caprioli J, Bresin E, et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859.

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Management Options: Overview

- Historical approach
  - Plasma therapy (infusion or exchange)
  - Liver-kidney transplantation
- Since 2011
  - Complement inhibitor therapy (eculizumab)

Treatment of aHUS

- Plasma exchange/infusion of plasma
  - Replace deficient CFH or remove anti-CFH antibodies
  - May **temporarily** help some patients aiding in normalization of hematologic parameters
  - End organ damage more difficult to reverse
- Immunosuppression/Rituximab
- Kidney/Liver Transplant
  - Disease recurs in 50% of patients who undergo kidney transplantation only
    - Graft failure occurs in 80-90% of those with recurrent disease
  - Provide complement proteins that are deficient
  - Very risky

Noris et al. NEJM 2009

Plasma Exchange Therapy for Complement Mediated TMA(aHUS)

- Very difficult to evaluate actual outcomes as these patients were often not diagnosed or labeled as “atypical TTP”
- Long term follow-up is very poor for this disease in the literature
- We may not have recognized some of the long term morbidity associated with chronic ongoing complement activation

Response to Plasma Therapy for aHUS

Affected Protein	Short-term Response (Remission Rate)	Long-term Outcome (Rate of Death or ESRD)
Factor H	60%	70%-80%
CFHR1, R3	70%-80%	30%-40%
CD46 (MCP)	No definitive indication for therapy	<20%
Factor I	30%-40%	60%-70%
Factor B	30%	70%
C3	40%-50%	60%
Thrombomodulin	60%	60%

Noris M, et al. *N Engl J Med.* 2009;361:1676-1687

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PE/PI for aHUS Has Proven to Be Clinically Inadequate[1-10]

- PE/PI is not sufficient to replace deficient or malfunctioning complement regulatory proteins[1-9]
  - Apheresis procedures themselves may also lead to complement activation via granulocyte aggregation[14-15]
- Ongoing complement activity, approximately four-fold higher than in normal patients, occurs in aHUS patients receiving PI[16]
- Complement dysregulation and TMA persist in aHUS patients on PE/PI, even if there is a transient impact on platelet count and LDH levels[2,16]

References: 1. Waters AM, Licht C. *Pediatr Nephrol.* 2011;26:41-57. 2. Legendre CM, Licht C, Muus P, et al. *N Engl J Med.* 2013;368:2169-2181. 3. Larakeb A, Leroy S, Frémeaux-Bacchi V, et al. *Pediatr Nephrol.* 2007;22:1967-1970. 4. Neuhaus TJ, Calonder S, Leumann EP. *Arch Dis Child.* 1997;76:518-521. 5. Remuzzi G, Ruggenenti P, Colledan M, et al. *Am J Transplant.* 2005;5:1146-1150. 6. Mache CJ, Acham-Roschitz B, Frémeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2009;4:1312-1316. 7. Vergouwen MD, Adriani KS, Roos YB, et al. *AJNR Am J Neuroradiol.* 2008;29:e34. 8. Loirat C, Macher M-A, Elmaleh-Berges M, et al. *Nephrol Dial Transplant.* 2010;25:3421-3425. 9. Malina M, Gulati A, Majid MA, et al. *Pediatr Nephrol.* 2011;26:1678. 10. Riedl M, Hofer J, A Rosales, et al. Initiale plasmatherapie bei patienten mit atypischem HUS: kein negative vorhersagewert für das outcome nach einem jahr. *Klin Pediatr.* 2011;223-P031. 11. Langman CB. *Haematologica.* 2012;97(suppl 1): Abstract 0490. 12. Caprioli J, Noris M, Brioschi S, et al; for the International Registry of Recurrent and Familial HUS/TTP. *Blood.* 2006;108:1267-1279. 13. Noris M, Caprioli J, Bresin E, et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859. 14. Boogaerts MA, Roelant C, Goossens W, et al. *Transfusion.* 1986;26:82-87. 15. Burnouf T, Eber M, Kientz D, et al. *J Clin Apheresis.* 2004;19:142-147. 16. Heinen S, Plluthero FG, van Elmeren VF, et al. *Mol Immunol.* 2013;54:84-88. 16. Cofiell R et al. Poster presented at the 55th Annual Meeting of ASH 2013, Abstract 2184.

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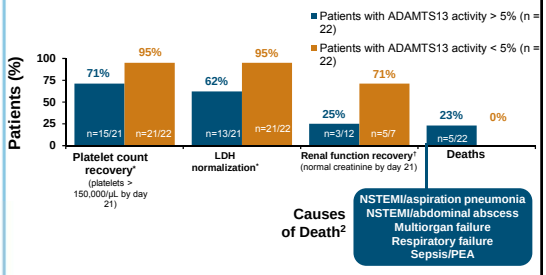
Among Patients with TMA Treated with PE/PI, Those with ADAMTS13 Activity >5% Have Increased Rates of ESRD and Premature Mortality

A retrospective analysis of 44 patients undergoing PE/PI for the treatment of TMA at Duke University Medical Center studied the time to recovery from laboratory abnormalities and rate of premature mortality in patients with TMA (follow-up period up to 21 days)[1]



Causes of Death[2]

- NSTEMI/aspiration pneumonia
- NSTEMI/abdominal abscess
- Multiorgan failure
- Respiratory failure
- Sepsis/PEA

* Of patients with available data; †Of patients with abnormal creatinine at baseline; NSTEMI, non-ST-segment elevation myocardial infarction; PEA, pulse-less electrical activity.

1. Pishko AM. *Blood.* 2014;124:Abstract 4192. 2. Pishko AM and Arepally GM. Presented at: 56th American Society of Hematology Annual Meeting and Exposition; December 6th-9th, 2014; San Francisco, CA. Poster 4192.

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Significant Morbidities and Mortality in aHUS can Occur Regardless of Overt Clinical Manifestation[1-6]

- In aHUS, complement-mediated damage can be devastating and can manifest differently depending on the individual's:[2,4,7,8]
  - Level of baseline complement activation
  - Exposure to complement amplification
  - Genetic background
- After initial diagnosis of aHUS, 42% (8/19) of patients progressed to end-stage renal disease or death without overt signs and symptoms of TMA[1]

References: 1. Frémeaux-Bacchi V, Fakhouri F, Garnier A, et al. *Clin J Am Soc Nephrol.* 2013;8:554-562. 2. Zuber J, Fakhouri F, Roumenina LT, et al. *Nat Rev Nephrol.* 2012;8:643-657. 3. Campistol JM, Arias M, Arriceta G, et al. *Nefrologia.* 2013;33:27-45. 4. Nester CM, Thomas CP. *Hematology Am Soc Hematol Educ Program.* 2012;2012: 617-625. 5. Sellier-Leclerc A-L, Frémeaux-Bacchi V, Dragon-Durey MA, et al; French Society of Pediatric Nephrology. *J Am Soc Nephrol.* 2007;18:2392-2400. 6. Loirat C, Frémeaux-Bacchi V. *Orphanet J Rare Dis.* 2011;6:60. 7. Noris M, Caprioli J, Bresin E, et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859. 8. Bu F, Maga T, Meyer NC, et al. *J Am Soc Nephrol.* 2013 Sep 12. [Epub ahead of print].

Assessing PE/PI Failure Recommendations from French Study Group for aHUS

Factors defining PE/PI failure after 5 daily plasma exchanges:

- Platelet count and LDH are not normalized[1]
- Serum creatinine is not reduced by at least 25%[1]

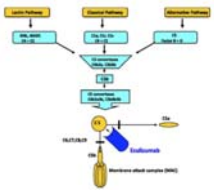
If TMA occurs in plasma dependent patients with detectable ADAMTS13 activity when withdrawing PE/PI, consider an alternative therapy

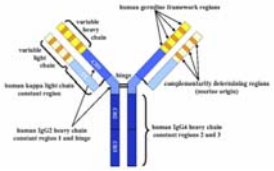
Zuber J et al. *Nat Rev Nephrol.* 2012 Nov;8(11):643-657.

Treatment of aHUS- Eculizumab

Mechanism of action

- Humanized, monoclonal antibody
- Binds with high affinity to C5 complement protein





Indications

- PNH- approved by FDA in 3/2007
- aHUS- approved by FDA in 9/2011

Brodsky. *Blood* 2009.

Eculizumab Multinational Clinical Program Includes Broad aHUS Patient Population

Age	2 Months[1]	Adults[1]
Duration from aHUS diagnosis to study	<1 Month[1]	286 Months[1]
Identified genetic Complement mutations	None identified[2]	Multiple per patient[2]
Platelet count in patients with TMA	Normal platelet count[1]	Reduced platelet count[1]
Degree of organ damage	CKD Stage 1[2]	CKD Stage 5[2]
Dialysis	None[3]	3/Week[3]
PE/PI	No intervention[1]*	230 Interventions[1]
Renal transplant	None[3]	3 Prior kidney grafts lost[3]

Please see full prescribing information for Soliris® (eculizumab).
1. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012; 2. Soliris® (eculizumab) European Public Assessment Report. Available at http://www.ema.europa.eu [accessed December 15, 2011]; 3. Data on file. Alexion Pharmaceuticals, Inc.

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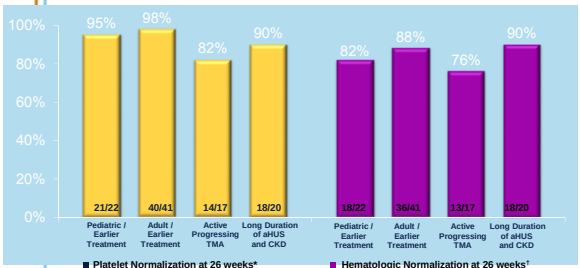
Approval of Eculizumab

	Design	Primary Outcomes	Secondary Outcomes
Study 1	Prospective, single arm (n=17) Median age: 28	**Platelet count:** - 26 week: mean increase 73k (82%) - 64 week: mean increase 91k (88%) **Hematologic Parameters:** - 26 week: 76% - 64 week: 88%	**TMA EF status:** - 26 week: 88% - 64 week: 88% **Decrease in Cr ≥ 25%** - 26 week: 65% - 64 week: 76% **Hemodialysis** - 80% discontinued
Study 2	Prospective, single arm (n=20) Median age: 28	**TMA EF status:** - 26 week: 80% - 62 week: 85% **Hematologic Parameters:** - 26 week: 90% - 62 week: 90%	**Decrease in Cr ≥ 25%** - 26 week: 15% - 62 week: 35% (*less improvement with chronic injury)

Legendre et al. NEJM 2013

Continued Improvement in Hematologic Markers of Complement-Mediated TMA Across All Studies



*Platelet normalization:
†Hematologic normalization:

1. Greenbaum L et al. ASN 2013. Abstract SA-PO849; 2. Fakhouri F et al. ASN 2013. Abstract FR-OR0571; 3. Legendre CM et al. *N Engl J Med.* 2013;368:2169-2181; 4. Licht et al. ASH 2013. Poster 2186. 4. Soliris® (eculizumab). Prescribing information. Alexion Pharmaceuticals, Inc.; 2014.

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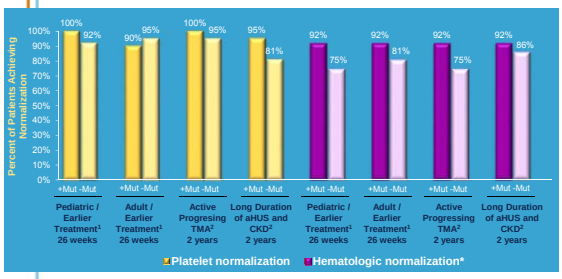
Rapid and Sustained Improvement in Hematologic Markers of Complement-Mediated TMA with or without Identified Genetic Mutation



+Mut = with mutation; −Mut = without mutation

Platelet normalization: normal platelet (≥150×10⁹/L) for 2 consecutive measurements ≥4 weeks apart

*Hematologic normalization: normal platelet (≥150×10⁹/L) and LDH levels for ≥2 consecutive measurements ≥4 weeks apart.

1. Data on file. Alexion Pharmaceuticals. Inc; 2. Al-Akash et al. ASH 2012. Poster 2085.

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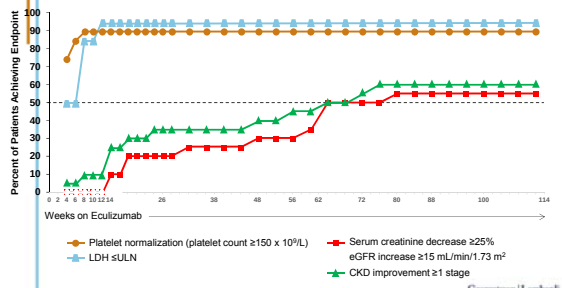
Rapid and Sustained Improvement in Hematologic Markers of Complement-Mediated TMA Followed by Continuous and Time-Dependent Reversal of Renal Damage with Chronic Eculizumab Treatment



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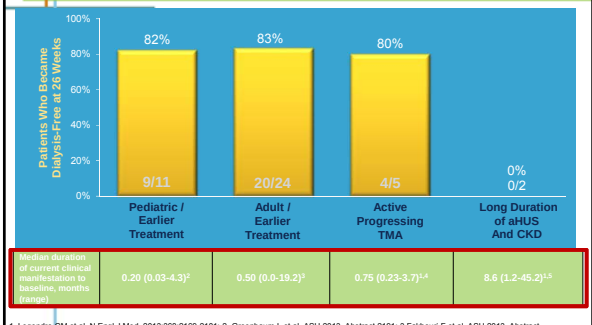
Dialysis Was Eliminated in 80% to 83% of Patients With Earlier Eculizumab Treatment at 26 Weeks[1-5]



Median duration of current clinical manifestation to baseline, months (range)	0.20 (0.03-4.3)[2]	0.50 (0.0-19.2)[3]	0.75 (0.23-3.7)[1,4]	8.6 (1.2-45.2)[1,5]

1. Legendre CM et al. N Engl J Med. 2013;368:2169-2181; 2. Greenbaum L et al. ASH 2013. Abstract 2191; 3.Fakhouri F et al. ASH 2013. Abstract 2179; 4. Greenbaum L et al. ASH 2012. Abstract 2084; 5. Licht C et al. ASH 2012. Abstract 985; 6. Soliris® (eculizumab) [package insert]. Alexion Pharmaceuticals; 4/2014.

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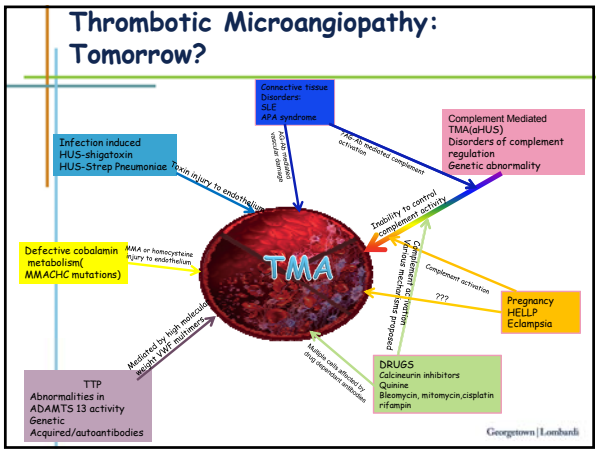
Thrombotic Microangiopathy: Tomorrow?
Connective tissue Disorders: SLE APA syndrome
Complement Mediated TMA(aHUS) Disorders of complement regulation Genetic abnormality
Infection induced HUS-shigatoxin HUS-Strep Pneumoniae
Toxin injury to endothelium
Toxin mediated vascular damage
APL Ab mediated complement activation
Inability to control complement activity
TMA
Defective cobalamin metabolism(MMACHC mutations)
MMA or homocysteine injury to endothelium
Complement activation
???
Pregnancy HELLP Eclampsia
Mediated by high molecular weight VWF multimers
TTP Abnormalities in ADAMTS 13 activity Genetic Acquired/autoantibodies
Multiple cells injured by drug dependent antibodies
DRUGS Calcineurin inhibitors Quinine Bleomycin, mitomycin,cisplatin rifampin
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BEST of ASCO®

ASCO POLICY UPDATE

CLIFFORD HUDIS, M.D.

Clifford A. Hudis, M.D., FASCO
CEO of American Society of Clinical Oncology

Dr. Hudis is the CEO of the American Society of Clinical Oncology (ASCO). Previously, he served for nearly two decades as the Chief of the Breast Medicine Service and Attending Physician at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City where he was also a Professor of Medicine at the Weill Medical College of Cornell University. He was co-chair of the Breast Committee of the Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group), Chair of the Scientific Advisory Committee of the Breast Cancer Research Foundation, a former Associate Editor of the Journal of Clinical Oncology, and the President of ASCO during its 50th anniversary, 2013-2014.

For almost 30 years he has worked to develop more effective treatment and prevention for breast cancer. His early work focused on translating the kinetic predictions of the Norton-Simon model into more effective dose-dense adjuvant inflammation, obesity, and cancer and his group described low grade, chronic white adipose inflammation in most overweight and obese women. They have made similar observations in other malignancies and risk groups and have used these insights to inform intervention studies and public policy initiatives at an international level.

BIOLOGIC THERAPIES AND THE ROLE OF BIOSIMILARS IN ONCOLOGY

EDWARD LI, PHARM D

Edward Li, PharmD, MPH, BCO
University of New England College of Pharmacy

Dr. Li is an Associate Professor in the Department of Pharmacy Practice at the University of New England College of Pharmacy. Dr. Li earned his Doctor of Pharmacy degree from the Philadelphia College of Pharmacy and his Master of Public Health from the University of New England. He completed a Pharmacy Practice Residency at the University of Wisconsin Hospital and Clinics and an Oncology Pharmacy Practice Residency at the University of Maryland School of Pharmacy. Dr. Li is a Board Certified Oncology Pharmacist who maintains a practice with the New England Cancer Specialists, the region's largest oncology group, located in Scarborough, Maine. He also works with New Century Health, a leading innovator of quality and cost management programs, to develop cancer treatment pathways. Before joining UNE, he was the Oncology Pharmacy Manager at the National Comprehensive Cancer Network, a not-for-profit organization whose clinical practice guidelines in oncology are the standard of care in the United States. His research focuses on cancer pharmacoepidemiology, pharmacoeconomics, and evaluating health policy issues as they relate to oncology practice.

BEST OF ASCO®
LUNG CANCER

SURESH RAMALINGHAM, M.D.

Dr. Suresh Ramalingam, MD
Professor
Director, Division of Medical Oncology
Emory School of Medicine
Department of Hematology & Medical Oncology

Dr. Suresh Ramalingam specializes in the treatment of thoracic malignancies. He has an active research program that focuses on development of new treatment options and individualized therapy for lung cancer. Dr. Ramalingam has over 100 peer-reviewed publications. Dr. Ramalingam serves as the chair of the Thoracic Malignancies Committee of the Eastern Cooperative Oncology Group (ECOG). He also serves on the editorial board of leading cancer journals such as Journal of Clinical Oncology, Cancer, Clinical Lung Cancer and Cancer, Chemotherapy and Pharmacology. Dr. Ramalingam is the section editor for chest malignancies for Cancer, the flagship journal of the American Cancer Society. Dr. Ramalingam is the recipient of several awards, including the 'James Eckman Award for Excellence in Teaching', Department of Hematology and Medical Oncology, Emory University, the Distinguished Cancer Scholar Award, and the prestigious NCI Clinical Trials Team Leadership Award.

LUNG CANCER – Non-Small Cell Metastatic

Abstract ID: 9012 (163941)

Title: A phase II open-label single-arm study of vandetanib in patients with advanced *RET*-rearranged non-small cell lung cancer (NSCLC): Luret study.

Authors: Takashi Seto, Kiyotaka Yoh, Miyako Satouchi, Makoto Nishio, Noboru Yamamoto, Haruyasu Murakami, Naoyuki Nogami, Kaname Nosaki, Yoshiko Urata, Seiji Niho, Atsushi Horiike, Takashi Kohno, Shingo Matsumoto, Shogo Nomura, Sakiko Kuroda, Akihiro Sato, Yuichiro Ohe, Takeharu Yamanaka, Atsushi Ohtsu, Koichi Goto; National Kyushu Cancer Center, Fukuoka, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; Hyogo Cancer Center, Akashi, Japan; Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan; Department of Thoracic Oncology, Hyogo Cancer Center, Akashi City, Japan; Department of Thoracic Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; National Cancer Center Research Institute, Tokyo, Japan; Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Kashiwa, Japan; National Cancer Center, Kashiwa, Japan; Office of Clinical Research Support, National Cancer Center Hospital East, Japan, Kashiwa, Japan; National Cancer Center Hospital, Tokyo, Japan; Department of Biostatistics,, Yokohama City University, Yokohama, Japan; National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: *RET* fusions were identified as new driver oncogenes of NSCLC in 2012 and observed in 1-2% of all NSCLC. Vandetanib is a multi-targeted tyrosine kinase inhibitor having RET kinase activity. **Methods:** This was a multicenter, single-arm phase II study to evaluate the efficacy and safety of vandetanib in pts with advanced *RET*-rearranged NSCLC who failed at least one prior chemotherapy. Vandetanib was administered orally at 300 mg once daily in 28-day cycles. *RET* fusion positive-pts were screened by a nationwide genomic screening network with 196 institutions in Japan participating (LC-SCRUM-Japan). The primary endpoint was objective response rate by independent review committee (ORR). This study required 17 pts, with ORR of 30% considered non-promising and 60% promising (one-sided alpha = 0.05; beta = 0.2). **Results:** 1536 pts with advanced NSCLC without *EGFR* mutation were screened in the LC-SCRUM-Japan from February 2013 to March 2015 and 34 pts (2%) with *RET*-rearranged NSCLC were identified. A total of 19 pts (10 *KIF5B-RET*, 6 *CCDC6-RET*, and 3 unknown-*RET*) were enrolled in this study and 17 pts were eligible for efficacy analysis. The median age was 59 (range 41-80 years) and 74% were female. All pts had adenocarcinoma and 68% were never a smoker. 63% of pts had received 2 or more prior chemotherapy (range 1-12). Among 17 eligible pts, ORR was 53% (90% CI, 31 to 74) of which 9 partial responses met the primary endpoint, and disease control rate was 88%. The median progression-free survival (PFS) was 4.7 months (95% CI, 2.8 to 8.3). According to *RET* fusion subtypes, ORR and median PFS were 83% (5/6) and 8.3 months in pts with *CCDC6-RET* versus 20% (2/10) and 2.9 months in those with *KIF5B-RET*. The median overall survival was 11.1 months (95% CI, 9.4 to not reached). The safety profile of vandetanib was similar to that reported previously. The most

common G3/4 toxicities were hypertension (58%), rash (16%), diarrhea (11%), and QTc prolongation (11%). **Conclusions:** Vandetanib showed marked antitumor activity in pts with advanced *RET*-rearranged NSCLC. In particular, it was indicated that *CCDC6-RET* subtype showed much higher sensitivity to vandetanib.

LUNG CANCER – Non-Small Cell Metastatic

Abstract ID: 9004 (169928)

Title: Local consolidative therapy (LCT) to improve progression-free survival (PFS) in patients with oligometastatic non-small cell lung cancer (NSCLC) who receive induction systemic therapy (IST): Results of a multi-institutional phase II randomized study.

Authors: Daniel Richard Gomez, George R. Blumenschein Jr., J. Jack Lee, Mike Hernandez, D. Ross Camidge, Robert Charles Doebele, Laurie E. Gaspar, Don Lynn Gibbons, Jose A. Karam, Brian D. Kavanagh, Ritsuko Komaki, Alexander V. Louie, David A. Palma, Anne S. Tsao, William Nassib William Jr., Jianjun Zhang, Stephen Swisher, John Heymach; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; University of Colorado, Aurora, CO; University of Colorado Anschutz Medical Campus, Aurora, CO; University of Colorado Cancer Center, Aurora, CO; Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Colorado Denver, Aurora, CO; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Radiation Oncology, London Regional Cancer Program, London, ON

Background: We performed a randomized study to assess the effect of aggressive LCT in patients with oligometastatic NSCLC who did not progress after IST. **Methods**: This study was performed at MD Anderson, U. Colorado, and London HSC, Canada. Eligibility: 1) histologically confirmed NSCLC, 2) Stage IV disease, 3) ≤ 3 metastases, and 4) no RECIST progression after IST. Appropriate IST was defined as either ≥ 4 cycles of platinum doublet therapy or ≥ 3 months of erlotinib/crizotinib for patients with EGFR mutations/ALK fusions, respectively. Patients were randomized to either LCT ([chemo]radiation or surgical resection of all sites) +/- systemic therapy (ST) vs. ST alone. The ST regimen was physician choice from predefined standard-of-care regimens. The primary endpoint was PFS, with the hypothesis that immediate LCT would improve PFS time from 4 months to 7 months (HR = 0.57) using ITT analysis. The planned study size was 94 randomized patients. Randomization was balanced dynamically by number of metastases, IST response, CNS metastases, nodal status, and EGFR/ALK status.

LUNG CANCER – Non-Small Cell Metastatic

Abstract ID: 108 (167889)

Title: Efficacy and safety of crizotinib in patients (pts) with advanced *MET* exon 14-altered non-small cell lung cancer (NSCLC).

Authors: Alexander E. Drilon, D. Ross Camidge, Sai-Hong Ignatius Ou, Jeffrey William Clark, Mark A. Socinski, Jared Weiss, Gregory J. Riely, Maria Winter, Sherry C. Wang, Katherine Monti, Keith D. Wilner, Paul K. Paik; Memorial Sloan Kettering Cancer Center, New York, NY; University of Colorado, Aurora, CO; University of California at Irvine, Irvine, CA; Massachusetts General Hospital Cancer Center, Boston, MA; University of Pittsburgh Medical Center, Pittsburgh, PA; Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill, NC; Pfizer Oncology, La Jolla, CA; Rho Inc., Chapel Hill, NC

Background: *MET* alterations leading to exon 14 skipping occur in ~4% of lung carcinomas, resulting in MET activation and sensitivity to MET inhibitors in vitro. Crizotinib, initially developed as a MET inhibitor, is currently approved for the treatment of *ALK*-positive NSCLC. We present crizotinib antitumor activity and safety data in pts with advanced *MET* exon 14-altered NSCLC. **Methods:** Pts with *MET* exon 14-altered NSCLC were enrolled into an expansion cohort of the ongoing phase I PROFILE 1001 study (NCT00585195) and received crizotinib at a starting dose of 250 mg BID. Responses were assessed using RECIST v1.0. **Results:** As of the data cut-off of Oct 30, 2015, 18 pts with *MET* exon 14-altered NSCLC had enrolled and 17 received treatment (15 response-evaluable, 2 not yet evaluable). Two pts discontinued treatment (1 due to an AE, 1 preferred another treatment formulation). Median age was 68 y (range 59–87). Tumor histology was as follows: 71% adenocarcinoma, 18% sarcomatoid adenocarcinoma, 6% adenosquamous carcinoma, and 6% squamous cell carcinoma. 65% were former and 35% never-smokers. Duration of treatment ranged from 0.5 to 9.1+ mo, with 88% of pts (15/17) still ongoing. Evidence of antitumor activity per RECIST was documented in 10/15 pts: 5 with confirmed PRs (all seen at the first scheduled tumor assessment at 8 wk ± 1 wk) and 5 with unconfirmed PRs (3 pts remained evaluable). Median PFS could not be calculated, with no deaths or PD by the data cut-off. Treatment-related AEs (TRAEs) were reported in 82% of pts; the most common were edema (35%) nausea (35%), vision disorder (29%), bradycardia (24%), and vomiting (24%). Most TRAEs were grade 1/2 in severity. One grade 3 TRAE (edema) and no grade 4/5 TRAEs were reported. Accrual of pts with *MET* exon 14-altered NSCLC continues. Updated data with a cut-off of Feb 2016 will be presented. **Conclusions:** Crizotinib has antitumor activity in pts with *MET* exon 14-altered NSCLC. The drug has a generally tolerable AE profile, consistent with that previously reported for pts with *ALK*-positive or *ROS1*-rearranged NSCLC. Further study of crizotinib in this pt population is warranted.

LUNG CANCER – Non-Small Cell Metastatic

Abstract ID: 9008 (167434)

Title: Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive *ALK*-positive non-small cell lung cancer (*ALK+* NSCLC): Primary results from the J-ALEX study.

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Background: ALC showed promising efficacy and tolerability in the phase I/II study (AF-001JP). Here, we conducted the randomized open-label phase III trial (J-ALEX study, JapicCTI-132316) to prove superior progression-free survival (PFS) of ALC to CRZ in *ALK+* NSCLC patients (pts) without prior ALK inhibitor treatment. **Methods:** *ALK+* NSCLC pts were randomized 1:1 either to receive ALC (300 mg b.i.d.) or CRZ (250 mg b.i.d.) and stratified by ECOG PS (0/1 vs 2), treatment line (1^{st} vs 2^{nd}), and clinical stage (IIIB/IV vs recurrence). Treatment on both arms was continued until disease progression or unacceptable toxicity. Primary endpoint was PFS according to the blinded independent review board. Secondary endpoints included overall survival, objective response rate, and safety. Under an assumption of expected hazard ratio (HR) of 0.643, 164 events were required to have 80% power with 2-sided alpha of 0.05. Three interim analyses (IA) for early stopping due to efficacy were planned after 33%, 50%, and 75% of required PFS events occurred. **Results:** 207 pts were enrolled at 41 centers in Japan between November 2013 and August 2015. 98%, 73%, and 64% of the pts were PS0-1, stage IV, and 1^{st} line, respectively. A second IA was performed on 6^{th}February 2016. Independent data monitoring committee recommended the release of study data because the superiority in PFS had been demonstrated. The PFS HR of ALC arm to CRZ arm was 0.34 (99.6826% CI: 0.17-0.70, stratified log-rank p<0.0001). Median PFS was not reached (95% CI: 20.3-Not Estimated) in ALC arm while it was 10.2 months (95%CI: 8.2-12.0) in CRZ arm. In the ALC arm, only constipation (36%) was an adverse event with >30% frequency, while in the CRZ arm nausea (74%), diarrhea (73%), vomiting (59%), visual disturbance (55%), dysgeusia (52%), constipation (46%), ALT elevation (32%), and AST elevation (31%) were seen in >30% pts. Grade 3-4 AEs occurred with greater frequency in the CRZ arm (ALC arm: 27% vs CRZ arm: 51%). There were no treatment-related deaths in either arm. **Conclusions:** At J-ALEX IA, ALC demonstrated significantly prolonged PFS compared with CRZ and was well tolerated with a favorable AE profile.

LUNG CANCER – Non-Small Cell/Small Cell/Other

Abstract ID: 8500 (168506)

Title: Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer.

Authors: Zhongxing X. Liao, J. Jack Lee, Ritsuko Komaki, Daniel Richard Gomez, Michael O'Reilly, Pamela Allen, Frank V. Fossella, John Heymach, George R. Blumenschein Jr., Noah C. Choi, Thomas Delaney, Stephen M. Hahn, Charles Lu, James D Cox, Radhe Mohan; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hosp Harvard Medcl School, Boston, MA; Massachusetts General Hospital, Boston, MA

Background: We assessed rates of and time to treatment failure (TF) [either grade ≥ 3 radiation pneumonitis (RP) or local recurrence (LR) within 12 months] in a Bayesian randomized trial of intensity-modulated radiotherapy (IMRT) vs. 3D proton therapy (3DPT), both with concurrent chemotherapy, for locally advanced non-small cell lung cancer (NSCLC). **Methods:** Assumptions for chosen sample size (n = 150) were that TF rate is log-normally distributed; IMRT will produce TF rates of 30% at 6 months (mos) and 40% at 12 mos; and 3DPT would reduce the TF rate by 10%. Pairs of IMRT and 3DPT plans were created for each patient. Patients were eligible for randomization only if both plans satisfied normal tissue constraints at the same radiation dose. Patients not eligible for randomization (NR) were treated with the modality producing the better plan. Patients denied coverage for protocol treatment were treated with the modality that was covered. **Results:** Of 255 enrolled patients, 149 were randomly allocated to IMRT (n = 92) or 3DPT (n = 57), and 106 received NRIMRT (n = 70) or NR3DPT (n = 36). Among randomized patients, patient characteristics were well balanced, but in 3DPT group, target volumes were larger (P= 0.071), and more patients received higher doses to tumors and had larger lung volumes receiving ≥ 30-80 Gy ($V_{30\text{-}80}$) than that in IMRT group. TF rates at 12 mo were 20.7% in all, 15.6% in IMRT, and 24.6% in 3DPT groups; corresponding median times to TF were 10.5 mos in all, in IMRT, and 3DPT groups. RP rates were 8.7% in all, 7.2% in IMRT, and 11.0% in 3DPT groups. The median times to RP were 4.3, 4.5, and 4.0 mos in all, in IMRT, and in 3DPT. The incidence of LR were 23.5%, 22.8%, and 24.6% in all, in IMRT, and in 3DPT. The median times to LR were 13.0, 12.7, and 13.4 mos in all, in IMRT, and in 3DPT. Among nonrandomized patients, the IMRT group was younger (P= 0.013) and had higher-stage disease (P= 0.071); lung $V_{20\text{-}40}$ was significantly lower in NR-3DPT patients, but was not different at other dose levels. The TF rates and time to TF were no different for NR-IMRT vs. NR-3DPT. **Conclusions:** No differences were found between IMRT vs. 3DPT in TF in this randomized trial.

LUNG CANCER – Non-Small Cell/Small Cell/Other

Abstract ID: 8507 (166472)

Title: E1505: Adjuvant chemotherapy +/- bevacizumab for early stage NSCLC—Outcomes based on chemotherapy subsets.

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Background: Adjuvant chemotherapy (chemo) for resected early stage NSCLC provides modest survival benefit. E1505 offers the first opportunity to study 4 modern cisplatin-based regimens in the adjuvant setting in the context of a single trial. As previously reported from this trial, the addition of bevacizumab (B) to adjuvant chemo failed to improve the primary endpoint of overall survival (OS HR=0.99; 95% CI: 0.82-1.19, p=0.91) or disease free survival (DFS HR=0.99; 95%CI: 0.85-1.15, p=0.89). Here we explore outcomes by chemo regimen utilized. **Methods:** Patients (pts) with resected early stage NSCLC, stratified by stage, histology, sex, and chemo option, were randomized 1:1 to chemo alone or chemo with B (15 mg/kg every 3 weeks for up to 1 year). Chemo consisted of a planned 4 cycles of every 3-week cisplatin (75 mg/m^2 d1) with investigator's choice of vinorelbine (V) (30 mg/m^2 d1,8), docetaxel (D) (75 mg/m^2 d1), gemcitabine (G) (1200 mg/m^2 d1,8), or pemetrexed (P) (500 mg/m^{2}d1). P was added in 2009 for non-squamous (NSq) pts only. **Results:** From 7/2007 to 9/2013, 1501 pts were enrolled: V 25%, D 23%, G 19% and P 33%. Arms were well balanced for known prognostic factors; 28% had Sq histology. Median f/up per chemo group is: V 54.3 months (mos); D 60.3 mos; G 57.0 mos; P 40.6 mos. When pts were pooled across +/- B arms and divided into NSq and Sq cohorts (to account for P restriction to NSq pts) there was no significant difference in OS or DFS by chemo regimen with the following logrank p-values: OS NSq, p=0.19; DFS NSq, p=0.67; OS Sq, p=0.96; DFS Sq, p=0.85. Toxicities were consistent with known profiles of the drugs. V was associated with more neutropenia and G with more thrombocytopenia. Sq pts had no differences in total Gr 3-5 toxicity by chemo groups, but NSq pts who received P had significantly less total Gr 3-5 toxicity (p<0.001) than NSq pts receiving other regimens. **Conclusions:** No differences in OS or DFS were observed between 4 different adjuvant cisplatin-based chemotherapy regimens for surgically resected early stage NSCLC patients.

LUNG CANCER – Non-Small Cell/Small Cell/Other

Abstract ID: LBA8505 (162941)

Title: Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC).

Authors: Charles M. Rudin, Maria Catherine Pietanza, Todd Michael Bauer, David R. Spigel, Neal Ready, Daniel Morgensztern, Bonnie S. Glisson, Lauren Averett Byers, Melissa Lynne Johnson, Howard A. Burris III, Francisco Robert, Donald K Strickland, Hany Zayed, Ramaswamy Govindan, Scott Dylla, Stanford L. Peng; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute, and Tennessee Oncology, PLLC., Nashville, TN; Sarah Cannon Research Institute, Nashville, TN; Duke University Medical Center, Durham, NC; Washington University School of Medicine in St. Louis, St. Louis, MO; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; Stemcentrx, Inc., South San Francisco, CA; Washington University School of Medicine, St. Louis, MO

Background: SCLC remains among the most deadly of malignancies. Rovalpituzumab tesirine is a first-in-class ADC comprised of a humanized monoclonal antibody against DLL3, a dipeptide linker, and a pyrrolobenzodiazepine (PBD) dimer toxin. DLL3 is highly expressed in neuroendocrine tumors, including approximately 80% of SCLC. The emerging results of the SCLC patients (pts) in a first-in-human study (NCT01901653) are reported here. **Methods**: Pts with progressive SCLC after at least 1 previous systemic therapy were eligible. Efficacy was assessed by the investigator via RECIST v1.1, and toxicity graded per CTCAE v4.03. When available, archived tumor tissue was assessed retrospectively for DLL3 expression by immunohistochemistry.

LUNG CANCER – Non-Small Cell/Small Cell/Other

Abstract ID: 8504 (165387)

Title: CONVERT: An international randomised trial of concurrent chemo-radiotherapy (cCTRT) comparing twice-daily (BD) and once-daily (OD) radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status (PS).

Authors: Corinne Faivre-Finn, Michael Snee, Linda Ashcroft, Wiebke Appel, Fabrice Barlesi, Adityanarayan Bhatnagar, Andrea Bezjak, Felipe Cardenal, Pierre Fournel, Susan Harden, Cécile Le Pechoux, Rhona Margaret McMenemin, Nazia Mohammed, Mary E.R. O'Brien, Jason R Pantarotto, Veerle Surmont, Jan Van Meerbeeck, Penella J. Woll, Paul Lorigan, Fiona Helen Blackhall; The University of Manchester, Institute of Cancer Sciences, Manchester, United Kingdom; St James Institute of Oncology, Leeds, United Kingdom; MAHSC-Trials Coordination Unit, The Christie NHS Foundation Trust, Manchester, United Kingdom; Lancashire Teaching Hospitals NHS Foundation Trust, Manchester, United Kingdom; Aix-Marseille University, Assistance Publique Hopitaux de Marseille, Marseille, France; University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; National Cancer Institute of Canada Clinical Trials Group, Kingston, Toronto, ON; Department of Medical Oncology, Catalan Institute of Oncology, Hospitalet (Barcelona), Spain; GFPC (France), Institut de Cancérologie de la Loire, St. Priest En Jarez, France; Addenbrookes Hospital, Cambridge, United Kingdom; Institut Gustave Roussy, Villejuif, France; Freeman Hospital, Newcastle upon Tyne, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; The Royal Marsden Hospital, Surrey, United Kingdom; University of Ottawa, Ottawa, ON; Universitar Ziekenhuis Ghent, Ghent, Belgium; Antwerp University, Antwerp, Belgium; Weston Park Hospital, Sheffield, United Kingdom; University of Manchester and The Christie NHS FT, Manchester, United Kingdom

Background: cCTRT is the standard of care for good PS LS-SCLC but there is no international consensus on a standard regimen. BD RT has not been adopted widely due to concerns regarding logistics and toxicity. Our aim was to compare overall survival and toxicity of BD with OD RT using modern conformal RT techniques given concurrently with chemotherapy. **Methods:** Patients were randomised 1:1 to receive 45Gy in 30 BD fractions over 3 weeks or 66Gy in 33 OD fractions over 6.5 weeks starting on day 22 of cycle 1 chemotherapy (4 to 6 cycles of Cisplatin 25mg/m^2 days 1-3 or 75mg/m^2 day 1 with Etoposide 100mg/m^2 days 1-3), followed by PCI if indicated. RT was planned using 3D conformal or IMRT. Patients were stratified by centre, 4/6 cycles CT and PS 0,1/2. The primary endpoint was 2-year survival and all analyses were by intention to treat. **Results:** 547 patients (274 BD and 273 OD) were recruited between April 2008 and November 2013 from 88 centres. Patients' characteristics were well balanced in both arms. 88% and 86% of patients in BD and OD arms received PCI. At a median follow up of 45 months for those alive; two-year survival was 56% (95% CI 50-61) vs 51% (95% CI 45-57) and median overall survival was 30 months (95% CI 24-34) versus 25 months (95% CI 21-31) (HR 1.17, 95% CI 0.95-1.45; p = 0.15) for BD and OD treatment, respectively. Toxicities were comparable except for significantly more grade 3/4 neutropenia (74% BD vs 65% OD, p = 0.03). There was no statistical difference, between BD and OD respectively, in rates of febrile neutropenia (23.4%, 18%), grade 2 oesophagitis (63%, 55%), grade 3/4 oesophagitis (19%, 19%), and grade 3/4 radiation pneumonitis was rare (2.5%, 2.2%). 3 patients died from RT toxicity within 3 months of completing RT (1 BD vs 2 OD). **Conclusions**: OD RT did not result in a superior survival or worse toxicity than BD RT, supporting the

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GASTROINTESTINAL CANCER (Colorectal) Cancer

Abstract ID: 3504 (161936)

Title: Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance).

Authors: Alan P. Venook, Donna Niedzwiecki, Federico Innocenti, Briant Fruth, Claire Greene, Bert H. O'Neil, James Edward Shaw, James Norman Atkins, Laura E. Horvath, Blase N. Polite, Jeffrey A. Meyerhardt, Eileen Mary O'Reilly, Richard M. Goldberg, Howard S. Hochster, Charles David Blanke, Richard L. Schilsky, Robert J. Mayer, Monica M. Bertagnolli, Heinz-Josef Lenz; University of California, San Francisco, San Francisco, CA; Duke University Medical Center, Durham, NC; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Mayo Clinic Cancer Center, Rochester, MN; Indiana University, Simon Cancer Center, Indianapolis, IN; Medstar Washington Hospital Center, Washington, DC; NSABP/NRG Oncology, and The Southeastern Medical Oncology Center, Goldsboro, NC; Alliance for Clinical Trials in Oncology, Naperville, IL; The University of Chicago, Chicago, IL; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH; Department of Medical Oncology, Yale University School of Medicine, New Haven, CT; Oregon Health & Science University, Portland, OR; American Society of Clinical Oncology, Alexandria, VA; Brigham and Women's Hospital, Boston, MA; University of Southern California, Los Angeles, CA

Background: 80405 found no OS or PFS difference when Bevacizumab (BV) or Cetuximab (Cet) was added to 1st-line FOLFOX or FOLFIRI in mCRC pts. As location of the 1° may affect mCRC outcome, we assessed the impact of 1° side (R v L) on OS and PFS in 80405 pts. **Methods:** 1° location was determined by chart review: 1137 pts w/KRAS *wt* (codons 12 and 13) in main cohort; 252 pts w/ KRAS *mut* tumors treated w/ BV or Cet pre-amendment. R-sided = cecum to hepatic flexure; L-sided = splenic flexure to rectum. Transverse (T) = hepatic to splenic flexure. PFS per investigator. Kaplan Meier and Cox regression methods used. **Results:** KRAS *wt* pts: Median age = 59; synchronous = 78%. 1° site: R – 280 (25%); L – 689 (61%); T- 62 (5%); unsure – 106 (9%). OS & PFS (Table) difference by side statistically significant if adjusted for age, gender, BV / Cet, chemotherapy, prior therapy. There was a significant 1° side by biologic interaction (P_{int} = 0.003, PFS and OS) but not by chemo, gender or RAS. OS, L-sided: Cet v BV, superiority (Log rank p = 0.04); R-sided: BV v Cet, superiority (p = 0.03). Results similar for PFS and if T colon allocated to R side. KRAS *mut* pts: 1°s: R - 35%; L- 50%. No statistically significant difference in any subset although OS favors L > R (only OS data shown). **Conclusions**: mCRC arising in the R v L colon are clinically different. In KRAS *wt* mCRC, pts w/ L-sided 1° tumor have superior OS and PFS v pts w/ R-sided 1°. Though not pre-planned analyses, OS and PFS were prolonged w/ Cet in L and w/BV in R but were poorer w/ Cet in R. Forthcoming molecular analysis of 1°s - e.g. BRAF, MSI, methylation - may provide a biological explanation. For now, stratification in mCRC studies by R v L 1° sidedness is indicated. These data support BV in 1st line treatment for mCRC pts w/R-sided 1° tumor regardless of KRAS status. Support: U10CA180821, U10CA180882.

GASTROINTESTINAL CANCER (Colorectal) Cancer

Abstract ID: 3512 (168547)

Title: FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—Prodige 14 – accord 21 (METHEP-2), a unicancer GI trial.

Authors: Marc Ychou, Michel Rivoire, Simon Thezenas, Rosine Guimbaud, Francois Ghiringhelli, Anne Mercier-Blas, Laurent Mineur, Eric Francois, Faiza Khemissa, Driffa Moussata, Yves Becouarn, Philippe Houyau, Thomas Aparicio, Rene Adam, Marie-Pierre Galais, Franck Audemar, Eric Assenat, Trevor Stanbury, Olivier Bouche; Montpellier Cancer Institute, Montpellier, France; Centre Léon Bérard, Lyon, France; Institut Régional du Cancer Montpellier, Montpellier, France; University Hospital of Rangueil, Toulouse, France; Centre Georges-François Leclerc, Dijon, France; Centre Hospitalier Privé de Saint-Grégoire, Saint-Grégoire, France; Radiotherapy and Oncology GI and Liver Unit, Institut Sainte-Catherine, Avignon, France; Department of Medical Oncology, Centre Antoine-Lacassagne, Nice, France; CH Saint Jean, Perpignan, France; CHU Tours, TOURS, France; Institut Bergonié, Bordeaux, France; Clinique Claude Bernard, Albi, France; Hôpital Avicenne, AP-HP, Bobigny, France; Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France; Centre François Baclesse, Caen, France; Centre hospitalier Côte Basque, Bayonne, France; Department of Medical Oncology, Hopital Saint Eloi, Montpelier, France; UNICANCER, Paris, France; CHU Robert Debré, Reims, France

Background: Liver metastases (LM) from colorectal cancer (CRC) are initially resectable in only 10-15% of patients (pts). The conversion to resectability following induction chemotherapy is an important strategy to increase survival. Our study was designed to determine the most appropriate chemotherapy (associated with a targeted therapy) for CRC pts with LM considered as initially unresectable.
Methods: This French phase II, multicenter, prospective trial, randomized pts between bi-chemotherapy (BiCT) versus tri-chemotherapy (TriCT). The population was initially stratified by targeted therapy depending on KRAS status and then by RAS status (from 02 Dec 2013 due to the change in cetuximab's [Cet] marketing authorization): Cet for wt(K)RAS pts and bevacizumab (Bev) for mtRAS pts. The hypothesis was to increase the rate of LM resection (R0-R1) from 50% with BiCT to 70% with TriCT (bilateral α-test 5%; power 90%). **Results:** 256 patients were randomized in 33 sites from February 2011 till April 2015: 126 BiCT (FOLFIRI [56 pts]; FOLFOX4 [70 pts]) and 130 TriCT (FOLFIRINOX). The resection rate (R0 or R1; CI95%) of the LM was 45.2% [36; 54] for pts treated with BiCT vs 56.9% [48; 66] for TriCT (p = 0.062).The LM resection rate (R0 or R1; CI95%) was 44.7% [35; 55] for pts treated with Bev (mtRAS) vs 55.6% [47; 64] for Cet (wtRAS) (p = 0.087). At the time of data analysis, the median follow-up (CI95%) was 22.5 months [19.6;29.5] for the BiCT pts and 23.5 months [19.8; 28.8] for the TriCT pts and at analysis 78 patients had died. The median overall survival (OS) is significantly different (p = 0.048): in the TriCT Arm the median OS was not reached and is 36 months [23.5;40.6] in the BiCT Arm. The severe toxicity rate was 37.6% for BiCT vs 41.7% for TriCT (p = 0.503). 38 BiCT pts and 34 TriCT pts had surgical

complications, with two deaths in each arm. **Conclusions:** First line FOLFIRINOX chemotherapy, in association with a targeted therapy, showed a higher rate of LM R0/R1 resections than standard BiCT (FOLFIRI or FOLFOX4) combined with the same targeted therapy, with a statistically significant difference in terms of OS.

GASTROINTESTINAL CANCER (Colorectal) Cancer

Abstract: 3503 (169985)

Title: NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA).

Authors: Van Karlyle Morris II, Kristen Keon Ciombor, Mohamed E. Salem, Halla Sayed Nimeiri, Syma Iqbal, Preet Paul Singh, Blase N. Polite, Dustin A. Deming, Emily Chan, James Lloyd Wade III, Tanios S. Bekaii-Saab, Hope Elizabeth Uronis, Manolo G Pasia, Gail Bland, Robert A. Wolff, Aki Ohinata, Chimela Ohaji, Jane Rogers, Padmanee Sharma, Cathy Eng; The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; Mayo Clinic, Rochester, MN, Rochester, MN; The University of Chicago, Chicago, IL; University of Wisconsin Hospitals and Clinics, Madison, WI; Vanderbilt University Medical Center, Nashville, TN; Cancer Care Center of Decatur, Decatur, IL; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Duke University Medical Center, Durham, NC; Clinical Research Support Center, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The incidence of SCCA continues to rise annually in the US. 20% of patients (pts) will develop metastatic (met) disease which lacks a consensus approach to treatment. SCCA is largely driven by immune evasion of HPV-specific CD8 and CD4 T cells which promote oncogenesis for SCCA. Nivolumab (Nivo), a monoclonal antibody targeting PD-1 on T cells, promotes immune-mediated anti-tumor activity of T cells against HPV-positive cells in vitro. This is the first phase II trial of Nivo for pts with refractory met SCCA. **Methods:** Previously treated but immunotherapy naïve met SCCA pts were eligible. PD-L1 expression was not required. HIV+ (CD4 count > 300/uL) and hepatitis B/C pts were eligible. A Simon two-stage phase II trial (Ho: $p < .05$, Ha: $p \geq .20$) was conducted. All pts were evaluated by RECIST Criteria 1.1. Pts received Nivo (3 mg/kg) IV every 2 weeks. Optional pre-treatment and on-treatment tissue biopsies and plasma samples were collected for immune biomarkers and HPV/p16 status. All correlatives were evaluated at MDACC by the Immunotherapy Platform team and the Core Facility. **Results:** 39 pts were screened across the ETCTN network (May 2015 - October 2015); 37 pts were eligible. Median age was 56 years (interquartile range [IQR], 51.1-63.6); M:F was 12:25. Median number of prior therapies: 2 (range 1-8). All pts were evaluable for toxicity; 33 pts were evaluable for response. Median number of cycles: 6 (IQR, 3-10). Seven (21%) pts had a partial response and 19 (58%) pts had stable disease; disease control rate of 79%. Ten pts (one HIV+) remain on study [7 pts for > 6 months (M)]. Median progression-free survival was 4.1M. Common adverse events (AE): fatigue, nausea, and rash. Six pts had grade 3 AE's: fatigue (N = 2) and one pt each of pneumonitis, rash, anemia, and hyperglycemia. **Conclusions:** Currently, there is no consensus approach for met SCCA. NCI9673 is the first prospective phase II trial of nivolumab in refractory metastatic SCCA. Single agent nivolumab demonstrated potentially meaningful activity and was well tolerated. Further evaluation of immune checkpoint therapy in met SCCA is justified. Updated clinical results will be presented. Exploratory correlative work is ongoing.

GASTROINTESTINAL (NONCOLORECTAL) CANCER

Abstract: 4005 (170054)

Title: NETTER-1 phase III: Efficacy and safety results in patients with midgut neuroendocrine tumors treated with ^{177}Lu-DOTATATE.

Authors: Jonathan R. Strosberg, Edward M. Wolin, Beth Chasen, Matthew H. Kulke, David L Bushnell Jr., Martyn E. Caplin, Richard P. Baum, Timothy J. Hobday, Andrew Eugene Hendifar, Kjell E. Oberg, Maribel Lopera Sierra, Dik J. Kwekkeboom, Philippe B. Ruszniewski, Eric Krenning, Pamela L. Kunz; Moffitt Cancer Center, Tampa, FL; University of Kentucky, Lexington, KY; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; Veterans Administration Medical Center, Iowa City, IA; Royal Free Hospital, London, United Kingdom; Zentralklinik Bad Berka, Bad Berka, Germany; Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA; Uppsala University Hospital, Uppsala, Sweden; Advanced Accelerator Applications, New York, NY; Erasmus University Medical Center, Rotterdam, Netherlands; Beaujon Hospital, Clichy, France; Erasmus Medical Center, Rotterdam, Netherlands; Stanford University School of Medicine, Stanford, CA

Background: There are limited therapeutic options for patients with advanced midgut NETs progressing on first-line somatostatin analog therapy. The purpose of this phase III trial was to evaluate the efficacy and safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) in patients with advanced, progressive sstr positive midgut NETs. **Methods:** 230 patients with grade 1-2 metastatic midgut NETs were randomized to Lutathera, 7.4 GBq every 8 weeks (x 4 administrations) vs Octreotide LAR 60 mg every 4 weeks. Primary endpoint was PFS (RECIST 1.1) with tumor assessment every 12 weeks. Secondary objectives included ORR, OS, toxicity and QoL. **Results:** In the intent-to-treat population (ITT), the median PFS was not reached for Lutathera and was 8.4 months with control ($p < 0.0001$, HR 0.21). There were 23 centrally confirmed disease progressions or deaths in the Lutathera arm and 67 in the Octreotide LAR 60 mg arm. The objective radiographic response rate (ORR) was 18% with Lutathera and 3% with control ($p = 0.0008$). Besides the scintigraphic ^{111}In-pentetreotide tumor uptake score (Krenning scale > = 2), tumor burden and Ki67 grade had no significant effect on clinical efficacy outcomes (PFS, OS, TTP) in the Cox regression models. Interim OS analysis (13 deaths in Lutathera group and 22 in control group; $p = 0.019$) strongly suggests an improvement in OS. Only 5% (6 patients) experienced dose modifying toxicity with Lutathera. Grade 3 or 4 adverse events of neutropenia, thrombocytopenia and lymphopenia occurred in 1%, 2% and 9% of patients in Lutathera arm vs. none in controls. **Conclusions:** The NETTER-1 trial provides evidence for a clinically meaningful and statistically significant increase in PFS and ORR, and suggests a potential survival benefit in patients with advanced midgut NETs treated with Lutathera in both ITT and PP analyses. Lutathera safety profile was found to be very favorable.

GASTROINTESTINAL (NONCOLORECTAL) CANCER

Abstract: 4000 (165706)

Title: A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study.

Authors: Marcel Verheij, Edwin PM Jansen, Annemieke Cats, Nicole C.T. van Grieken, Neil K Aaronson, Henk Boot, Pehr A. Lind, Elma Meershoek – Klein Kranenbarg, Marianne Nordsmark, Hein Putter, Anouk Kirsten Trip, Johanna W. van Sandick, Karolina Sikorska, Harm van Tinteren, Cornelis J. H. Van De Velde; Department of Radiation Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, Netherlands; The Netherlands Cancer Institute Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Pathology, VU University Medical Center, Amsterdam, Netherlands; Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; Karolinska Institute, Stockholm, Sweden; Department of Surgical Oncology, Leiden University Medical Center, Leiden, Netherlands; Aarhus University Hospital, Aarhus, Denmark; Department of Medical Statistics, Leiden University Medical Center, Leiden, Netherlands; Netherlands Cancer Institute - Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; Department of Surgical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Leiden University Medical Center, Leiden, Netherlands

Background: The mainstay of potentially curative treatment of gastric cancer is radical surgical resection. Because most patients in the Western world present with advanced stages long-term survival remains poor at about 25%, with local recurrences as part of treatment failure in up to 80% of cases. Postoperative chemoradiotherapy (CRT) and perioperative chemotherapy (CT) have demonstrated a survival benefit over surgery alone. The current randomized phase III CRITICS-study (NCT00407186) investigated whether chemoradiotherapy after neo-adjuvant chemotherapy and adequate (D2) surgery leads to improved overall survival (OS) in comparison with postoperative chemotherapy. Furthermore, toxicity of both treatment regimens was explored. **Methods:** Patients with stage Ib-IVa resectable gastric cancer were randomized after diagnosis. Neo-adjuvant CT was prescribed in both arms and consisted of 3 courses of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC). After gastric cancer resection, patients received another 3 courses of ECC/EOC or CRT (45 Gy in 25 fractions combined with weekly cisplatin and daily capecitabine). Primary endpoint is OS; secondary endpoints are: disease free survival, toxicity profile and quality of life. **Results:** Between January 2007 and April 2015, 788 patients from The Netherlands, Sweden and Denmark were randomized (393 CT; 395 CRT). Baseline characteristics were well balanced with 70% males and a median age of 61 years. 84% completed 3 cycles before surgery. In the CT arm 46% and in the CRT arm 55% completed treatment according to protocol. After a median follow-up of 50 months, 405 patients have died. The 5-year survival is 41.3% for CT and 40.9% for CRT (p=0.99). Toxicity was mainly hematological (grade III or higher: 44% vs 34%; p=0.01) and gastrointestinal (grade III or higher: 37% vs 42%; p=0.14) for CT and CRT, respectively. **Conclusion:** No significant difference in overall survival was found between postoperative chemotherapy and chemoradiotherapy.

GASTROINTESTINAL (NONCOLORECTAL) CANCER

Abstract: LBA4006 (162546)

Title: ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma.

Authors: John P. Neoptolemos, Dan Palmer, Paula Ghaneh, Juan W. Valle, David Cunningham, Jonathan Wadsley, Tim Meyer, Alan Anthoney, Bengt Glimelius, Stephen Falk, Ralf Segersvard, Jakob R. Izbicki, Gary William Middleton, Paul J. Ross, Harpreet Wasan, Alec Mcdonald, Tom David Lewis Crosby, Eftychia Eirini Psarelli, Pascal Hammel, Markus W. Buchler; University of Liverpool, Liverpool, United Kingdom; Department of Medical Oncology, The Christie NHS Foundation Trust; University of Manchester, Manchester, United Kingdom; Royal Marsden Hospital, Surrey, United Kingdom; Weston Park Hospital, Sheffield, United Kingdom; UCL Cancer Institute, University College London,, London, United Kingdom; Leeds Cancer Research UK Clinical Centre, Leeds, United Kingdom; Uppsala University, Uppsala, Sweden; Bristol Haematology and Oncology Centre, Bristol, United Kingdom; Karolinska Institute, Stockholm, Sweden; University Medical Center Hamburg-Eppendorf, Hamburg, Germany; University of Birmingham, Surrey, United Kingdom; Guy's Hospital, London, United Kingdom; Hammersmith Hospital, Imperial College, London, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Velindre Cancer Centre, Cardiff, United Kingdom; Hôpital Beaujon, Clichy, France; University of Heidelberg, Heidelberg, Germany

Background: The ESPAC-3 trial compared adjuvant GEM with 5-fluorouracil/folinic acid for resected pancreatic cancer. GEM is the standard of care based on similar survival and less toxicity. ESPAC-4 aimed to determine whether combination chemotherapy with GEM/CAP improved survival compared to GEM monotherapy. **Methods:** Patients with pancreatic ductal adenocarcinoma were randomized within 12 weeks of surgery (stratified for R0/R1 resection margin status and country) to have either six 4 week cycles of IV GEM alone or GEM with oral CAP. The primary endpoint was overall survival; secondary endpoints were toxicity, relapse free survival, 2 and 5 year survival and quality of life. 722 patients (480 expected events), 361 in each arm, were needed to detect a 10% difference in 2 year survival rates with 90% power (log-rank test with 5% two-sided alpha).

BEST of ASCO®

MEDICARE POLICY UPDATE

THOM MITCHELL, M.D.

Thom Mitchell, M.D., Medical Director
Cahaba GBA

Dr. Mitchell received his undergraduate degree from Cornell University. After two years of graduate work, he enrolled in Cornell University Medical College. He trained in internal medicine at Vanderbilt University and became the director of emergency services at Metropolitan Nashville General Hospital. He has practiced emergency medicine for 25 years. During that time, he also served as the market medical director for Aetna Health Plans of Tennessee and as the assistant medical director for a start-up Medicare Advantage plan, which was based in Nashville Tennessee. He joined Cahaba GBA three years ago as an associate medical director and was promoted to senior contractor medical director in February of 2015. He continues to practice emergency medicine part-time.

Medicare Policy Updates 2016

GASCO Annual Meeting
September 10, 2016

Thom R. Mitchell, MD, FACP, FACEP
Senior Contractor Medical Director

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- This presentation was current at the time it was created.
- Although every effort has been made to assure accurate information, responsibility for correct claim submission lies with the provider of the services.
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Agenda

- Medicare Contracting
- Cancer Chemo Coverage
- Appeals/Reconsiderations
- Comprehensive Error Rate Testing
- Evaluation & Management Errors
- Comprehensive Care, Transitional Care, Advanced Care services and CPT codes
- Program Innovations
- Website & General Information

Medicare Contracting

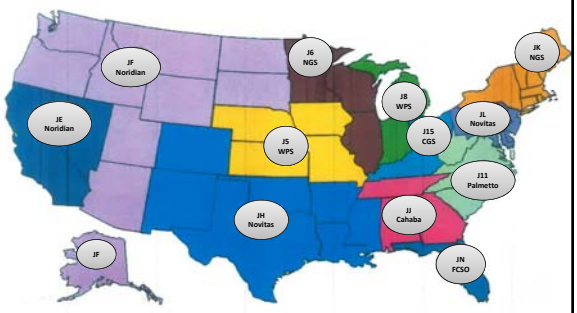
- MAC (Medicare Administrative Contractor)
- DMEMAC (Durable Medical Equip MAC)
- HH&H (Home Health and Hospice)
- CERT (Comprehensive Error Rate Testing)
- RA (Recovery Auditors)
- ZPIC (Zone Program Integrity Contractor)
- QIC (Qualified Independent Contractor)
- QIO (Quality Improvement Organization)
  - Beneficiary and Family Centered Care
  - Quality Innovation Network
- SMRC (Supplemental Medical Review Contractor)

Quality Improvement Organizations

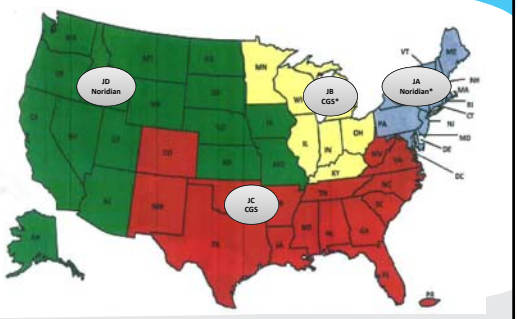
- BFCC-QIO
- Beneficiary and Family Centered Care
  - Beneficiary and Family Centered Care
  - **Kepro**
  - www.keprogio.com
- QIN-QIO
- Quality Innovation Network
  - **Alliant-Georgia Medical Care Foundation (GA, NC)**
  - www.alliantquality.org
  - **atom Alliance (AL, IN, KY, MS, TN)** 3340 Players Club Parkway, Suite 300 Memphis, TN 3812 800-528-2655
  - http://atomalliance.org

www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs.html

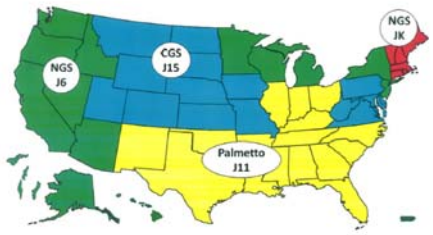
MAC A/B Jurisdiction Map



DME MAC Jurisdiction



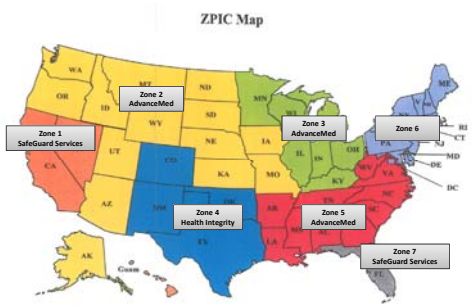
Home Health & Hospice (HH&H)



RA Contractors

A. Diversified Collection Service (DCS)
B. CGI
C. Cotiviti, Inc. (www.Cotiviti.com/RAC)
D. HealthData Insights (HDI)

ZPIC Contractors



Anti-Cancer Chemo Coverage

- Coverage outlined in the Medicare Benefit Policy Manual (PUB 100-2 Ch. 15 Sec.50.4.5
- FDA approved VS. “Off-label”
- Off-label based, medically accepted indications are supported in either one or more of the compendia or in peer-reviewed medical literature
- Cahaba Chemotherapy Article A52701

Appeals/Redeterminations

- MR uses NCCN Drugs and Biologic Compendium
- If in Last Column NCCN Category is 2A or above appeal is overturned
- If in Last Column NCCN Category is 2B or below appeal is affirmed
- If conflict between ICD-10 code column and the narrative in the other NCCN columns, we use the narrative

Comprehensive Error Rate Testing Program

- Established by CMS to monitor the accuracy of claim payment in the Medicare Fee-For-Service program
- Sampling methodology, randomly selected claims based on services with the highest historical improper payments
- Communication with the provider all has CMS letterhead (contractors are invisible)
- Preferred method of record exchange is fax (mail is secondary)
  - Include bar coded cover sheet or Claim ID (CID) number on submitted documentation
- Reimbursement recouped by the MAC
- Same appeal rights as Medicare

Comprehensive Error Rate Testing Program

- CERT Documentation Contractor
  - https://www.certprovider.com
  - Fax or mail documentation
- CERT Review Contractor
  - Determines error rate for the MAC
  - Same appeal rights as under Medicare
- CERT Statistical Contractor
- CERT Report Website Contractor
  - Maintains https://www.cms.hhs.gov/cert

Comprehensive Error Rate Testing Program

November 2016 Forecasting Report For MAC Jurisdiction J

1. Summary

The CERT statistical contractor calculates contractors' projected 2016 national improper payment amounts and rates on a quarterly basis, **based upon claims completely reviewed**. This report includes reviewed claims data from the sampling period July 2014 through June 2015, as of ***July* 27, 2016**.

Table 1.1: Showing Error Rate for 2016 by "Claims Type"

Claims Type	Paid Claims Error Rate (for reviewed claims)	95% Confidence Interval	Number of sampled claims (Completely Reviewed)	Error Rate (partial imputation)*
Overall JJ	12.3%	9.6% - 14.9%	2,749	12.3%
Part B	10.2%	5.4% - 14.9%	1,305	10.2%
Overall Part A	13.2%	10.3% - 16.0%	1,444	13.2%
Part A(excl Inpatient Hospital PPS)	20.4%	15.4% - 25.4%	513	20.4%
Part A(Inpatient Hospital PPS)	3.3%	2.4% - 4.1%	931	3.3%

*For the pool of incomplete reviewed claims, the errors for claims waiting feedback or documentation are imputed with historical error rate based on the assigned error category. The claims that have not been reviewed are not included.

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Comprehensive Error Rate Testing Program

PART B Top 10 – By Type of Service

Table 2.1 Top 10 Type of Service - Sorted by Projected Improper Payment

PART B Type of Service	Projected Error Rate	Projected Improper Payment	Number of Claims Sampled	95% Confidence Interval	Proportion of Overall Error
Overall JJ Part B	10.2%	$603,829,624	1,305	5.4% - 14.9%	
Lab tests - other (non-Medicare fee schedule)	42.4%	$120,452,644	285	30.0% - 54.8%	17.6%
Hospital visit - initial	36.8%	$57,580,916	73	28.9% - 44.8%	8.4%
Hospital visit - subsequent	19.1%	$56,376,616	129	13.5% - 24.7%	8.3%
Minor procedures - other (Medicare fee schedule)	31.3%	$48,766,332	80	18.5% - 44.0%	7.1%
Office visits - established	5.4%	$44,942,173	98	2.5% - 8.2%	6.6%
Hospital visit - critical care	45.9%	$36,159,398	26	33.8% - 58.0%	5.3%
Minor procedures - musculoskeletal	51.3%	$33,877,269	13	4.0% - 98.5%	5.0%
Office visits - new	23.2%	$32,841,509	34	13.8% - 32.6%	4.8%
Ambulance	7.7%	$24,715,996	66	0.3% - 15.1%	3.6%
Nursing home visit	30.9%	$24,106,250	28	20.0% - 41.7%	3.5%

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Comprehensive Error Rate Testing Program

Service Type	Services Incorrectly Coded	Insufficient Documentation	No Documentation
Hospital Initial	69%	29%	2%
Hospital Subs	67%	32%	1%
Office New	93%	7%	0%
Office Estab	83%	17%	0%

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Why does this matter?

- CMS requires that we recoup the payments
  - You did the work and deserve to be reimbursed
- We use it as an indicator of vulnerabilities
- CMS evaluates MACs based on CERT performance
  - Contract awards influenced by CERT rates
  - CERT rates play a role in Award Fees
- Congress may act on them

How to Prevent CERT E&M Errors

- Assign an individual to be your CERT contact person
  - Communicate with your billing company
  - Hospitalists communicate with the hospital medical records
  - Set up a process to receive and respond to medical record requests
- Return the records to the CERT Documentation Contractor in a timely fashion
- Ensure medical record documentation is complete, accurate and supports the level of service billed
  - Train your coders
  - Do not reward up-coding
  - Physician coders?

How to Prevent CERT Errors

- Clear legible signatures
- Validate that the claim contains the correct ICD-10 and CPT codes
- Physician Extenders
  - If you bill with physician PIN sign and certify that you participated in the evaluation and care

Observation E&M

- **Primary provider directing the observation care**
- Initial observation care 99218-99220
- Subsequent observation care 99224-99226
- Observation care discharge 99217
- Observation or inpatient care/admit & discharge on same DOS
- 99234-99236

- **Consultants Office or other outpatient visits**
- New patient 99201-99205
- Established patient 99211-99215

OIG 2016 Work Plan

- Oversight of provider based status of free standing facilities and clinics
- Duplicate graduate medical education payments (direct and indirect)
- Bone marrow and stem cell transplant (dx and unbundling)
- IMRT correct billing and not billing as part of developing an IMRT plan (DL36743)
- Physician home visits (in lieu of an office or outpatient R&N)
- Use of prolonged services E&M codes (99354-99416)
- Does Medicaid monitor group homes and SNF transfers to ED
- Do state agencies follow up on SNF deficiencies

Home Health Certification

- Effective 1/1/2015
- Certify benefit eligibility (billed with G0180, G0179 recert)
- Face to face encounter is required (billed with E&M)
- Need for extra documentation (narrative) scaled back or eliminated
- HH agency will provide medical records describing the beneficiary's condition and supporting eligibility for services
- Requirements:
  - Confined to home
  - Need skilled services
  - Under care of a physician
  - Care plan established and reviewed by a physician
  - Face to face encounter with physician or practitioner reviewed and signed by the physician

Home Health Certification

- Your Home Health/Hospice Medicare contractor's website may be accessed to obtain information regarding eligibility and documentation requirements. Additional references are as follows:
- CMS MLN Article (MM9119 Revised) Manual Updates to Clarify Requirements for Physician Certification and Recertification of Patient Eligibility for Home Health Services
- Certifying Patients for the Medicare Home Health Benefit
- Medicare Home Health Agency (HHA) Center

Chronic Care Management

- CPT 99490 20 minute unit of clinical staff time directed by a health care professional per month
  - Multiple chronic conditions expected to last at least 12 months
  - Physician directed
  - Initiated with a comprehensive E&M, annual wellness or initial preventive physical exam visit
  - Comprehensive care plan established, implemented, revised or monitored
  - Obtain consent from the beneficiary
  - Must be able to document the services and time (certified EHR tech.)
  - 24/7 access to management services
  - Facility and provider may bill separately
  - Frequently Asked Questions
  - http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1516.pdf

Transitional Care Management

- To transition the beneficiary from an inpatient environment to the community
- Begins with a qualified discharge from a facility
- 30 day period begins on the day of discharge and continues for the next 29 days
- Interactive contact within 2 business days from the D/C
- Face to face visit must occur with in 7 (CPT 99496) or 14 (CPT 99495) days
- DOS the date of the face to face
- May be provided by telecommunication
- Includes many non-face-to-face services
- May report other R&N E&M services during the period
- https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/Transitional-Care-Management-Services-Fact-Sheet-ICN908628.pdf

Advanced Care Planning

- 1/1/2016 Advanced Care Planning (99497, 99498)
  - Face-to-face service including the explanation and discussion of advance directives
  - When reasonable & necessary for the diagnosis or treatment of injury or illness
  - Can be billed –
    - On same day as E/M
    - During period covered by TCM, CCM, or global surgery
- May be an element of the Annual Wellness Visit
  - Deductible and coinsurance will be waived
  - Must be billed with modifier 33 (preventive services)
- https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/Downloads/FAQ-Advance-Care-Planning.pdf

CMS Open Payments

- Required by the Patient Protection and Affordable Care Act
- Disclose financial relationships for doctors and hospitals
  - Explanation of the data
  - Required reporting by manufacturers and group purchasing organizations
- www.cms.gov/openpayments

Unused Drugs or Biologicals

- MLN MM5923 Updated 2013
- MACs **may** require use of modifier JW to identify unused drug or biologicals from single use vials or single use packages that are appropriately discarded
- Change Request 9603
- Effective January 3, 2017 these claims **shall** be submitted with the JW modifier.
- Documentation must be in the medical record
- https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/MM9603.pdf

Oncology Care Model

- Chemotherapy episode of care
- 24/7 clinician with access to medical records
- ONC certified EHR
- Care plan with the 13 components in the Institute of Medicine Care Management Plan
- Medicare FFS claims followed for 6 months
- $160 per month paid to participant
- Benchmark calculated based on diagnosis
- If performance is less than the benchmark would lead to a bonus
- Quality measures play a role

Accountable Health Communities Model

- Funding to test ways to address the health-related social needs of Medicare and Medicaid beneficiaries
  - Food insecurity
  - Inadequate or unstable housing
  - Utility needs
  - Interpersonal violence
  - Transportation
- Funding not to meet these needs but to find ways to use community services to address them
- Concept is by addressing these would decrease medical utilization and cost
- Requested letter of intent (2/8/2016)

Accountable Health Communities Model

- Fact Sheet
- https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-01-05.html

- AHCM Homepage
- https://innovation.cms.gov/initiatives/ahcm/

Comprehensive Primary Care Plus

- Based on Comprehensive Primary Care initiative running Oct. 2012-Dec 2016
- Regionally based multi-payer payment reform and care delivery transformation
- CMS will work with commercial insurance plans and Medicaid agencies to provide financial support necessary for practices to make fundamental changes in their care delivery.
- Key Primary Care Functions: (1) access and continuity; (2) care management; (3) comprehensiveness and coordination; (4) patient and caregiver engagement and (5) planned care and population health
- Payer proposals to partner with CMS in 20 regions
- Practices apply to participate (July15-Sept. 1, 2016)
- https://innovation.cms.gov/iniatives/comprehensive-primary-care-plus/

Transforming Clinical Practice Initiative Support and Alignment Networks 2.0

- Leverage primary and specialist care transformation work and learning to catalyze the adoption of Alternative Payment Models on a large scale.
- Designed to support clinician practices through nationwide, collaborative and peer-based learning networks that facilitate practice transformation
- Goals:
  - Reducing total cost of care
  - Improving the quality of care delivered
  - Rapidly transitioning practices through the phases of transformation in preparation for participation in and alignment with Alternative Payment Models and Advanced Alternative Payment Models
- Letter of intent by July 1, 2016 to transformation@cms.hhs.gov

Other Innovations

- Comprehensive Care for Joint Replacement Model
- Cardiovascular Disease Risk Reduction Model
- Medicare Diabetes Prevention Program
- Precertification
  - Power assist devices
  - Elective ambulance transportation
  - Hyperbaric oxygen therapy
- Episode Payment Models
  - Hip Fracture
  - Acute MI
  - CABG

Websites

- www.cms.hhs.gov
  - CERT
  - RAs
  - LCDs (Local Coverage Determinations)
  - NCD (National Coverage Determinations)
- www.cahabagba.com
  - LCDs
  - Chemo Article
- www.certprovider.com
  - CERT Documentation Contractor

Cahaba GBA

QUESTIONS?

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PERSONALIZED MEDICINE FOR LOCALIZED PANCREATIC CANCER

DOUGLAS B. EVANS, M.D.

Douglas B. Evans, MD
Donald C. Ausman Family Foundation
Professor in Surgery and Chair

Douglas B. Evans, MD is the Donald C. Ausman Family Foundation Professor of Surgery and Chair of the Department of Surgery at The Medical College of Wisconsin. Prior to joining the Medical College of Wisconsin in January 2009, he was the Hamill Foundation Distinguished Professor of Surgery at The University of Texas M. D. Anderson Cancer Center. He is board-certified in surgery, and his clinical interests include treatment of pancreatic cancer and tumors of the endocrine system (thyroid, parathyroid, adrenal). Dr. Evans is based at Froedtert Hospital and holds appointments at the Clement J. Zablocki VA Medical Center and Children's Hospital of Wisconsin.

Dr. Evans' research interests focus on translational laboratory research in the biology of pancreatic cancer and in clinical trial development for patients with localized disease. He has completed a number of investigator-initiated clinical trials, including a National Cancer Institute Specialized Programs of Research Excellence (NIH P20 SPORE) pancreatic cancer grant. At M. D. Anderson, his endocrine surgery group worked extensively on the genotype-phenotype correlations in multiple endocrine tumors and was the first to define the role for ultrasound in the preoperative management of patients with thyroid cancer. He was twice awarded the Outstanding Teacher Award at M. D. Anderson Cancer Center in 1995 and 2003. He also received the Faculty Achievement Award in Clinical Research in 1998. Since joining MCW, he has forged the Program in Pancreatic Cancer Research including a clinical database, a tissue bank, a personalized cancer treatment clinical trial, and ongoing laboratory research.

Dr. Evans is a fellow of the American College of Surgeons, and a member of the editorial boards of Surgery and the American Journal of Surgery and is Editor of the Pancreatic Tumors Section of the Annals of Surgical Oncology. He served on the editorial board for the seventh edition of the AJCC (American Joint Committee on Cancer) Cancer Staging Manual, and chaired the committee that revised the staging system for pancreatic cancer. He has served on various national medical advisory committees and has worked extensively with patient advocacy groups including the Pancreatic Cancer Action Network (PanCAN) and the Lustgarten Foundation. In 2013 and 2014, Dr. Evans served as the Chair of the Pancreatic Cancer Action Network-American Association for Cancer Research Acceleration Network Grants Scientific Review Committee.

He has authored or co-authored 262 journal articles and has edited seven books. He has delivered more than 70 invited lectureships nationally, most recently at Harvard Medical School, The Ohio State University, Vanderbilt University, Carolinas Medical Center, and the University of Calgary, amongst others. He has also been invited to present his research findings at international meetings in New Zealand, Belgium, France, Sweden, Japan, and elsewhere. He was awarded an American College of Surgeons Traveling Fellowship in 1999.

Dr. Evans completed a general surgery residency at Dartmouth in 1988 followed by a surgical oncology fellowship at the University of Texas, M. D. Anderson Cancer Center. He received his medical degree from Boston University School of Medicine in 1983, and his bachelor of science from Bates College in Lewiston, Maine, in 1978.

BEST of ASCO®

MULTIPLE MYELOMA

SAGAR LONIAL, M.D.

Sagar Lonial, MD, FACP
Professor
Department of Hematology and Medical Oncology
Winship Cancer Institute of Emory University

Dr. Lonial is internationally recognized as a leading authority in multiple myeloma treatment and research. As a medical oncologist at the Winship Cancer Institute, Dr. Lonial treats patients with multiple myeloma and is a lead member of the bone marrow transplantation team and clinical trials team. He is board certified in hematology, oncology and internal medicine.

Dr. Lonial is involved in numerous professional organizations including the American Society of Clinical Oncology, American Society of Hematology, and the American Society for Blood and Marrow Transplantation. He serves as Vice Chair of the Myeloma Committee in the Eastern Cooperative Oncology Group and as Chair of the Steering Committee for the Multiple Myeloma Research Consortium. Additionally, he is on the board of directors for the International Myeloma Society, and on the scientific Advisory Board for the International Myeloma Foundation.

Dr. Lonial earned his medical degree from the University of Louisville School of Medicine. He completed his internship and residency at Baylor College of Medicine in Houston, Texas, followed by a fellowship in hematology and oncology at Emory University School of Medicine in Atlanta, Georgia.

Dr. Lonial has worked in the field of immunotherapy and cancer since his arrival at Emory, and in the previous 3 years has spent time developing the B-cell malignancy program with respect to novel targeted agents in laboratory models as well as early clinical trials. His previous laboratory work has focused on evaluating the impact of purified dendritic cell subsets on the nature of immune responses against antigen, and he has completed several trials evaluating the impact of cytokines on dendritic cell content and post-transplant immune recovery.

Most recently, Dr. Lonial has focused on combinations of novel agents as therapy for myeloma and lymphoma, particularly evaluating combinations that may result in synergistic inhibition of the PI3-K/Akt pathway. His lab has recently received funding from the MMRF, the Lymphoma Research Foundation, and The Leukemia & Lymphoma Society.

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract ID: 8000 (167867)

Title: Upfront autologous stem cell transplantation (ASCT) versus novel agent-based therapy for multiple myeloma (MM): A randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial).

Authors: Michele Cavo, Antonio Palumbo, Sonja Zweegman, Meletios A. Dimopoulos, Roman Hajek, Lucia Pantani, Meral Beksac, Ruth Wester, Hans E. Johnsen, Ulf-Henrik Mellqvist, Maria Teresa Petrucci, Christoph Driessen, Francesco Di Raimondo, Rossella Troia, Annalisa Pezzi, Bronno van der Holt, Ka Lung Wu, Heinz Ludwig, Francesca Gay, Pieter Sonneveld; Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliera Citta` della Salute e della Scienza di Torino, Torino, Italy; Department of Hematology, VU University Medical Center, Amsterdam, Netherlands; School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; Masaryk University Hospital, Brno, Czech Republic; Ankara Universitesi Tip Fakultesi, Ankara, Turkey; Erasmus Medical Center, Department of Hematology, Rotterdam, Netherlands; Department of Hematology, Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark; South Elvsborg Hospital, Borås, Sweden; Department of Hematology, Sapienza University of Rome, Rome, Italy; Kantonsspital St. Gallen, St. Gallen, Switzerland; Division of Hematology, Ospedale Ferrarotto, University of Catania, Catania, Italy; HOVON Data Center, Erasmus MC Cancer Institute-Clinical Trial Center, Rotterdam, Netherlands; ZNA Stuivenberg, Department of Hematology, Antwerp, Belgium; Wilhelminen Cancer Research Institute, Wilhelminenspital, Department of Medicine, Center of Oncology, Hematology and Palliative Care, Vienna, Austria; Erasmus Medical Center, Rotterdam, Netherlands

Background: The role of upfront ASCT for newly diagnosed (ND) MM (NDMM) patients (pts) has been questioned in the novel agent era. **Methods:** A phase 3 study was designed to compare [random (R) 1] 4 cycles of bortezomib-melphalan-prednisone (VMP) vs high-dose melphalan (HDM) and single or double ASCT (this latter limited to centers applying a tandem ASCT policy) as intensification therapy following induction with bortezomib-cyclophosphamide-dexamethasone and subsequent collection of peripheral blood stem cells. Consolidation therapy with bortezomib-lenalidomide-dexamethasone vs no consolidation (R2) was planned after VMP and HDM, followed by lenalidomide maintenance until progression or toxicity in both treatment arms. Primary study end point was progression-free survival (PFS) from R1. A first prespecified interim analysis was performed in January 2016 when at least 33% of the required events had been observed. Results are herein reported. **Results:** From February 2011 through April 2014, 1503 pts aged ≤65 years with symptomatic NDMM were registered. Of these, 1308 pts were eligible for R1 and 1266 who were randomized (1:1 ratio; stratification by ISS stage) to VMP (512 pts) or HDM (1±2 ASCT) (754 pts) were analyzed. Median follow up from R1 was 24 months. PFS was significantly prolonged in pts randomized to HDM (HR=0.76; 95% CI=0.61-0.94; P=0.010), a benefit

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract ID: 8001 (168948)

Title: Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): A meta-analysis (MA) of overall survival (OS).

Authors: Michel Attal, Antonio Palumbo, Sarah A. Holstein, Valerie Lauwers-Cances, Maria Teresa Petrucci, Paul G. Richardson, Cyrille Hulin, Patrizia Tosi, Kenneth Carl Anderson, Denis Caillot, Valeria Magarotto, Philippe Moreau, Gerald Marit, Zhinuan Yu, Philip L. McCarthy; CHU Purpan, Toulouse, France; Department of Hematology, University of Torino, Torino, Italy; Roswell Park Cancer Institute, Buffalo, NY; University La Sapienza, Rome, Jersey; Department of Hematology, Sapienza University of Rome, Rome, Italy; Dana-Farber Cancer Institute, Boston, MA; Hematology Department, University Hospital, Nancy, France; Seràgnoli Institute of Hematology and Medical Oncology, Bologna University, Bologna, Italy; Dijon University Hospital Center, Dijon, France; Myeloma Unit, Division of Hematology, University of Torino, AOU S. Giovanni Battista, Torino, Italy; University Hospital Hotel-Dieu, Nantes, France; Service d'Hématologie Clinique, Hôpital du Haut Leveque CHU de Bordeaux, Bordeaux, France; Celgene Corporation, Summit, NJ

Background: Several studies demonstrate that LEN MNTC post ASCT reduces the risk of disease progression or death in patients (pts) with MM by ≈ 50% (Attal *NEJM* 2012; McCarthy *NEJM* 2012; Palumbo *NEJM* 2014). However, these studies were not powered for OS. To assess the effect of LEN MNTC post ASCT on OS, an MA was conducted. **Methods:** A prospectively planned MA assessed the OS of LEN vs placebo/no MNTC (control; CTL) after ASCT. A search identified 17 randomized controlled trials (RCTs) using LEN post ASCT. 3 RCTs (IFM 2005-02, CALGB 100104 [Alliance], GIMEMA RV-209) met prespecified inclusion criteria (had pt-level data, a CTL arm, and achieved database lock for primary efficacy analysis of NDMM pts receiving LEN post ASCT). A March 2015 cutoff of the 3 RCTs enabled sufficient OS events to test treatment effect (HR = 0.78). **Results:** In the 3 RCTs, 1209 pts were randomized from 2005 to 2009 to receive LEN (n = 605) 10 mg/day on days 1-21/28 (GIMEMA) or 1-28/28 (IFM and CALGB) or CTL (n = 604). With a median follow-up of 6.6 yrs, 491 pts (41%) had died. Baseline characteristics were generally balanced in the pooled data. After induction and single (82%) or tandem (18%) ASCT, 55% of pts achieved a complete response (CR) or very good partial response (VGPR). Median OS for LEN vs CTL was not reached vs 86 mos (HR = 0.74; 95% CI, 0.62-0.89; log-rank P = .001), and 5-, 6-, and 7-yr OS were longer in LEN vs CTL group (71% vs 66%, 65% vs 58%, and 62% vs 50%, respectively). Fisher's combination test confirmed the significant OS benefit of the MA (P = .001). Pts who achieved ≤ PR post ASCT benefited from LEN (HR = 0.86; 95% CI, 0.65-1.15) as well as pts with CR/VGPR (HR = 0.70; 95% CI, 0.54-0.90). OS benefit was generally consistent across subgroups. Heterogeneity test showed significant difference across trials (P = .047). The potential impact of baseline/disease characteristics, as well as 2nd-line therapy (IFM and CALGB), on OS will be explored and presented. Second primary malignancy data will be presented. **Conclusions:** This large MA demonstrates that LEN MNTC significantly prolonged OS vs CTL post ASCT, including in pts who achieved CR, demonstrating benefit in pts in all response categories.

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract ID: 8011

Title: Phase Ib venetoclax combined with bortezomib and dexamethasone in relapsed/refractory multiple myeloma.

Author(s): Philippe Moreau, Asher Alban Akmal Chanan-Khan, Andrew Warwick Roberts, Amit Agarwal, Thierry Facon, Shaji Kumar, Cyrille Touzeau, Susan Diehl, Jaclyn Cordero, Jeremy A Ross, Wijith Munasinghe, Ming Zhu, Ahmed H. Salem, Joel Leverson, Paulo Cesar Maciag, Maria E. Verdugo, Simon J Harrison; CHU de Nantes, Hotel Dieu—HME, Nantes, France; Mayo Clinic Florida, Jacksonville, FL; Royal Melbourne Hospital, Parkville, Australia; University of Arizona, Tucson, AZ; CHRU Lille - Hôpital Claude Huriez, Lille, France; Division of Hematology, Mayo Clinic, Rochester, MN; AbbVie, Inc, North Chicago, IL; Peter MacCallum Cancer Centre, East Melbourne, Australia

Background: BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival. Bortezomib (B) inhibits MCL-1 activity, and venetoclax (VEN), an oral, selective BCL-2 inhibitor, enhances its efficacy in MM xenograft models. **Methods:** In this phase 1b study of VEN with B and dexamethasone (D) in relapsed/refractory (RR) MM, pts received daily VEN, per assigned dose escalation (DE) cohorts (50–1200 mg), combined with B (1.3 mg/m^{2}SC) and D (20 mg PO) for 11 cycles, and VEN alone thereafter. **Results:** 45 pts were enrolled as of 9/17/15. Median age was 65; 29/16 M/F; 24 ISS stage II/III. The median (range) number of prior lines of therapy was 4 (1–13). 38 pts received prior B (19 refractory), 36 had lenalidomide (26 refractory), and 32 had prior SCT. AEs occurring in ≥ 30% of pts were constipation (40%), diarrhea (38%), thrombocytopenia (33%), insomnia (29%). Grade 3/4 AEs in ≥ 10%: thrombocytopenia (22%), anemia (16%). SAEs in ≥ 2 pts were pneumonia (n = 3), cardiac failure, embolism, pyrexia, respiratory failure, sepsis, thrombocytopenia (n = 2 each). One DLT was observed, and MTD was not reached. 30 pts discontinued (DC): 24 related to PD (3 died), 2 due to AE, 4 withdrew consent. Dose-normalized PK for VEN with BD was similar to VEN monotherapy. 41/45 pts were evaluable for efficacy (Table). Preliminary results also indicate that pts with 1–3 prior lines of therapy (N = 18) had higher ORR (83.3%) vs. pts with 4–6 (N = 13, 38.5% ORR) or ≥ 7 prior lines of therapy (N = 10, 10% ORR). **Conclusions:** VEN with BD has an acceptable safety profile and evidence of anti-tumor activity in RR MM; response rates were highest in pts naïve or sensitive to prior B, or with 1–3 prior therapies. Currently, DE is complete and safety expansion ongoing at 800 mg.

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract: 8032

Title: Phase I venetoclax monotherapy for relapsed/refractory multiple myeloma.

Author(s): Shaji Kumar, Ravi Vij, Jonathan L. Kaufman, Joseph Mikhael, Thierry Facon, Brigitte Pegourie, Lotfi Benboubker, Cristina Gasparetto, Martine Amiot, Philippe Moreau, Susan Diehl, Stefanie Alzate, Jeremy A Ross, Martin Dunbar, Ming Zhu, Suresh K Agarwal, Joel Leverson, Paulo Cesar Maciag, Maria E. Verdugo, Cyrille Touzeau; Division of Hematology, Mayo Clinic, Rochester, MN; Washington University School of Medicine, St. Louis, MO; Winship Cancer Institute of Emory University, Atlanta, GA; Mayo Clinic, Scottsdale, AZ; Service des Maladies du Sang Place de Verdun, Lille, France; University Hospital, Grenoble, France; Centre Hospitalier Universitaire Tours-Hopital Bretonneau, Tours, France; Duke University Medical Center, Durham, NC; CHU de Nantes, Hotel Dieu—HME, Nantes, France; AbbVie, Inc, North Chicago, IL

Background: The anti-apoptotic protein BCL-2 has been implicated in the survival of multiple myeloma (MM) cells. Venetoclax (VEN) is an oral, highly selective BCL-2 inhibitor, which induces cell death in MM cell lines and primary samples, particularly those with t(11;14), a high BCL-2 and low BCL-$_{xL}$profile. **Methods:** In this phase 1 study of VEN monotherapy in relapsed/refractory (R/R) MM, objectives are to evaluate safety, PK, RPTD, and preliminary efficacy. After 2-week dose-ramp-up, VEN was given daily at 300, 600, 900, or 1200 mg in dose escalation (DE) cohorts and 1200 mg in safety expansion (SE). **Results:** As of 9/17/15, 48 pts were enrolled: 30 DE and 18 SE. Median age was 65; 28 were ISS stage II/III. Median (range) prior therapies: 5 (1–15). 45 had prior bortezomib (32 refractory), 46 lenalidomide (37 refractory), and 40 had SCT. 18 pts had t(11;14). AEs in ≥ 30% of pts were diarrhea (40%), nausea (40%), thrombocytopenia (31%). Grade 3/4 AEs in ≥ 10%: thrombocytopenia (29%), anemia, neutropenia (17% each). SAEs in ≥ 2 pts were sepsis (n = 3), cough, malignant neoplasm progression, and pyrexia (2 each). Median (range) time on VEN was 1.9 (0.2–13.8) months. 33 (69%) pts discontinued (DC): 26 related to PD, 4 due to AEs (worsening shortness of breath, hypokalemia, nausea, lung disorder), 2 withdrew consent, 1 due to death (brain hemorrhage following injury). 5 deaths occurred (3 PD, 1 brain hemorrhage, 1 lung disorder). 2 DLTs were seen at 600 mg (cohort was expanded): epigastric pain, nausea with abdominal pain. Steady state mean C_{max} and AUC_{24} were ~dose proportional at all doses except 900 mg (n = 21). 43 of 48 pts were evaluable for efficacy (table). In CR pts, responses were maintained for 9.7 (600 mg) and 9.0 months (900 mg, ongoing). VGPR was reported for 3 pts, all 1200 mg. **Conclusions:** VEN monotherapy has a tolerable safety profile in R/R MM. Preliminary efficacy, including CR, and VGPR, support VEN single agent activity in this population, primarily in t(11;14) pts

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract ID: LBA4 (172609)

Title: Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study.

Authors: Antonio Palumbo, Asher Alban Akmal Chanan-Khan, Katja Weisel, Ajay K. Nooka, Tamas Masszi, Meral Beksac, Ivan Spicka, Vania T.M. Hungria, María-Victoria Mateos, Tomer Martin Mark, Ming Qi, Jordan Mark Schecter, Himal Amin, Xiang Qin, William Deraedt, Tahamtan Ahmadi, Andrew Spencer, Pieter Sonneveld; University of Torino, Torino, Italy; Mayo Clinic Florida, Jacksonville, FL; Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Tubingen, Germany; Emory University Winship Cancer Center, Atlanta, GA; Fovarosi Onkormanyzat Szent Laszlo Korhaza, Hematologia, Budapest, Hungary; Ankara Universitesi Tip Fakultesi, Ankara, Turkey; Vseobecna Fakultni Nemocnice V Praze, Prague, Czech Republic; Irmandade da Santa Casa de Misericordia de SÃ£o Paulo, Sao Paulo, Brazil; University Hospital of Salamanca/IBSAL, Salamanca, Spain; New York Presbyterian Weill CornellÂ Hospital, New York, NY; Janssen Research and Development, LLC, Raritan, NJ; Janssen Research & Development, Raritan, NJ; Janssen Research & Development LLC, Raritan, NJ; Johnson and Johnson, Philadelphia, PA; Alfred Hospital, Melbourne, Australia; Erasmus Medical Center, Rotterdam, Netherlands

Background: Daratumumab (D), a human anti-CD38 IgGκ mAb, induces deep and durable responses with a favorable safety profile in RRMM pts. We report a pre-specified interim analysis of the first randomized controlled study of D (CASTOR; NCT02136134). **Methods:** Pts with ≥1 prior line of therapy were randomized (1:1) to 8 cycles (q3w) of bortezomib (V)/dexamethasone (d) (V: 1.3 mg/m^{2}sc on Days 1, 4, 8, 11; d: 20 mg po on Days 1, 2, 4, 5, 8, 9, 11, 12) ± D (16 mg/kg iv qw in Cycles 1-3, Day 1 of Cycles 4-8, then q4w until progression). Primary endpoint was PFS.

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract: 8005

Title: Updated data from a phase II dose finding trial of single agent isatuximab (SAR650984, anti-CD38 mAb) in relapsed/refractory multiple myeloma (RRMM).

Author(s): Joshua Ryan Richter, Thomas G. Martin, Ravi Vij, Craig Cole, Djordje Atanackovic, Jeffrey A. Zonder, Jonathan L. Kaufman, Joseph Mikhael, William Bensinger, Meletios A. Dimopoulos, Todd M. Zimmerman, Nikoletta Lendvai, Parameswaran Hari, Enrique M. Ocio, Cristina Gasparetto, Shaji Kumar, Corina Oprea, Eric Charpentier, Stephen Anthony Strickland, Jesus San Miguel; Hackensack University Medical Center, Hackensack, NJ; University of California at San Francisco, San Francisco, CA; Washington University, St. Louis, MO; University of Michigan Comprehensive Cancer Center, Ann Arbour, MI; Huntsman Cancer Institute, Salt Lake City, UT; Karmanos Cancer Institute, Detroit, MI; Winship Cancer Institute of Emory University, Atlanta, GA; Mayo Clinic, Scottsdale, AZ; Fred Hutchinson Cancer Research Center, Seattle, WA; National and Kapodistrian University of Athens, Athens, Greece; University of Chicago, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; Medical College of Wisconsin, Milwaukee, WI; University Hospital of Salamanca, Salamanca, Spain; Duke University Medical Center, Durham, NC; Mayo Clinic, Rochester, MN; Sanofi Oncology, Cambridge, MA; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of Navarra, Pamplona, Spain

Background: Isatuximab (ISA) is a humanized anti-CD38 monoclonal antibody with multiple modes of action for killing tumor cells through direct tumor targeting and immune cell engagement. Here, we report updated data from an ongoing Phase II dose finding study of ISA monotherapy in patients (pts) with RRMM (NCT01084252). **Methods:** Pts with RRMM (≥3 lines of anti-MM therapy or refractory to immunomodulatory drugs [IMiDs] and proteasome inhibitors [PIs]) were randomized to ISA 3 mg/kg Q2W, 10 mg/kg Q2W x 2 cycles then Q4W, or 10 mg/kg Q2W. Randomization stratified by prior pomalidomide and/or carfilzomib therapy. Emerging PK data prompted enrollment of a 4th treatment arm at 20 mg/kg QW x 4 doses then Q2W. 1 cycle = 28 days. Primary objective: evaluation of ISA activity (overall response rate [ORR; IMWG]). **Results:** 97 pts treated: median age, 62.5 (38–85) y; median time from diagnosis, 5.9 (1.2–24.1) y; ISS stage 3, 37%; median prior lines of therapy, 5 (2–14); 86%, 61%, 80%, 57%, 88% refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, or IMiD+PI, respectively. 24/56 cytogenetics-evaluable pts (43%) had t(4;14) and/or del(17p). Median treatment duration, 13.1 wks; 22 pts remain on treatment (cut-off Nov 2015). ORR: 9% (2/23), 20% (5/25), 29% (7/24) & 24% (6/25) at ISA 3 Q2W, 10 Q2W/Q4W, 10 Q2W, & 20 mg/kg QW/Q2W, respectively; 14/20 responders continue without progression. At ≥10 mg/kg: ORR was 24% (18/74), similar in subgroups (age, CrCl, prior lines of therapy), and 44% (8/18) in pts with abnormal cytogenetics. Median time to 1st response, 1.35 mo; median duration of response at data cut-off, 6.6 mo. Most common adverse events (AEs) were nausea (33%), fatigue (30%), dyspnea (26%), and cough (24%), which were typically grade ≤2. Infusion-associated reactions (IARs) occurred in 49% of pts, mostly grade ≤2, 94% during the 1st infusion. 6 pts discontinued therapy due to AEs, 2 due to IARs. **Conclusions:** ISA monotherapy is active and generally well tolerated in heavily pretreated RRMM, with efficacy greatest at ≥10 mg/kg (ORR 24%). ORR was similar in subgroups, including high-risk cytogenetics. Progression-free survival and overall survival data will be presented.

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract ID: 8008

Title: Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study.

Author(s): Amrita Y. Krishnan, Prashant Kapoor, Joycelynne Palmer, Shaji Kumar, Sagar Lonial, Myo Htut, Chatchada Karanes, Nitya Nathwani, Michael Alan Rosenzweig, Firoozeh Sahebi, George Somlo, Lupe Duarte, Stephen J. Forman, Jesus G. Berdeja; City of Hope, Duarte, CA; Division of Hematology, Mayo Clinic, Rochester, MN; Winship Cancer Institute of Emory University, Atlanta, GA; Judy and Bernard Briskin Center for Myeloma;City of Hope, Arcadia, CA; City of Hope, Judy and Bernard Briskin Center for Myeloma, Duarte, CA; Judy and Bernard Briskin Center for Myeloma;City of Hope, Duarte, CA;Kaiser Permanente Southern California, Duarte, CA; Division of Biostatistics, City of Hope National Medical Center, Duarte, CA; Sarah Cannon Research Institute, Nashville, TN

Background: Triplet regimens combining an immunomodulatory agent, a proteasome inhibitor (PI) and steroid are used to treat newly diagnosed and relapsed MM. While Ix, an oral PI with single agent activity can be combined with lenalidomide (LEN), patients(pts) with R/R MM are often LEN refractory. POM has single agent activity in LEN refractory pts, and can be combined with intravenous PI Carfilzomib (CAR) . An entirely oral regimen leveraging the efficacy of PI/POM in RR MM would be of benefit. Herein we report safety and preliminary efficacy data of the Ix/POM/DEX combination in Len R/R MM, a Multiple Myeloma Research Consortium trial. **Methods:** Primary objectives: 1) determine the maximum tolerated dose (MTD) of Ix and 2) evaluate anti-tumor activity of the triplet. Dose levels tested: Dose level (DL) 1: Ix 3mg d1,8,15; POM 4mg d1-21; DEX 40mg d1,8,15,22. DL2: Ix 4mg d1,8,15; with identical POM /DEX; 28day treatment cycles. Eligibility: R/R MM after > 1 prior therapy. LEN refractory, and ≤ grade(gr) 1 peripheral neuropathy PN. Pts treated until progression or unacceptable toxicity. Design: Phase I study utilized a standard 3+3 design; dose limiting toxicities (DLTs) defined during cycle 1. **Results:** To date, 21pts treated; 20 evaluable for toxicity. Six pts treated on DL1, 14 treated on DL2 -the MTD/Phase II dose (P2D). Median(range): age 63yrs (48-77); time from diagnosis: 3.7 years (1.0-8.9); prior therapies 3(1-6)/ prior transplant n = 17(85%); double(LEN/Bortezomib(BOR)) or triple(LEN/BOR/CAR) refractory 11(55%). Phase I: DL1 expanded to n = 6 after 1/3 pts experienced DLT (gr3 lung infection); no further DLT seen on DL2. AEs related to POM +/- Ix in > 20% of pts: gr3 lymphocyte decrease, gr1 neutrophil decrease ≥ Grade3 AEs: anemia (n = 2); neutropenia (n = 6), thrombocytopenia (n = 3). Response: Gehan 1ststage of 2; n = 9 pts treated ORR:33% (1 VGPR, 2 PR); Clinical Benefit Response (CBR):67%; median cycles 1.5 (1-16); follow-up 1.3 months (0.8, 14.0). Including DL1 pts, ORR:40%. **Conclusions:** Full dose Ix with standard dose POM/DEX is well tolerated. Preliminary response rates are promising given that > 50% of pts were dual refractory and early into treatment course.

HEMATOLOGIC MALIGNANCIES – Plasma Cell Dyscrasia

Abstract ID: 8010

Title: Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Final efficacy and safety analysis.

Author(s): María-Victoria Mateos, Robert Z. Orlowski, David Samuel DiCapua Siegel, Donna Ellen Reece, Philippe Moreau, Enrique M. Ocio, Jatin J. Shah, Paula Rodríguez-Otero, Nikhil C. Munshi, David Avigan, Joy Yang Ge, Patricia Maria Marinello, Jesus San Miguel; University Hospital of Salamanca/IBSAL, Salamanca, Spain; The University of Texas MD Anderson Cancer Center, Houston, TX; John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; Princess Margaret Cancer Centre, Toronto, ON, Canada; University Hospital Hotel-Dieu, Nantes, France; Clinica Universidad De Navarra, Pamplona, Spain; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Merck & Co., Inc., Kenilworth, NJ; University of Navarra, Pamplona, Spain

Background: Pembrolizumab (pembro) is a monoclonal antibody against PD-1 that helps to restore antitumor immune surveillance. KEYNOTE-023 (NCT02036502) is a phase 1 dose-escalation study evaluating safety and efficacy of pembro in combination with lenalidomide (len) and low-dose dexamethasone (dex) in patients with RRMM. **Methods:** Patients with RRMM who failed ≥ 2 prior therapies enrolled. Modified 3 + 3 design was used for dose determination with cohorts of 3-6 patients treated with pembro 2 mg/kg Q2W + len 10 mg or 25 mg on days 1-21 and dex 40 mg weekly, repeated every 28 days. After preliminary MTD/MAD identification, additional patients received pembro 200 mg Q2W + len and dex for dose confirmation. Upon final MTD, patients enrolled in the dose expansion phase. Treatment continued for 24 mo or until confirmed disease progression or unacceptable toxicity. Response evaluated monthly using IMWG 2006. **Results:** 3 DLTs from the pembro 2 mg/kg, 25-mg len cohort were observed in 17 patients in the dose determination/confirmation phase: grade 3/grade 4 neutropenia, grade 3 pneumonia, and grade 3 tumor lysis syndrome with grade 4 hyperuricemia. Based on dose confirmation phase, pembro 200 mg + len 25 mg and dex 40 mg was the MTD/MAD. As of Sep 22, 2015, an additional 33 patients were enrolled in the expansion phase. Median age for the total population was 62 y, 72% had ≥ 3 prior therapies, 76% were refractory to len, and 30% had double refractory disease. 36 patients (72%) experienced treatment-related AEs, most commonly thrombocytopenia (28%) and neutropenia (24%). With a median follow-up of 9.7 mo (range, 4.3-18.4), 13/17 (76%) patients evaluated for efficacy in dose determination/confirmation responded to treatment, including 4 VGPRs (2 in len-refractory) and 9 PRs (3 in len-refractory), with median duration of response 9.7 mo (range, 0+-16.7+). 3 patients (18%) had stable disease. 94% had a reduction in M protein or free light chains. Updated efficacy data for all 50 patients will be presented. **Conclusions:** Pembro in combination with len and dex was associated with a tolerable safety profile and promising antimyeloma activity in heavily pretreated patients with RRMM.

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GYNECOLOGICAL CANCER

SHARAD GHAMANDE, M.D.

Sharad Ghamande, M.D.
Augusta University

Dr. Ghamande completed his Fellowship in Gynecologic Oncology at Roswell Park Cancer Institute in Buffalo, New York in 2000. He also completed Fellowship programs at both Memorial Sloan Kettering Cancer Center and M.D. Anderson. His Residency in Obstetrics and Gynecology was completed at Boston Medical Center in Boston, Massachusetts. He is board certified in both Obstetrics and Gynecology and Gynecologic Oncology.

Dr. Ghamande was inducted into the Alpha Omega Alpha Honor Medical Society during his time at the Boston Medical Center Program.

Dr. Ghamande enjoys a dual role as an Associate Professor at the Medical College of Georgia and working in the private sector.

In his spare time, he enjoys spending time with his family.

GYNECOLOGIC CANCER

Abstract ID: 5501 (166142)

Title: Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: An interim analysis.

Authors: Jonathan A. Ledermann, Philipp Harter, Charlie Gourley, Michael Friedlander, Ignace Vergote, Gordon J. S. Rustin, Clare L. Scott, Werner Meier, Ronnie Shapira-Frommer, Tamar Safra, Daniela E. Matei, Anitra Fielding, Stuart Spencer, Philip Rowe, Elizabeth S. Lowe, Ursula A. Matulonis; University College London, London, United Kingdom; Kliniken Essen Mitte, Essen, Germany; University of Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom; UNSW Clinical School, Prince of Wales Hospital, Randwick, Australia; University of Leuven, Leuven, Belgium; Mount Vernon Hospital, Northwood, United Kingdom; Royal Melbourne Hospital, Parkville, Australia; Frauenklinik, Evangelisches Krankenhaus Duesseldorf, Duesseldorf, Germany; Chaim Sheba Medical Center, Tel Hashomer, Israel; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Indiana University School of Medicine, Indianapolis, IN; AstraZeneca, Macclesfield, United Kingdom; AstraZeneca, Gaithersburg, MD; Dana-Farber Cancer Institute, Boston, MA

Background: In a phase II study (NCT00753545, Study 19), maintenance monotherapy with the EU/US-approved PARP inhibitor olaparib significantly improved PFS, and times to first and second subsequent therapy or death (TFST and TSST), vs placebo in PSR SOC pts. Pts with a *BRCA1/2* mutation (*BRCA*m) derived the greatest benefit from olaparib. Analyses after a data cut-off (DCO) on Nov 26, 2012 did not show a significant OS improvement with olaparib in the full analysis set (FAS) (58% maturity; HR 0.88, 95% CI 0.64–1.21, *P* =0.44) or *BRCA*m subgroup (52% maturity; HR 0.73, 95% CI 0.45–1.17, *P*= 0.19) (Ledermann *et al*, *Lancet Oncol* 2014). We report updated OS, evaluated after 77% of pts had died (DCO: Sep 30, 2015). **Methods:** Pts received olaparib (400 mg bid, capsules) or placebo after response to platinum-based therapy. *BRCA*m status was known for 254/265 pts (96%) from germline or tumor tests. **Results:** Maintenance olaparib gave pts an OS advantage vs placebo; analyses suggest that the results seen in the FAS may have been driven by the *BRCA*m group. Investigations into the contribution of pts who were non-*BRCA*m but homologous recombination repair deficient are ongoing. In the FAS, 5-yr survival was 29.2% and 20.4% in the olaparib and placebo arms, respectively (36.9% and 24.3% in *BRCA*m pts). At the 2015 DCO, 15 pts remained on olaparib (*BRCA*m, n = 8) and 1 on placebo (*BRCA*m, n = 1). 18/136 FAS pts (13.2%) received olaparib for > 5 yrs (by subgroup: 11/74 *BRCA*m pts [14.9%]; 7/62 non-*BRCA*m pts [11.3%]). There was no change to the safety profile and no new cases of MDS/AML were reported since the 2012 DCO. **Conclusions:** There is an OS advantage for pts in Study 19 receiving maintenance olaparib after response to platinum therapy. Long-term treatment with maintenance olaparib was observed. This analysis supports prior Study 19 data in pts with *BRCA*m PSR SOC showing a significant PFS benefit and delay to TFST and TSST with olaparib.

GYNECOLOGIC CANCER

Abstract ID: 5505

Title: The MITO8 phase III international multicenter randomized study testing the effect on survival of prolonging platinum-free interval (PFI) in patients with ovarian cancer (OC) recurring between 6 and 12 months after previous platinum-based chemotherapy: A collaboration of MITO, MANGO, AGO, BGOG, ENGOT, and GCIG.

Author(s): Sandro Pignata, Giovanni Scambia, Francesco Raspagliesi, Viviana Murgia, Carmela Pisano, Vanda Salutari, Alessandra Bologna, Roberto Sorio, Gabriella Ferrandina, Cosimo Sacco, Ignace Vergote, Gennaro Cormio, Enrico Breda, Saverio Cinieri, Sabrina Chiara Cecere, Uwe A. G. Wagner, Gennaro Daniele, Ciro Gallo, Francesco Perrone, Maria Carmela Piccirillo; Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione Pascale, IRCCS, Napoli, Italy; Universita Cattolica del Sacro Cuore di Roma, Unità di Ginecologia Oncologica UOC, Rome, Italy; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Santa Chiara Hospital, Trento, Italy; Medical Oncology Unit, IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia, Italy; Centro di Riferimento Oncologico-IRCCS, Aviano, Italy; Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche, Università Cattolica del Sacro Cuore, Campobasso, Italy; Dipartimento di Oncologia, Azienda Ospedaliero-Universitaria S. M. della Misericordia, Udine, Italy; Universitaire Ziekenhuizen UZ Leuven, Leuven, Belgium; University of Bari, Bari, Italy; S. Giovanni Calibita- Fatebenefratelli Hospital, Roma, Italy; Sen Antonio Perrino Hospital, Francavilla Fontana, Italy; Philipps Univ Marburg, Marburg, Germany; Seconda Università, Napoli, Italy

Background: A longer PFI is associated with better outcomes in patients with OC. It has long been hypothesized that artificially prolonging PFI by introducing a non-platinum based chemo (NPBC) might improve the sensitivity to following platinum. **Methods:** OC patients, ≤2 previous chemo, recurring/progressing 6-12 months after previous platinum-based chemo (PBC), ECOG PS ≤2, residual peripheral neuropathy ≤2, were randomized to receive experimental NPBC (pegylated liposomal doxorubicin or topotecan or gemcitabine, standard dose and timing) followed at progression by PBC (carboplatin/paclitaxel or carboplatin/gemcitabine if residual neurotoxicity, standard dose and timing) or the reverse standard treatment sequence. Primary endpoint: overall survival (OS). With 80% power in detecting a HR of 0.67, 0.05 two-tailed α, 193 events were required for primary analysis and 250 patients were planned. Analyses are based on intention to treat. **Results:** The trial was stopped prematurely due to slow recruitment with 215 patients randomized to the experimental (n=107) and standard arm (n=108). Final analysis was anticipated in agreement with the IDMC and was performed with 141 deaths and 177 events for progression free survival after second treatment from randomization (PFS2). Median age was 62; 94% of patients had received one previous line of chemotherapy; median platinum free interval before randomization was 8 months. Median follow-up was 38 months. In the experimental arm, median time from randomization to beginning of PBC was 7.8 months (IQ range: 3.7-13.3). In the experimental vs standard arm, median OS was 21.8 vs 24.5 months (HR 1.38, 95% CI: 0.99-1.94, p=0.06); median PFS2 was 12.8 vs 16.4 months (HR 1.41, 95% CI: 1.04-1.92, p=0.025). No toxic death or unexpected toxicity was reported. **Conclusions:** The MITO8 trial shows that prolonging PFI by introducing a NPBC does not improve and even worsens efficacy outcomes in patients with partially platinum sensitive recurrent OC.

GYNECOLOGIC CANCER

Abstract ID: 5508 (167372)

Title: Baseline quality of life (QOL) as a predictor of stopping chemotherapy early, and of overall survival, in platinum-resistant/refractory ovarian cancer (PRROC): The GCIG symptom benefit study (SBS).

Authors: Felicia Roncolato, Rachel O'Connell, Luke Buizen, Florence Joly, Anne Lanceley, Felix Hilpert, Aikou Okamoto, Eriko Aotani, Sandro Pignata, Paul P. Donnellan, Amit M. Oza, Elisabeth Avall-Lundqvist, Jonathan S. Berek, Katrin Marie Sjoquist, Kim Gillies, Martin R. Stockler, Madeleine Trudy King, Michael Friedlander, GCIG Symptom Benefit group; St George Hospital, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia; Centre François Baclesse, Caen, France; University College London Teaching Hospitals, London, United Kingdom; Department of Obstetrics and Gynecology, University of Schleswig-Holstein, Kiel, Germany; The Jikei University School of Medicine, Tokyo, Japan; Kanagawa Academy of Science and Technology, Kawasaki-City, Japan; National Cancer Institute of Naples, Naples, Italy; Galway University Hospital, Galway, Ireland; Princess Margaret Cancer Centre, Toronto, ON; Department of Oncology and Department of Clinical Experimental Medicine, Linköping University and Karolinska Institutet, Linköping, Sweden; Stanford Women's Cancer Center, Stanford, CA; Psycho-oncology Co-operative Research Group (PoCoG), The University of Sydney, Sydney, Australia; The Prince of Wales Hospital, Randwick, Australia

Background: 110 (19%) of the 570 women with PRROC enrolled in SBS stopped chemotherapy within 8 weeks. We sought to identify baseline characteristics, including QOL and clinical factors, that were associated with overall survival and stopping chemotherapy early. **Methods:** QOL domains were measured with the EORTC QLQ-C30 and QLQ-OV28. QLQ-C30 subscales were dichotomised using cut-points recommended by Diouf et al (The Oncologist 2015). Cox's Proportional Hazards regression was used to assess univariable and multivariable associations with overall survival. Clinical factors for the multivariable model were selected using backward elimination; candidate variables included those with $P<0.05$ in univariable analyses. The association between baseline QOL domains and stopping chemotherapy early was determined by categorising the QOL domains and using a chi-squared test. **Results:** Univariable analyses of baseline QOL data (N=545) showed that physical function (PF), role function (RF), global health status (GHS) and abdominal/GI symptoms (AGIS) were significantly associated with OS (all $p<0.001$). Multivariable analyses included haemoglobin, ascites, neutrophil to lymphocyte ratio, platelet count, log serum CA125, and abdominal/GI symptoms. All 4 QOL domains remained significant in multivariable models ($p=0.001$, $p=0.005$, $p=0.014$, $p=0.027$ respectively). Low GHS, RF, PF and high AGIS were all significantly associated with stopping chemotherapy within 8 weeks (all $p<0.007$). **Conclusions:** GHS, PF, RF and AGIS were independent predictors for OS and are

significantly associated with stopping chemotherapy early. Assessment of QOL could help identify patients with PRROC unlikely to benefit from palliative chemotherapy.

GYNCOLOGIC CANCER

Abstract ID: 5515

Title: Pembrolizumab in patients with advanced cervical squamous cell cancer: Preliminary results from the phase Ib KEYNOTE-028 study.

Author(s): Jean-Sebastien Frenel, Christophe Le Tourneau, Bert H. O'Neil, Patrick Alexander Ott, Sarina Anne Piha-Paul, Carlos Alberto Gomez-Roca, Emilie Van Brummelen, Hope S. Rugo, Shari Thomas, Sanatan Saraf, Mei Chen, Andrea Varga; Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France; Institut Curie, Paris, France; Indiana University, Simon Cancer Center, Indianapolis, IN; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Institut Claudius Regaud, Toulouse, France; The Netherlands Cancer Institute, Amsterdam, Netherlands; University of California, San Francisco, San Francisco, CA; Merck & Co., Inc., Kenilworth, NJ; Gustave Roussy, Villejuif, France

Background: Median survival is limited to only ~7 months in patients (pts) with metastatic or recurrent cervical cancer despite current treatments. Upregulation of the PD-1/PD-L1 pathway on tumor or infiltrating immune cells may negatively regulate immunity and contribute to disease progression. Pembrolizumab, an anti–PD-1 antibody, blocks the interaction between PD-1 and its ligands, PD-L1/PD-L2. Results from the cervical cancer cohort of KEYNOTE-028 (NCT02054806), a phase 1b study to evaluate the safety and efficacy of pembrolizumab in pts with advanced solid tumors, are presented.**Methods:** Key eligibility criteria included advanced cervical squamous cell cancer, failure of prior systemic therapy, ECOG PS 0-1, and PD-L1 expression in ≥1% of tumor or stroma cells by IHC. Pembrolizumab 10 mg/kg was given every 2 wk for up to 24 mo or until confirmed progression, intolerable toxicity, death, or withdrawal of consent. Response was assessed every 8 wk for the first 6 mo and every 12 wk thereafter. The primary end point was ORR per RECIST v1.1 by investigator assessment. **Results:** 24 pts with advanced cervical cancer were enrolled; median age was 41.5 y, 75.0% had an ECOG PS of 1, and 62.5% had received ≥2 prior therapies for metastatic disease. As of Dec 10, 2015, median follow-up duration was 48.9 wk (range, 5.6-90 wk). 18 (75.0%) pts experienced a treatment-related adverse event (TRAE), with pyrexia (n =4) and rash (n = 3) occurring in ≥10% of pts. 5 (20.8%) pts had grade 3 TRAEs, 2 of whom discontinued pembrolizumab (colitis, Guillain-Barre syndrome). No grade 4 or 5 TRAEs occurred. ORR (confirmed) was 12.5% (3/24; 95% CI, 2.7%-32.4%; all were PRs); the median duration of response was 19.3 wk (range, 17.7-52.0 wk). The stable disease (SD) rate was 12.5% (3/24; 95% CI, 2.7%-32.4%); the median duration of SD was 19.6 wk (range, 16.3-29.7+ wk). The 6-mo PFS rate was 13.0%; the 6-mo OS rate was 66.7%.**Conclusions:** Pembrolizumab was well tolerated and showed promising antitumor activity in pts with PD-L1^{+} advanced cervical squamous cell cancer. The clinical benefit of pembrolizumab in advanced cervical cancer will be further investigated in the phase 2 KEYNOTE-158 trial (NCT02628067).

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BREAST CANCER
RUTH O'REGAN, M.D.

Ruth M. O'Regan, MD
Chief Hematology/Oncology Division
University of Wisconsin
Division Head of Hematology and Oncology in the Department of Medicine
University of Wisconsin School of Medicine and Public Health.

Dr. O'Regan is an internationally recognized breast-cancer physician and researcher with particular expertise on breast cancers that are resistant to current therapies.

A native of Dublin, Ireland, O'Regan previously was a professor of hematology and medical oncology at Emory University, where she held the Louisa and Rand Glenn Family Chair in Breast Cancer Research. Additionally, O'Regan was the medical director at Glenn Family Breast Center of Emory University, director of the Breast Cancer Translational Research Program at the Winship Cancer Institute, and chief of hematology and medical oncology at the Georgia Cancer Center for Excellence at Grady Memorial Hospital.

In her dedication to training the next generation of physicians, O'Regan served as vice chair for educational affairs in the department of hematology and medical oncology and as director of the hematology/oncology fellowship program at Emory University.

With a highly active research program focused on identifying mechanisms of resistance to breast-cancer therapies and development of new therapies, O'Regan has been principal investigator for numerous grants and clinical trials.

Her research group has made significant discoveries about the role of the PI3 Kinase-mTOR pathway in triple-negative breast cancer, showing that mTOR inhibition can sensitize breast-cancer cells to upstream growth-factor inhibitors. These discoveries resulted in a novel clinical trial for patients with metastatic breast cancer.

Dr. O'Regan was previously a member of the San Antonio Breast Cancer Symposium Planning Committee, in addition to serving on numerous other committees, study sections and advisory boards.

ASCO 2016: Breast Cancer
Georgia Association of Clinical Oncology Annual meeting
Atlanta, GA, September 10th, 2016

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SCHOOL OF MEDICINE AND PUBLIC HEALTH

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Disclosures

- Advisor:
  - Pfizer, Lilly
- Research support:
  - Novartis, Pfizer

Topics to discuss

- ER-positive breast cancer:
  - Extending endocrine therapy (Plenary)
  - CDK inhibition in metastatic disease (Absts. 507, 510, 512)
- HER2-positive
  - T-DM1 pre-operatively (Abst. 500)
  - Trastuzumab biosimilar (Abst. 503)
- (Neo)-adjuvant chemotherapy (Absts. 1000, 1002, 1003)
- Novel agents for TNBC (Absts. 1009, 1011)
- Surgery in patients with metastatic breast cancer (Absts. 1005, 1006)

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

HARVARD MEDICAL SCHOOL | Massachusetts General Hospital Cancer Center

CCTG MA.17R

Extending adjuvant Letrozole for 5 years after completing an initial 5 years of Aromatase Inhibitor therapy alone or preceded by Tamoxifen in Postmenopausal Women with Early-Stage Breast Cancer: A Randomized Phase III Open Label Trial

P. E. Goss, MD, PhD, FRCPC, FRCP(UK)

Goss PE, Ingle JN, Pritchard K, Robert N, Muss H, Gralow J, Gelmon K, Whelan T, Strasser-Weippl K, Rubin S, Sturtz K, Wolff AC, Winer E, Hudis C, Stopeck A, Thaddeus Beck J, Kaur JS, Whelan K, Tu D, Parulekar WR

MA.17R Trial Schema and Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

Oct 2004 - May 2009
n = 1918

Any duration of prior Tamoxifen

4.5-6 yrs of Aromatase Inhibitor

Letrozole 2.5 mg po od

RANDOMIZE

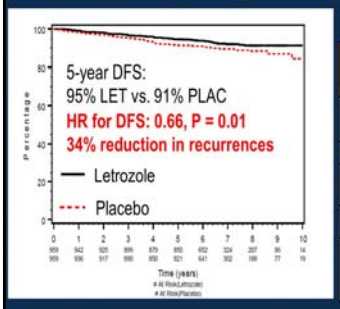
Letrozole 2.5 mg po od

Placebo

5 yrs

- ER+ and/or PR+ breast cancer
- Postmenopausal and disease-free
- Completed 4.5-6 years of adjuvant AI
- Any time of prior TAM
- Minimum life expectancy ≥5 years (no exclusion for age alone)

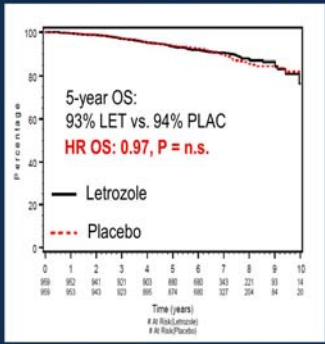
MA.17R Primary Endpoint: DFS at med F/U of 6.3 yrs



	LET	PLAC
DFS events	67 (7.0)	98 (10.2)
Distant recurrences	42	53
Loco-regional recurrences	19	30
Bone recurrences	28	37
New Contralateral breast cancers[§] CBC	13 (1.4)	31 (3.2)

58% reduction in CBC

MA.17R – Overall Survival at med F/U of 6.3 yrs



MA.17R – Toxicity: Fractures During Treatment

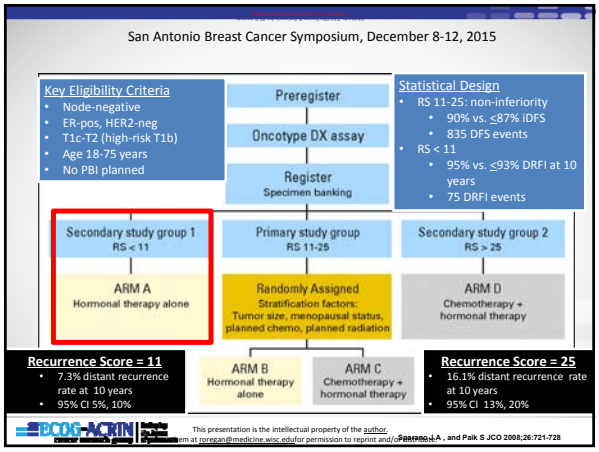
	Letrozole	Placebo	P-Value
	n (%)	n (%)	
Bone fractures	133 (14)	88 (9)	0.001
Location of bone fractures			
Spinal	17 (1.8)	9 (0.9)	0.12
Wrist	27 (2.8)	16 (1.7)	0.09
Pelvis	1 (0.1)	7 (0.7)	0.08
Hip	7 (0.7)	6 (0.6)	0.79
Femur	9 (0.9)	4 (0.4)	0.17
Tibia	5 (0.5)	4 (0.4)	0.74
Ankle	19 (2.0)	11 (1.2)	0.14
Other	68 (7.1)	48 (5.0)	0.06
New onset osteoporosis	109 (11)	54 (6)	<0.0001

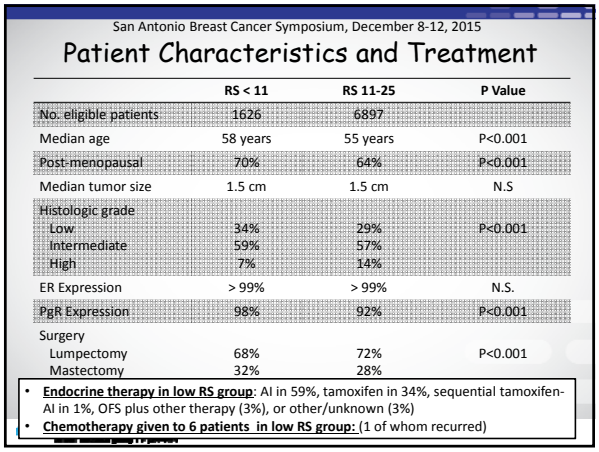
MA.17R – Summary & Conclusions

- MA.17R is the first study to show benefit of extending AI beyond 5 years resulting in a 34% reduction in disease recurrences
- No worsening of QOL was observed on extended letrozole
- No new toxicities associated with long-term letrozole occurred
- Bone health remains important for risk/benefit consideration
- Importantly, unlike many anti-cancer therapies, AIs are readily accessible and therefore our results will further improve the outcome of many women with breast cancer around the world

My take

- Several caveats with results
  - Low event rate (especially for distant recurrence)
  - Much of the benefit in reducing contralateral breast cancer
  - Required event number not reached at time of this analysis
  - Await NSABP B-42
  - Definition of DFS did not include deaths from other causes
- Fracture rate increased despite use of bisphosphonates
- Which patients really need extended adjuvant endocrine therapy is justified?

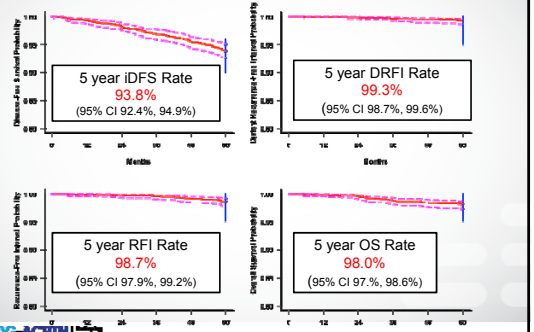




No. of events: 88 iDFS events and 30 deaths within 5 years of registration, including 18 recurrences (10 distant as first event), 15 second primary breast cancers, 43 other second primary cancers, 12 deaths without another event

San Antonio Breast Cancer Symposium, December 8-12, 2015

5-year event rate in cancers with recurrence scores 10 or less did not receive chemotherapy



ECOG-ACRIN

EORTC - 10041 BIG - 3-04

MINDACT

« Microarray for node negative [1-3 node +] disease may avoid chemotherapy »

Primary analysis of the EORTC 10041/ BIG 3-04 MINDACT study: A prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint®) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes

Martine Piccart, Emiel Rutgers, Laura van't Veer, Leen Slaets, Suzette Delaloge, Giuseppe Viale, Jean Yves Pierga, Peter Vuylsteke, Etienne Brain, Suzan Vrijaldenhoven, Peter Neijenhuis, Bruno Coudert, Tineke Smilde, Miguel Gil, Alastair Thompson, Isabel T. Rubio, Rodolfo Passalaqua, Erika Matos, Urlike Nitz, Mauro Delorenzi, Geraldine Thomas, Theodora Goulioti, Carolyn Straehle, Konstantinos Tryfonidis, Jan Bogaerts & Fatima Cardoso

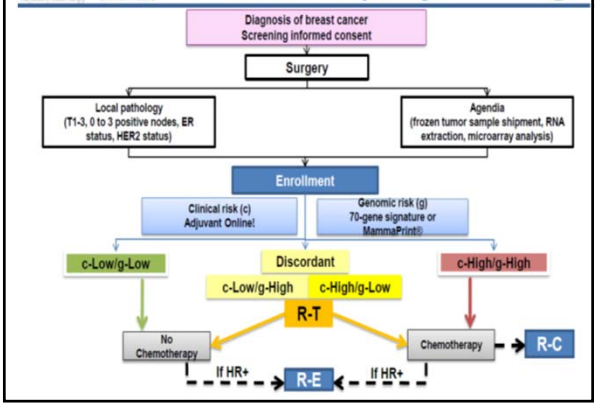
On behalf of the European Commission supported TRANSBIG consortium and MINDACT investigators

Presented at AACR, April 18, 2016

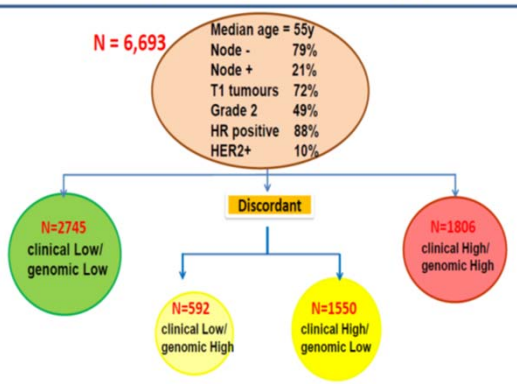
1

EORTC BIG

The MINDACT study design

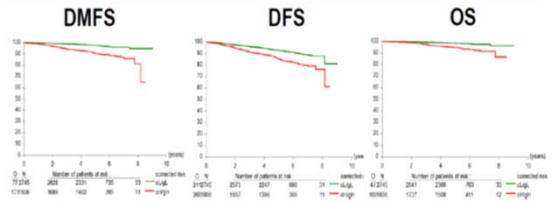


The MINDACT study: Patient demographics



Clinical outcome of the MINDACT population at 5y median follow-up

A) CONCORDANT RISK GROUPS (using corrected risk)



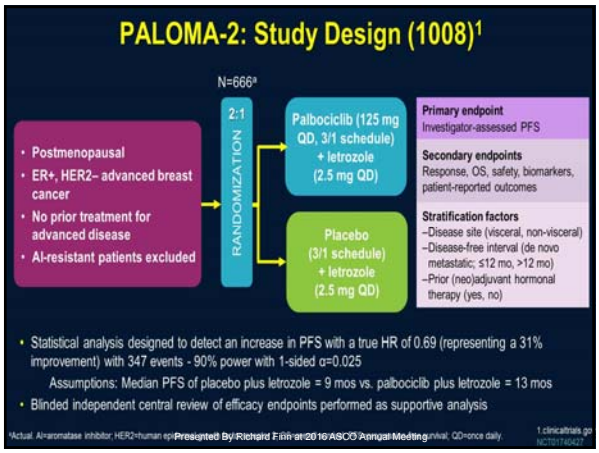
	% at 5y (95% CI)	% at 5y	% at 5y
cL/gL	**97.6** (96.9 – 98.1)	**92.8** (91.7 – 93.7)	**98.4** (97.8 – 98.9)
cH/gH	**90.6** (89.0 – 92.0)	**85.3** (83.4 – 87.0)	**94.7** (93.4 – 95.7)

PALOMA-2: Primary Results From a Phase 3 Trial of Palbociclib Plus Letrozole Compared With Placebo Plus Letrozole in Postmenopausal Women With ER+/HER2– Advanced Breast Cancer

Richard S. Finn,[1] Miguel Martin,[2] Hope S. Rugo,[3] Stephen Jones,[4] Seock-Ah Im,[5] Karen Gelmon,[6] Nadia Harbeck,[7] Oleg N. Lipatov,[8] Janice M. Walshe,[9] Stacy Moulder,[10] Eric Gauthier,[11] Dongrui R. Lu,[11] Sophia Randolph,[11] Veronique Dieras,[12] Dennis J. Slamon[1]

[1]David Geffen School of Medicine, Los Angeles, CA, USA; [2]Hospital Gregorio Maranon, Universidad Complutense, Madrid, Spain; [3]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]US Oncology Research, The Woodlands, TX, USA; [5]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [6]British Columbia Cancer Agency, Vancouver, BC, Canada; [7]Brustzentrum der Universitaet Muenchen (LMU), Munich, Germany; [8]SBMI Republican Clinical Oncologic Dispensary, Ufa, Russian Federation; [9]All-Ireland Cooperative Oncology Research Group (ICORG), Ireland; [10]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [11]Pfizer Inc, La Jolla, CA, USA; [12]Institut Curie, Paris, France

Presented By Richard Finn at 2016 ASCO Annual Meeting


PALOMA-2: Study Design (1008)[1]
N=666[a]
2:1
RANDOMIZATION
• Postmenopausal
• ER+, HER2– advanced breast cancer
• No prior treatment for advanced disease
• AI-resistant patients excluded
Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)
Placebo (3/1 schedule) + letrozole (2.5 mg QD)
Primary endpoint
Investigator-assessed PFS
Secondary endpoints
Response, OS, safety, biomarkers, patient-reported outcomes
Stratification factors
–Disease site (visceral, non-visceral)
–Disease-free interval (de novo metastatic; ≤12 mo, >12 mo)
–Prior (neo)adjuvant hormonal therapy (yes, no)
• Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided α=0.025
Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos
• Blinded independent central review of efficacy endpoints performed as supportive analysis
[a]Actual. AI=aromatase inhibitor; HER2=human epi
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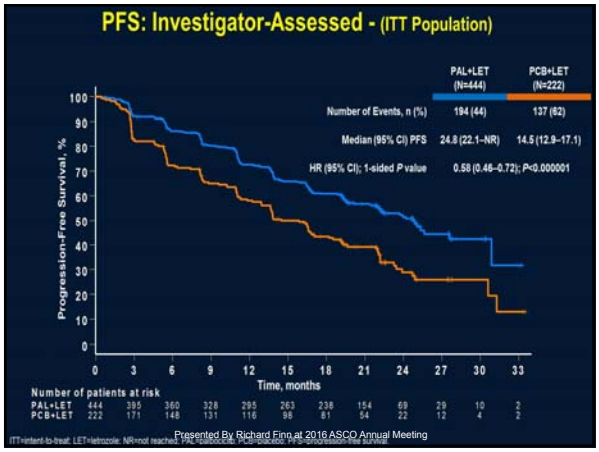
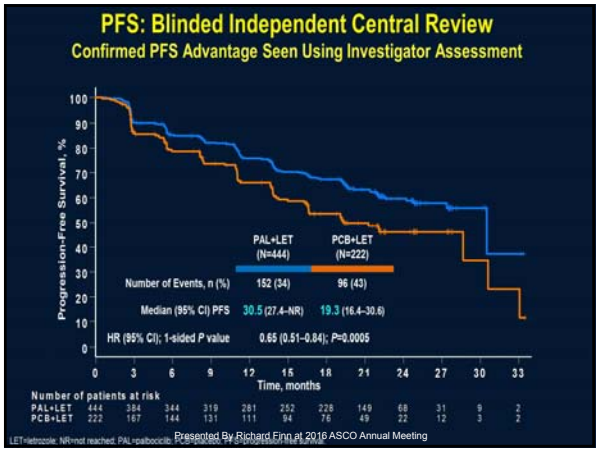
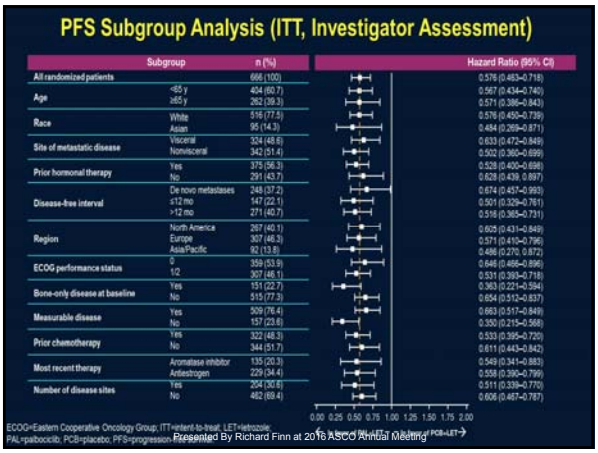
rvival; QD=once daily.
1.clinicaltrials.go
NCT01740427


PFS: Investigator-Assessed - (ITT Population)
PAL+LET (N=444)
PCB+LET (N=222)
Number of Events, n (%) 194 (44) 137 (62)
Median (95% CI) PFS 24.8 (22.1–NR) 14.5 (12.9–17.1)
HR (95% CI); 1-sided P value 0.58 (0.46–0.72); P<0.000001
Progression-Free Survival, %
Time, months
Number of patients at risk
PAL+LET 444 395 360 328 295 263 238 154 69 29 10 2
PCB+LET 222 171 148 131 116 98 81 54 22 12 4 2
Presented By Richard Finn at 2016 ASCO Annual Meeting
ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival


PFS: Blinded Independent Central Review
Confirmed PFS Advantage Seen Using Investigator Assessment
PAL+LET (N=444)
PCB+LET (N=222)
Number of Events, n (%) 152 (34) 96 (43)
Median (95% CI) PFS 30.5 (27.4–NR) 19.3 (16.4–30.6)
HR (95% CI); 1-sided P value 0.65 (0.51–0.84); P=0.0005
Progression-Free Survival, %
Time, months
Number of patients at risk
PAL+LET 444 384 344 319 281 252 228 149 68 31 9 2
PCB+LET 222 167 144 131 111 94 76 49 22 12 3 2
Presented By Richard Finn at 2016 ASCO Annual Meeting
LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival

PFS Subgroup Analysis (ITT, Investigator Assessment)



ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; LET=letrozole; PAL=palbociclib; PCB=placebo; PFS=progression-free survival

Key Secondary Efficacy Endpoints

	Palbociclib + Letrozole (N=444)	Placebo + Letrozole (N=222)	Odds Ratio (95% CI)	1-Sided P Value (Exact)
ITT population	**444**	**222**		
Objective response rate,[a] % (95% CI)	**42%** (37.5–46.9)	**35%** (28.4–41.3)	1.40 (0.98–2.01)	0.0310
Clinical benefit response rate,[b] % (95% CI)	**85%** (81.2–88.1)	**70%** (63.8–76.2)	2.39 (1.58–3.59)	<0.0001
Patients with measurable disease	**338**	**171**		
Objective response rate,[a] % (95% CI)	**55%** (49.9–60.7)	**44%** (36.9–52.2)	1.55 (1.05–2.28)	0.0132
Clinical benefit response rate,[b] % (95% CI)	**84%** (80.0–88.0)	**71%** (63.3–77.5)	2.23 (1.39–3.56)	0.0003

ITT=intent-to-treat; NA=not applicable. Values presented as n (%) unless noted otherwise. [a]Confirmed complete response + partial response. [b]Confirmed complete response + partial response + stable disease ≥24 weeks.

Consistent Clinical Benefit Seen Across PALOMA Studies

	1003[1] (PALOMA-1)	1008 (PALOMA-2)	1023[2] (PALOMA-3)
Design	Phase 2 Open label	Phase 3 Placebo control	Phase 3 Placebo control
Endocrine partner	Letrozole	Letrozole	Fulvestrant
Patients on study, N	n=165	n=666	n=521
Efficacy (palbociclib vs control arm)			
Primary endpoint: PFS			
HR	0.49	0.58	0.46
Median PFS, mo	20.2 vs 10.2(↑10.0mos)	24.8 vs 14.5 (↑10.3mos)	9.6 vs 4.6
Secondary endpoints, %			
ORR (ITT, measurable disease)	43 vs 33, 55 vs 39	42 vs 35, 55 vs 44	19 vs 9, 25 vs 11
CBR (ITT)	81 vs 58	85 vs 70	67 vs 40

CBR=clinical benefit response; ITT=intent-to-treat; [1]Finn RS, Dering J, Conklin D, et al. Breast Cancer Res. 2015; 2. Cristofanilli et al. Lancet Oncol. 2016

MONARCH 1

Results from a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2- breast cancer, after chemotherapy for metastatic disease.

Maura N. Dickler, MD[1]; Sara M. Tolaney, MD, MPH[2]; Hope S. Rugo, MD[3]; Javier Cortés, MD PHD[4,5]; Véronique Diéras, MD[6]; Debra Patt, MD, MPH, MBA[7,8]; Hans Wildiers, MD[9]; Martin Frenzel, PHD[10]; Andrew Koustenis, BS[10]; José Baselga, MD PHD[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Institute, Boston, MA; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [5]Ramón y Cajal University Hospital, Madrid, Spain; [6]Institut Curie, Paris, France; [7]Texas Oncology, Austin, TX; [8]US Oncology, Dallas, TX; [9]Department of General Medical Oncology, University Hospital Gasthuisberg, Leuven, Belgium; [10]Eli Lilly and Company, Indianapolis, IN

Abemaciclib is a Selective Inhibitor of CDK4 & 6

- Abemaciclib is 14X more potent against CDK4/cyclin D1 than CDK6/cyclin D3 in enzymatic assays[1]
  - This differential potency may have clinical implications
- In a phase I trial of abemaciclib[2]
  - Single agent activity was observed in a subgroup of heavily pretreated patients with HR+ MBC
  - Neutropenia was not a dose limiting toxicity (DLT) and continuous dosing was feasible

[1]Lallena MJ et al. *Cancer Research* 2015;75 (Suppl 15): Abstract 3101. [2]Patnaik A et al. *Cancer Discov* 2016; doi:10.1158/2159-8290.CD-16-0095

MONARCH 1: Phase 2 Study Design

Previously-treated HR+/HER2- MBC → Abemaciclib 200 mg orally Q12H → Treatment continued until unacceptable toxicity or PD

Primary objective

To evaluate abemaciclib with respect to confirmed objective response rate based on investigator assessment (per RECIST v1.1)

Secondary objectives

Duration of response, progression-free survival, overall survival, clinical benefit rate, safety

Statistical design

A sample size of 128 patients provides 82% power, assuming a true response rate of 25%, to exclude an ORR of ≤15% on the lower bound of the 95% CI at 12 months follow-up

MONARCH 1: Prior Therapies

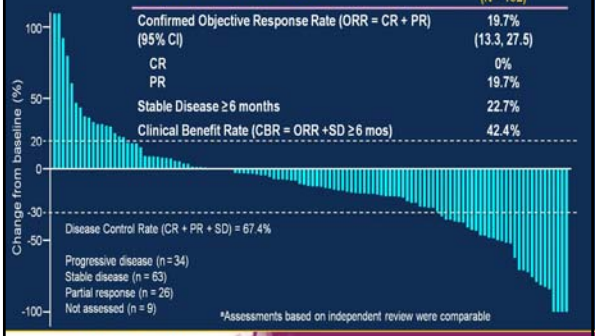
- Median number of prior systemic regimens (any setting) was 5 (range 2-11)
- 100% of patients received taxanes in any setting
- Median number of prior systemic regimens for metastatic disease was 3 (range 1-8)

Endocrine Therapy for Metastatic Disease	N=132 n (%)
# of Regimens	
1	48 (36.4)
2	25 (18.9)
3	24 (18.2)
≥ 4	18 (13.6)
Prior fulvestrant	67 (50.8)

Chemotherapy for Metastatic Disease	N=132 n (%)
# of Regimens	
1	67 (50.8)
2	64 (48.5)
3	1 (0.8)
Taxanes	91 (68.9)
Capecitabine	73 (55.3)

MONARCH 1: Response Summary

Investigator Assessed Response[a]	Abemaciclib 200 mg (N = 132)
Confirmed Objective Response Rate (ORR = CR + PR) (95% CI)	19.7% (13.3, 27.5)
CR	0%
PR	19.7%
Stable Disease ≥ 6 months	22.7%
Clinical Benefit Rate (CBR = ORR + SD ≥ 6 mos)	42.4%



[a]Assessments based on independent review were comparable

MONARCH 1: Most Common Adverse Events

Investigator Assessed TEAEs[a] >20% (N=132)	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %	All Grades %
Diarrhea	41.7	28.8	19.7	0	90.2
Fatigue	21.2	31.1	12.9	0	65.2
Nausea	39.4	20.5	4.5	0	64.4
Decreased appetite	28.0	14.4	3.0	0	45.5
Abdominal pain	22.0	14.4	2.3	0	38.6
Vomiting	22.7	10.6	1.5	0	34.8
Headache	13.6	6.8	0	0	20.5
Lab abnormalities[b]					
Creatinine increased[c]	46.9	50.8	0.8	0	98.5
White blood cell decreased	18.5	44.6	27.7	0	90.8
Neutrophil count decreased	17.7	43.1	22.3	4.6	87.7[d]
Anemia	30.0	38.5	0	0	68.5
Platelet count decreased	28.9	10.2	2.3	0	41.4

[a]CTCAE Version 4.03. [b]N = 130 for lab abnormalities listed, except platelet count decreased (N=128). [c]Abemaciclib is a competitive inhibitor of OCT2, MATE1, and MATE2-K, efflux transporters of creatinine; cystatin C calculated GFR was not raised. [d]One patient who received cytotoxic chemotherapy within the 30 day follow up window experienced febrile neutropenia

Abstract 512

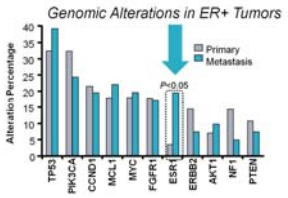
Efficacy of Palbociclib Plus Fulvestrant in Patients With Metastatic Breast Cancer and *ESR1* Mutations in Circulating Tumor DNA

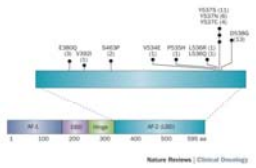
Nicholas C. Turner,[1] Yuqiu Jiang,[2] Ben O'Leary,[1] Sarah Hrebien,[1] Massimo Cristofanilli,[3] Fabrice André,[4] Sibylle Loibl,[5] Patricia A. English,[2] Ke Zhang,[2] Sophia Randolph,[2] Cynthia Huang Bartlett,[6] Maria Koehler,[6] Sherene Loi[7]

[1]Royal Marsden Hospital and Institute of Cancer Research, London, UK; [2]Pfizer Inc, La Jolla, CA, USA; [3]Robert H Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Chicago, IL, USA; [4]Institut Gustave Roussy, Villejuif, France; [5]German Breast Group Forschungs GmbH, Neu-Isenburg, Germany; [6]Pfizer Inc, New York, NY, USA; [7]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Presented at ASCO 2016; June 3, 2016; Chicago, IL, USA

ESR1 Mutation Background

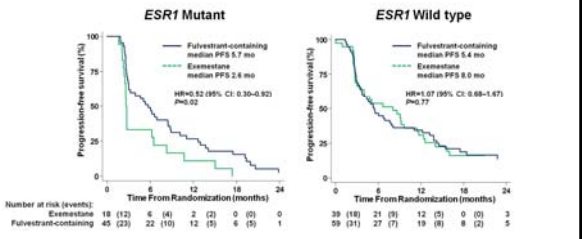




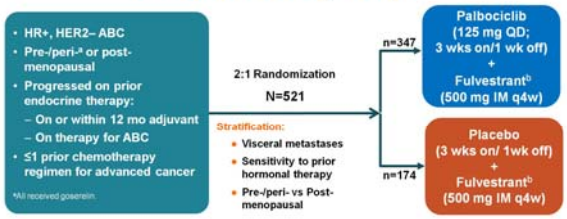
ESR1 mutations occur in ~20% of AI-resistant, ER+ breast cancer

AI=aromatase inhibitor; ER=estrogen receptor.

ESR1 Mutation Analysis by Digital PCR in the Randomized Phase III SoFEA Study



PALOMA-3 Study Design



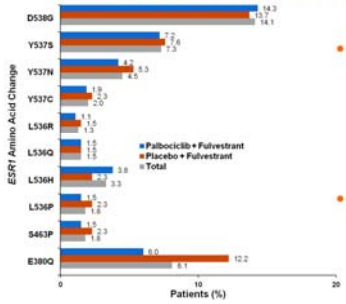
- **Baseline plasma samples collected for circulating tumor DNA analysis were processed within 1 hour of venipuncture.**

[b]Administered on Days 1 and 15 of Cycle 1.

Clinicaltrials.gov: NCT01942135. Turner et al. *NEJM*. 2015.

Presented By Nicholas Turner at 2016 ASCO Annual Meeting

ESR1 Mutations in PALOMA-3



- *ESR1* mutations were detected in 27% (106/396) of patients with plasma samples
  - Amino acid changes P535H and V534E were not detected
- *ESR1* mutations were polyclonal in 38% (40/106) of mutation-positive patients

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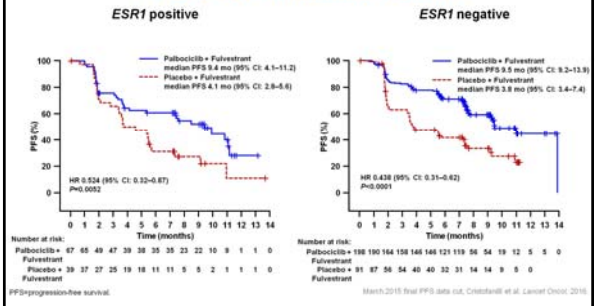
PFS by *ESR1* Mutation Status



PFS=progression-free survival.

March 2015 final PFS data cut. Cristofanilli et al. *Lancet Oncol*. 2016.

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Summary: ER-positive MBC abstracts

- PALOMA-2 provides level 1 evidence for benefit of palbociclib in first-line setting
  - Does everyone need CDK inhibition first-line?
- Abemaciclib alone is active in heavily pre-treated patients
  - Await MONARCH trials results
- Role of ESR1 mutations evolving

Pathologic complete response rates after neoadjuvant trastuzumab emtansine (T-DM1) + pertuzumab vs docetaxel + carboplatin + trastuzumab + pertuzumab (TCH+P) treatment in patients with HER2-positive early breast cancer (KRISTINE/TRIO-021)

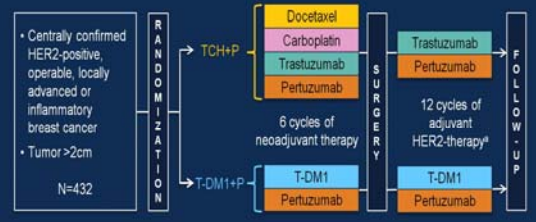
Sara A. Hurvitz,[1] Miguel Martin,[2] W. Fraser Symmans,[3] Kyung Hae Jung,[4] Chiun-Sheng Huang,[5] Alastair M.Thompson,[3] Nadia Harbeck,[6] Vicente Valero,[3] Daniil Stroyakovskiy,[7] Hans Wildiers,[8] Karen Afenjar,[9] Rodrigo Fresco,[10] Hans-Joachim Helms,[11] Jin Xu,[12] Yvonne G. Lin,[12] Joseph Sparano,[13] Dennis Slamon[1]

[1]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [2]Hospital Gregorio Marañón, Universidad Complutense, Madrid, Spain; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [5]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [6]Breast Center, University of Munich (LMU), Munich, Germany; [7]Moscow City Oncology Hospital, Stepanovskoye, Moscow, Russia; [8]University Hospitals Leuven, Leuven, Belgium; [9]Translational Research in Oncology, Paris, France; [10]Translational Research in Oncology, Montevideo, Uruguay; [11]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

ASCO ANNUAL MEETING '16

Presented by: Dr Sara Hurvitz

KRISTINE Study Design

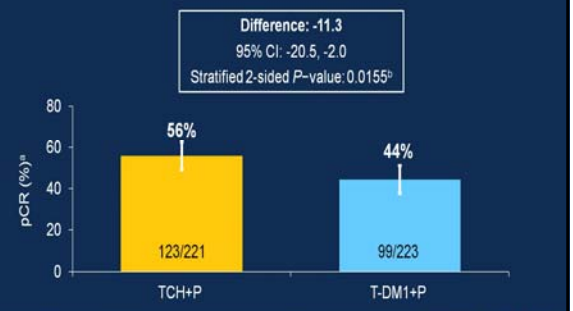


Primary endpoint: pCR by local assessment (ypT0/is, ypN0)

- **Stratification factors:** local HR status, geographic location, and clinical stage at presentation

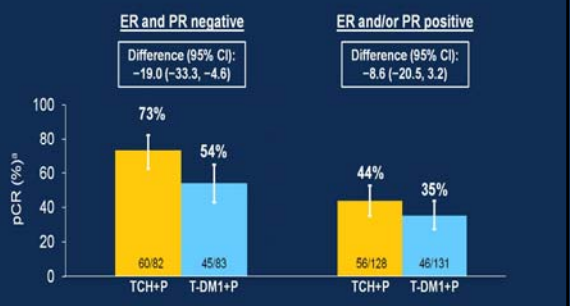
[a]Adjuvant chemotherapy was recommended for patients in the T-DM1+P arm who had residual disease in lymph node(s) or in the breast (>1cm).

Primary Endpoint: pCR (ypT0/is, ypN0)



[a]pCR rate and 95% CI are shown. Patients with missing or unevaluable pCR status were considered nonresponders: TCH+P, 7 (3.2%); T-DM1+P, 18 (8.1%). Treatment discontinuation in the neoadjuvant phase for progressive disease: TCH+P, 0% of patients; T-DM1+P, 7% of patients.
[b]Cochran-Mantel-Haenszel Chi-square.

pCR by Central ER/PR Receptor Status



[a]ypT0/is, ypN0; patients with missing or unevaluable pCR status were considered nonresponders. Twenty patients had "unknown" ER/PR status by central analysis.

HERITAGE Study: A Randomized Double Blind Phase III Safety and Efficacy Trial of the Proposed Trastuzumab Biosimilar, MYL-1401O vs Herceptin

Hope S. Rugo[1], Abhijit Barve[2], Cornelius F. Waller[3], Miguel Hernandez-Bronchud[4], Jay Herson[5], Jinyu Yuan[2], Alexey Manikhas[6], Igor Bondarenko[7], Guzel Mukhametshina[8], Gia Nemsadze[9], Joseph D. Parra[10], Maria Luisa T. Abesamis-Tiambeng[11], Kakhaber Baramidze[12], Charuwan Akewanlop[13], Ihor Vynnychenko[14], Virote Sriuranpong[15], Gopichand Manillapalli[16], Sirshendu Ray[17], Eduardo Patricio Yanez Ruiz[18], Eduardo Pennella[2]

University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, **USA**[1]; Mylan Inc., **USA**[2]; University of Freiburg Medical Center, **Germany**[3]; Quiron-Dexeus, Barcelona, **Spain**[4]; Johns Hopkins, **USA**[5]; City Clinical Oncology Dispensary, Saint Petersburg, **Russia**[6]; Dnipropetrovsk State Medical Academy, **Ukraine**[7]; Regional Clinical Oncological Center, Kazan, **Russia**[8]; Institute of Clinical Oncology, Tbilisi, **Georgia**[9]; St. Luke's Medical Center Global City, Taguig City, **Philippines**[10]; Cardinal Santos Medical Center, Manila, **Philippines**[11]; Golden Fleece 21 Century Health House Ltd, Tbilisi, **Georgia**[12]; Siriraj Hospital, Bangkok, **Thailand**[13]; Sumy State University, Sumy, **Ukraine**[14]; Chulalongkorn Memorial Hospital, Bangkok, **Thailand**[15]; City Cancer Center, Vijayawada, **India**[16]; Curie Manavata Cancer Centre, Nasik, **India**[17]; Instituto Clínico Oncológico del Sur (ICOS), Temuco, **Chile**[18].

Presented at ASCO ANNUAL MEETING '16

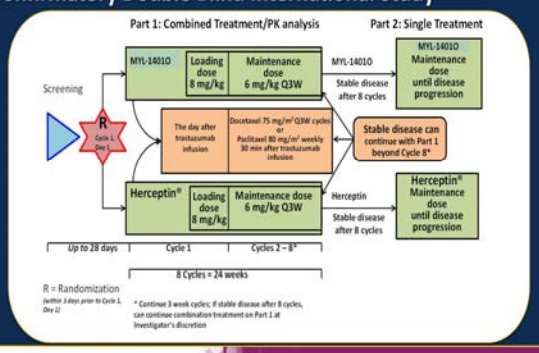
Presented by: Dr. Hope S. Rugo

Abbreviated Development for Biosimilars

- The underlying presumption
  - A molecule shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting*
  - Extensive structural/functional characterization of the proposed trastuzumab biosimilar and Herceptin was demonstrated; this analytical characterization serves as the foundation of biosimilarity
- Development program must include additional data:
  - PK exposure in humans
  - Confirm similar safety, efficacy and immunogenicity

* Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). 2015. page 3. (Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.)

Heritage Study Design: Confirmatory Double Blind International Study



Efficacy: Ratio of ORR & Difference between ORR (ITT1 Population)

	MYL-1401O + Taxane N= 230	Herceptin + Taxane N= 228
Overall response rate n (%)	160 (69.6)	146 (64.0)
95% CI	(63.62, 75.51)	(57.81, 70.26)
Ratio of ORR: MYL-1401O/Herceptin (FDA)	1.09	
90% CI	(0.974, 1.211)	
95% CI	(0.954, 1.237)	
Difference in ORR: MYL-1401O-Herceptin (EMEA)	5.53	
90% CI	(-1.70, 12.69)	
95% CI	(-3.08, 14.04)	

Results confirmed efficacy equivalence based on ratio of ORR & difference in ORR

Progression Free Survival at Week 24 (ITT1 Population)

	MYL-1401O + Taxane	Herceptin + Taxane
Subject status		
Number of subjects	230	228
Events, n (%)	41 (17.8)	48 (21.1)
Log-rank test: p-value	0.303	
Cox proportional hazard[1]		
Unstratified hazard ratio (95% CI)		
Number of subjects	230	228
Hazard ratio (95% CI)	0.80 (0.529, 1.218)	
p-value	0.302	
Stratified hazard ratio (95% CI)		
Number of subjects	220	220
Hazard ratio (95% CI)	0.75 (0.488, 1.143)	
p-value	0.179	

No significant difference in PFS at 24 weeks

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Serious Adverse Events (Safety Population at Week 24)

Preferred Term	MYL-1401O + Taxane	Herceptin + Taxane
	N = 247 n (%)	N = 246 n (%)
Number of patients with at least 1 SAE	94 (38.1)	89 (36.2)
Neutropenia	68 (27.5)	62 (25.2)
Febrile neutropenia	11 (4.5)	10 (4.1)
Leukopenia	4 (1.6)	12 (4.9)
Pneumonia	4 (1.6)	5 (2.0)

Similar to historical Herceptin + taxanes safety information in MBC

TEAE: treatment-emergent adverse event; Percentages are based on the number of patients in the safety population (N); n: number of patients with TEAEs

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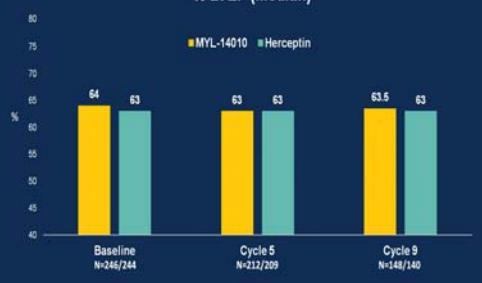
No Difference in Left Ventricular Ejection Fraction (LVEF): Safety Population



No difference in the median LVEF between the two arms

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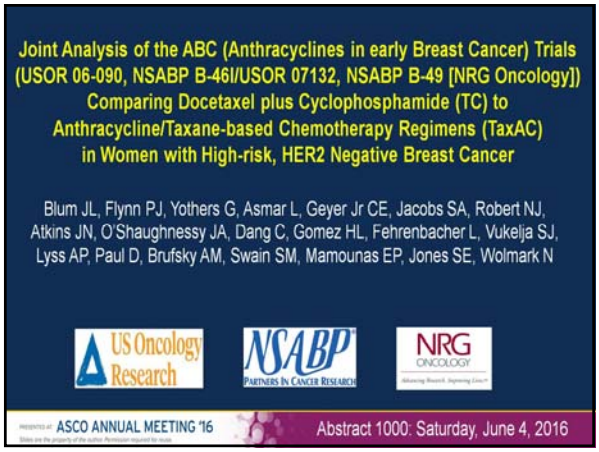
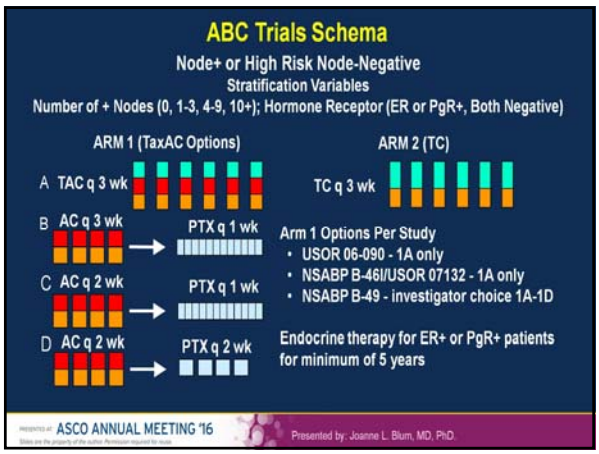
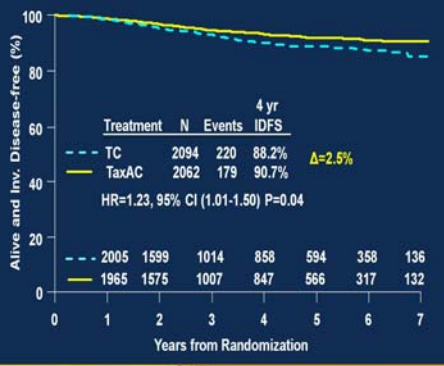
Summary: HER2-positive abstracts

- T-DM1 plus pertuzumab inferior to TCHP for pathologic complete response but less toxic
- Trastuzumab biosimilar appears equal to trastuzumab in HER2-positive metastatic breast cancer:
  - Similar efficacy (RR and PFS)
  - Similar toxicity (cardiotoxicity and immunogenicity)

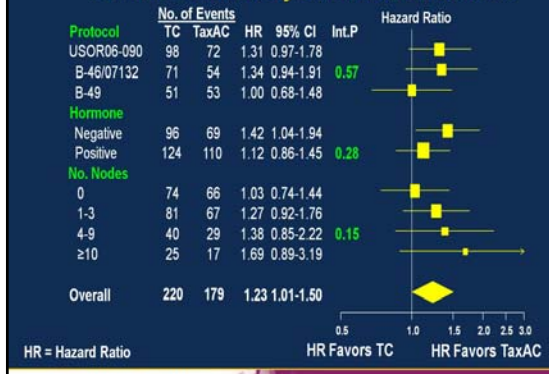




ABC Trials: Invasive Disease Free Survival



Forest Plot of IDFS By Stratification Variables



ABC Trials: IDFS by Hormone and Nodal Status

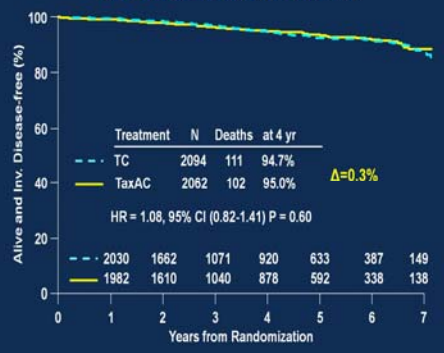
Exploratory Analysis

	Pts TaxAC	Pts TC	Events TaxAC	Events TC	4 yr IDFS TaxAC	4 yr IDFS TC	4 yr IDFS Delta	HR (95% CI)
ER/PgR (-)								
N-	459	488	37	52	89.5	87.0	2.5%	1.31 (0.86-1.99)
1-3 N+	153	119	21	28	85.5	74.6	10.9%	1.58 (0.90-2.79)
4+ N+	42	40	11	16	71.8	60.8	11.0%	1.34 (0.62-2.91)
ER or PgR (+)								
N-	358	378	29	22	91.5	94.2	- 2.7%	0.69 (0.39-1.19)
1-3 N+	771	789	46	53	94.3	92.3	2.0%	1.14 (0.77-1.69)
4+ N+	279	280	35	49	87.2	81.4	5.8%	1.46 (0.95-2.26)

ABC Trials: First IDFS Events (N)

Type of Events	TC N=2094	TaxAC N=2062	Total N=4156
Local Regional	46	34	80
Distant	110	75	185
Recur site unknown	19	12	31
CBC	3	3	6
Leukemias	0	5	5
Other 2nd Primary	20	22	42
Death	22	28	50
Total	220	179	399

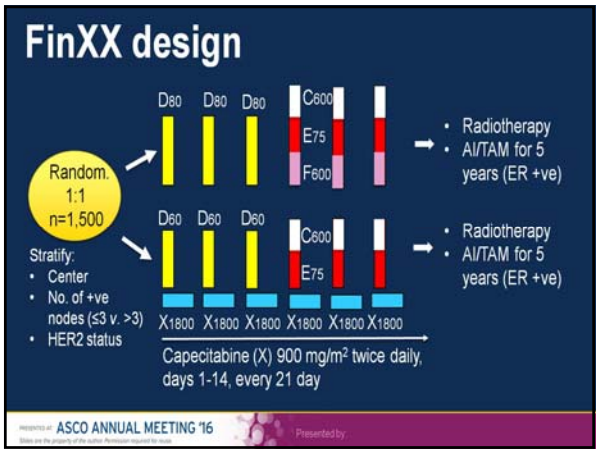
ABC Trials: Overall Survival



Abstract #1001

Adjuvant capecitabine in combination with docetaxel, epirubicin, and cyclophosphamide in the treatment of early breast cancer: 10-year survival results from the randomized FinXX trial.

Heikki Joensuu, Pirkko-Liisa Kellokumpu-Lehtinen, Riikka Huovinen, Arja Jukkola-Vuorinen, Minna Tanner, Riitta Kokko, Johan Ahlgren, Päivi Auvinen, Outi Lahdenperä, Sanna Kosonen, Kenneth Villman, Paul Nyandoto, Greger Nilsson, Ismo Jantunen, Maija Murashev, Paula Poikonen-Saksela, Vesa Kataja, Petri Bono, Henrik Lindman


FinXX design
D80 D80 D80 C600 E75 F600
Random. 1:1 n=1,500
D60 D60 D60 C600 E75
Stratify:
• Center
• No. of +ve nodes (≤3 v. >3)
• HER2 status
X1800 X1800 X1800 X1800 X1800 X1800
Capecitabine (X) 900 mg/m² twice daily, days 1-14, every 21 day
• Radiotherapy
• AI/TAM for 5 years (ER +ve)
• Radiotherapy
• AI/TAM for 5 years (ER +ve)
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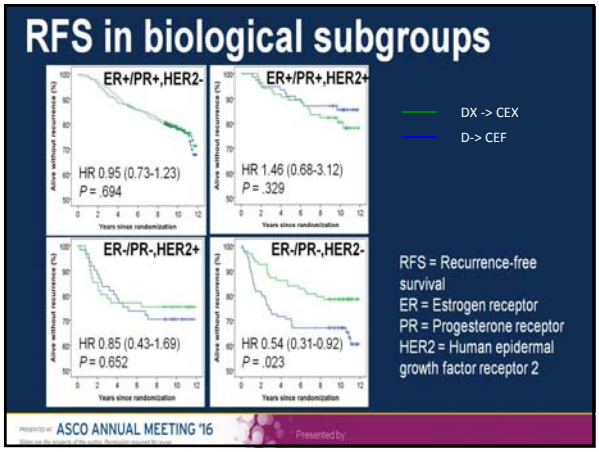
Presented by:


RFS in biological subgroups
ER+/PR+,HER2-
HR 0.95 (0.73-1.23)
P = .694
ER+/PR+,HER2+
HR 1.46 (0.68-3.12)
P = .329
ER-/PR-,HER2+
HR 0.85 (0.43-1.69)
P = 0.652
ER-/PR-,HER2-
HR 0.54 (0.31-0.92)
P = .023
DX -> CEX
D-> CEF
RFS = Recurrence-free survival
ER = Estrogen receptor
PR = Progesterone receptor
HER2 = Human epidermal growth factor receptor 2
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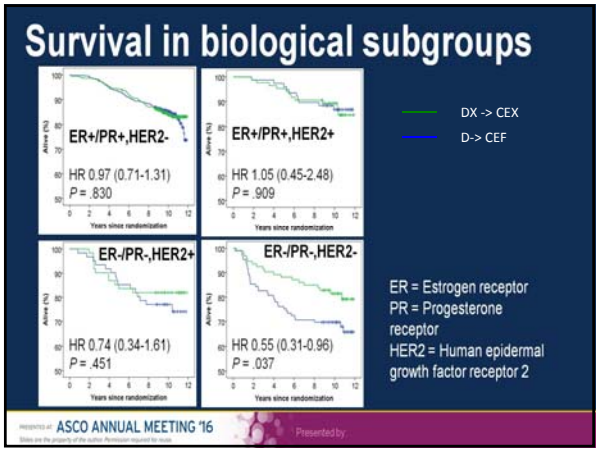
Survival in biological subgroups
ER+/PR+,HER2-
HR 0.97 (0.71-1.31)
P = .830
ER+/PR+,HER2+
HR 1.05 (0.45-2.48)
P = .909
ER-/PR-,HER2+
HR 0.74 (0.34-1.61)
P = .451
ER-/PR-,HER2-
HR 0.55 (0.31-0.96)
P = .037
DX -> CEX
D-> CEF
ER = Estrogen receptor
PR = Progesterone receptor
HER2 = Human epidermal growth factor receptor 2
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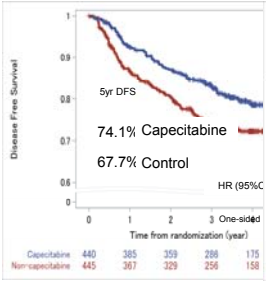
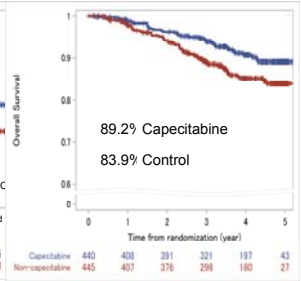
CREATE-X

Disease Free Survival

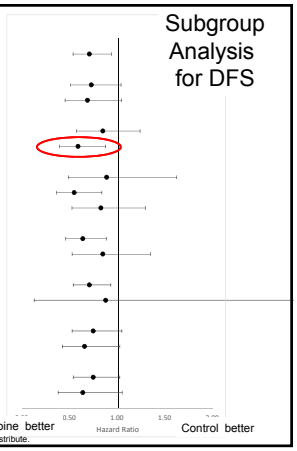


Overall Survival



Subgroup Analysis for DFS

Category (n)	HR (95%CI)
Total (885)	0.70 (0.53-0.93)
Age ≤50 (531)	0.72 (0.50-1.03)
>50 (354)	0.68 (0.45-1.04)
HR + (561)	0.84 (0.57-1.23)
HR – (296)	0.58 (0.39-0.87)
ypN0 (345)	0.88 (0.48-1.62)
ypN1 (339)	0.54 (0.36-0.83)
ypN2or3 (199)	0.82 (0.52-1.29)
Path grade 0-1b (482)	0.63 (0.45-0.88)
by NAC 2,3 (385)	0.84 (0.52-1.34)
Taxane + (849)	0.70 (0.53-0.93)
- (36)	0.87 (0.12-6.24)
5FU containing + (529)	0.74 (0.52-1.04)
- (356)	0.65 (0.42-1.02)
Japanese (599)	0.74 (0.53-1.02)
Korean (286)	0.63 (0.37-1.05)



Capecitabine better — Control better

ETNA (Evaluating Treatment with Neoadjuvant Abraxane)

randomized phase III study comparing
neoadjuvant nab-Paclitaxel (nab-P) versus Paclitaxel (P)
both followed by anthracycline regimens in women with HER2-negative high-risk breast cancer: A Michelangelo study

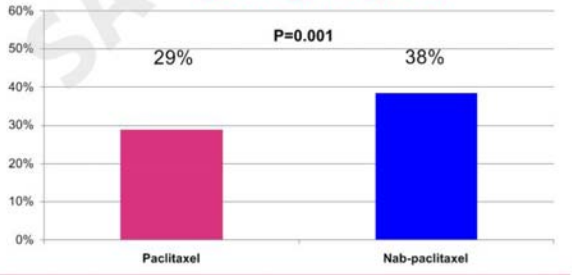
in collaboration with GEICAM and BCRC-WA

Luca Gianni, Mauro Mansutti, Antonio Anton, Lourdes Calvo, Giancarlo Bisagni, Begoña Bermejo, Vladimir Semiglazov, Marc Thill, Jose Ignacio Chacon, Arlene Chan, Serafin Morales, Isabel Alvarez, Arrate Plazaola, Milvia Zambetti, Andrew D. Redfern, Christian Dittrich, Rebecca Alexandra Dent, Domenico Magazzù, Pinuccia Valagussa, Ignacio Tusquets

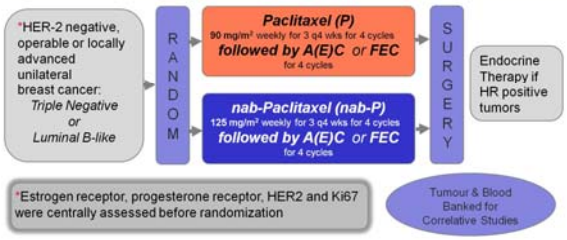
Presented By Luca Gianni at 2016 ASCO Annual Meeting

Gepar septo

Primary endpoint (pCR: ypT0 ypN0)



Scheme of the Phase III randomized ETNA trial



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Primary endpoint: pCR rate

	ITT population	
	P (349)	*nab*-P (346)
pCR rate	**18.6%**	**22.5%**
95% CI	14.7 - 23.1	18.2 - 27.3
Difference: P - *nab*-P (95% CI)	**-3.9 (-9.9, 2.1)**	
***Odds ratio (95% CI)**	**0.77 (0.52, 1.13)**	
***p-value**	**0.1858**	

*Cochran-Mantel-Haenszel test, controlling for tumor subtype and disease stage and quantified by OR and rate difference

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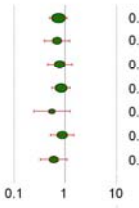
Subgroup Analysis: pCR rate

Category	Subgroup	*nab*-P %	P %	*nab*-P	P	OR (95% CI)
	All	22.5	18.6			0.77 (0.52 - 1.13)
Tumor subtype	Luminal B-like	13.9	10.0			0.69 (0.39 - 1.21)
	Triple negative	41.3	37.3			0.85 (0.49 - 1.45)
Stage	Non-locally advanced	23.1	20.7			0.87 (0.57 - 1.31)
	Locally advanced	20.7	12.5			0.55 (0.24 - 1.25)
Age	<=50	22.0	20.7			0.90 (0.53 - 1.51)
	>50	23.1	16.1			0.63 (0.35 - 1.14)



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Chemotherapy abstracts

- Overall anthracycline-taxane based regimens superior to docetaxel-cytoxan but..
  - Benefit greatest in ER-negative cancers and no difference in ER+ node-negative cancers
- Capecitabine appears effective in TNBC
- Nab-paclitaxel not the winner in ETNA, even in TNBC
  - Anthracycline-standard taxanes ± carboplatin for TNBC pre-op
  - ER-positive cancers in general have poor response to pre-op chemotherapy (even in luminal B), consider pre-op endocrine therapy (ALTERNATE trial)

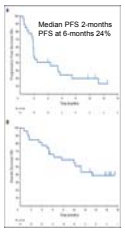
Efficacy of single agent PDl-1 antibodies in heavily pre-treated TNBC

KEYNOTE-012

TNBC
PD-L1+
Median prior Rx 2

Pembrolizumab 10mg/kg q2w

Best response	n=27
Overall response	19%
Complete response	4%
Partial response	15%
Stable disease	26%
Progressive disease	48%



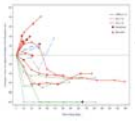
Nanda et al J Clin Oncol 2016

TNBC
69% PD-l1+ (IHC 2/3)
89% prior Rx ≥ 4*

Alezolizumab q3w*

* 15mg/kg, 20mg/kg or 1200 flat dose
* not all in metastatic setting

Best response	n=21
Overall response	19%
Complete response	9%
Partial response	9%
PFS at 24-weeks	33%



Median DOR: NR
(range: 18 to 56+ weeks)

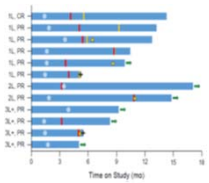
Emens et al Proc AACR 2015

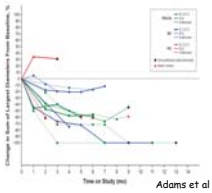
Phase Ib study of atezolizumab + nab-paclitaxel: results

Best response	First-line (n=13	Second-line (n=9)	Third-line (n=10)
Overall response*	46%	22%	40%
Complete response	8%	0%	0%
Partial response	38%	22%	40%
Stable disease	38%	67%	30%
Progressive disease	15%	0%	30%

*Responses seen in PDL1 + and PDL1 - cancers

AE	All grade	Grade 3-4
Fatigue	34%	-
Pyrexia	25%	-
Nausea	16%	-
Diarrhea	19%	1%
Neuropathy	19%	-
Neutropenia	22%	9%

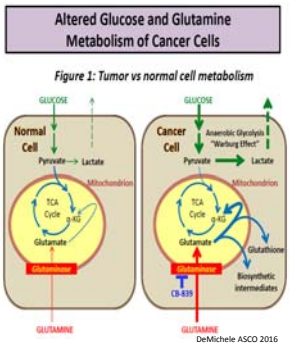




Adams et al ASCO 2016

Tumor cells are reliant on glutamine for growth

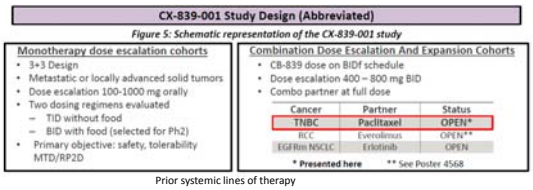
- Glutamine is the most abundant amino acid in the plasma
- Glutamine is converted to glutamate by the enzyme, **glutaminase**
- Glutamate and its metabolites drive crucial cellular pathways that support cancer cell growth
- Glutaminase is encoded by the gene *GLS*, expression of which is associated with metastases and increased in TNBC
- CB-839 is a potent and selective inhibitor of glutaminase



Gross Mol Cancer Ther 2014

DeMichele ASCO 2016

CX-889-001: Study design and prior therapies



Prior systemic lines of therapy

Median range	3-5 (0 – 8)
0	13%
1 - 2	33%
3 - 4	13%
≥ 5	40%

DeMichele ASCO 2016

CX-889-001: Results and safety

Response	Total	400mg BID	600mg BID	800mg BID
	14	7	4	3
PR	21%	0	50%	33%
SD	43%	43%	25%	67%
CBR	64%	43%	75%	100%
PD	36%	57%	25%	0

Response	Prior taxane (Adj/met)	Prior taxane (neo/adj)	No taxane
	5	4	5
PR	40%	25%	
CBR	60%	50%	80%

Adverse event (all grades)	Paclitaxel/CB-839	CB-839
Alopecia	33%	0%
Fatigue	33%	33%
Neutropenia	33%	5%
Vomiting	33%	14%
Nausea	27%	26%
Photophobia	27%	11%
Elevated LFTs	20%	14%
All grade ≥3 AE	33%*	30%

* neutropenia, lymphopenia, nephrolithiasis

DeMichele ASCO 2016

A Prospective Analysis of Surgery and Survival in Stage IV Breast Cancer (TBCRC 013)

King TA, Lyman JP, Gonen M, Reyes S, Boafo C, Plichta J, Hwang ES, Rugo HS, Liu M, Boughey JC, Jacobs LK, Krontiras H, McGuire K, Storniolo A, Nanda R, Golshan M, Isaacs C, Meszoely IM, Van Poznak C, Babiera G, Norton L, Morrow M, Wolff AC, Winer EP, Hudis CA

Translational Breast Cancer Research Consortium

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TBCRC 013: Cohort A Outcomes

- 112pts with de novo Stage IV disease and an intact primary tumor
- 1st line systemic therapy per treating physician
- Responders to 1st line therapy (stable, partial, or complete response of distant disease per treating physician) offered opportunity to discuss elective surgery
- Elective surgery - surgery performed in the absence of local symptoms or the need for local control
- Patient and tumor characteristics, response to systemic therapy and surgery of the primary tumor were correlated with 3yr OS using log rank, Kaplan Meier and Cox regression

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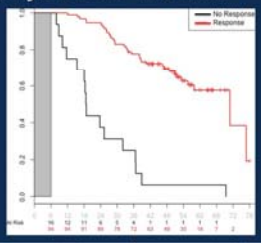
Survival: Responders vs Non-Responders Landmark analysis at 6 months

6 mos, surrogate for time to response assessment after 1st line therapy, per treating physician



	N	median survival, mos	30 mo survival (95%CI)	P
R	90	65 mos (52-NR)	78% (70-87)	< 0.001
NR	16	13 mos (9-31)	24% (10-55)	

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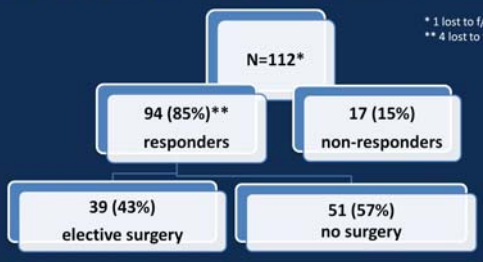
TBCRC 013: Surgical Uptake



* 1 lost to f/u
** 4 lost to f/u

Median time to elective surgery 7 mos (3-20mos)

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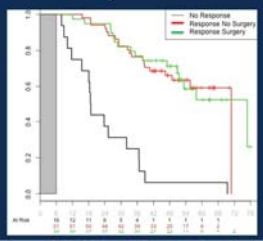
Multivariate Analysis: Survival

Stepwise Cox regression: including age, size, ECOG, HR, Her2, tumor grade, response and surgery



	N	Median Survival, mos	30 mos survival (95%CI)
Non-Responders	16	13 mos (9-31)	24% (10-55)
Responders, No Surgery (red)	51	65 mos (50-NR)	76% (66-89)
Responders, Surgery (green)	39	71 mos (46-NR)	77% (65-91)

ASCO ANNUAL MEETING '16

Presented By Tari King at 2016 ASCO Annual Meeting

A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish Study (Protocol MF07-01)

Atilla Soran, MD, MPH, FACS, Magee-Womens Hospital of UPMC
Vahit Ozmen, Serdar Ozbas, Hasan Karanlik, Mahmut Muslumanoglu, Abdullah Igci, Zafer Canturk, Zafer Utkan, Cihangir Ozaslan, Turkkan Evrensel, Cihan Uras, Erol Aksaz, Aykut Soyder, Umit Ugurlu, Cavit Col, Neslihan Cabioğlu, Betül Bozkurt, Efe Sezgin, Ronald Johnson, Barry Lembersky.
On behalf of the Turkish Federation of Breast Diseases Societies
ClinicalTrials.gov identifier number is NCT00557986

Presented By Atilla Soran at 2016 ASCO Annual Meeting

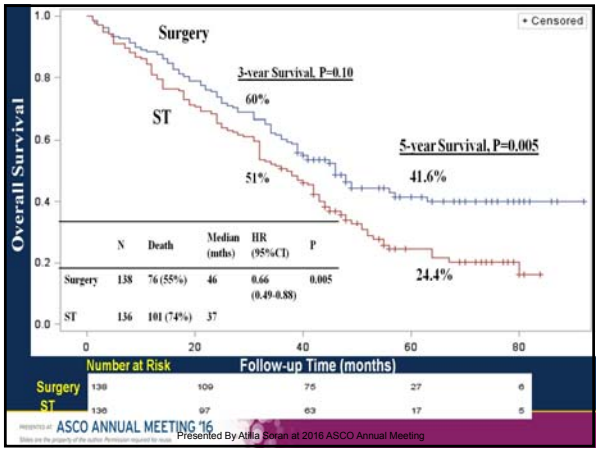
MF07-01: Design

At Presentation Stage IV BC

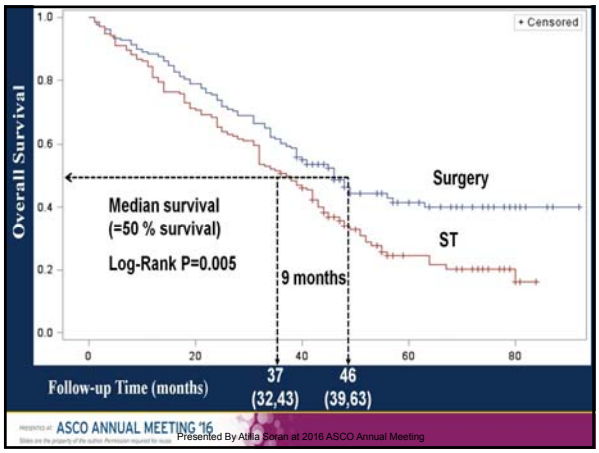
- Systemic Therapy → Local Therapy for local progression
- Local Therapy of Breast ± Axilla → Systemic therapy

Overall Survival
Local Progression
Morbidity
QoL

Presented By Atilla Soran at 2016 ASCO Annual Meeting



Presented By Atilla Soran at 2016 ASCO Annual Meeting



Presented By Attila Soran at 2016 ASCO Annual Meeting

Practice changing?

- To some extent:
  - Extending AI therapy beyond 5-years?
  - Benefit of adjuvant anthracyclines in high risk disease
  - ? Biosimilars are the future
- Confirmatory:
  - First-line benefit of palbociclib in ER+ MBC
  - Capecitabine activity in TNBC
- Equipoise:
  - Role of breast surgery in metastatic disease

Practice changing?

- Disappointing:
  - T-DM1 as pre-operative therapy in HER2+ cancers (less toxic but not quite ae effective)
- Promising:
  - Role of liquid biopsies
  - Immune check-point inhibitors in TNBC
  - Glutaminase inhibition
  - Anti-Trop-2-SN-38 antibody-drug conjugate, (IMMU-132)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