Genitourinary Cancer Update
ASCO 2017

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Disclosures

Grants to institution	Consultant	
Boehringer-Ingelheim	Pfizer	Uptodate (author)
Bayer	Genentech	PER (speaker)
Onyx-Amgen	Novartis	Biotheranostics
Merck	Argos	Exelixis
Celgene	Merck	Bristol-Myers-Squibb
Pfizer	Sanofi	Janssen
Sanofi	Agensys	Amgen
Novartis	Astrazeneca	Eisai
	Clinical Care Options	NCCN

PROSTATE CANCER

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LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

Karim Fizazi,[1] NamPhuong Tran,[2] Luis Fein,[3] Nobuaki Matsubara,[4] Alfredo Rodriguez-Antolin,[5] Boris Y. Alekseev,[6] Mustafa Özgüroğlu,[7] Dingwei Ye,[8] Susan Feyerabend,[9] Andrew Protheroe,[10] Peter De Porre,[11] Thian Kheoh,[12] Youn C. Park,[13] Mary B. Todd,[14] Kim N. Chi,[15] on behalf of the LATITUDE Investigators

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

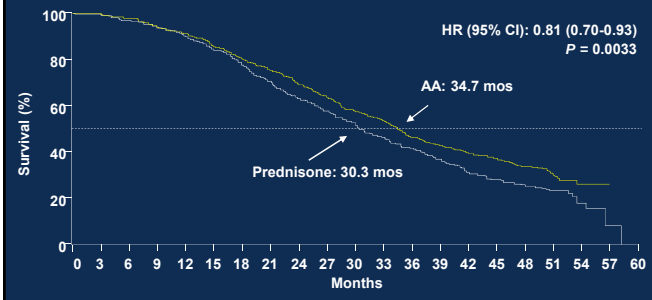
N Engl J Med. 2017 June 4 [Epub ahead of print].

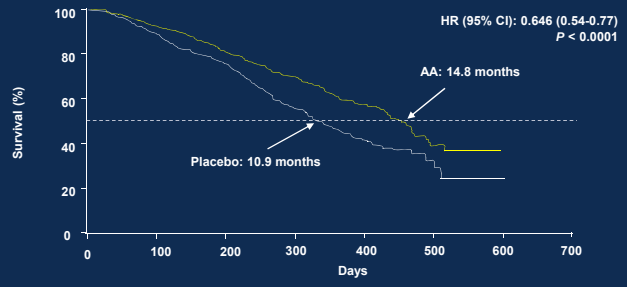
ADT + docetaxel: a new standard of care for men with mCNPC and high metastatic burden (2015)

Overall Survival	ADT + DOC	ADT		
	Median (mos)	Median (mos)	HR (95% CI)	*P* Value
GETUG-15[1]	62.1	48.6	0.88 (0.68-1.14)	0.3
CHAARTED[2]	57.6	47.2	0.73 (0.59-0.89)	0.0018
STAMPEDE[3]	60	45	0.76 (0.62-0.92)	0.005

1. Gravis G, et al. *Eur Urol*. 2016:70:256-262. 2. Sweeney C, et al. *N Engl J Med*. 2015;373:737-746; Sweeney C, et al. *Ann Oncol*. 2016;27(Suppl 6):243-265. 3. James N, et al. *Lancet*. 2016;387:1163-1177; and Vale C, et al. *Lancet Oncol* 2016;17:243-256.

Abiraterone acetate (AA) extends survival in mCRPC
(pre and post-docetaxel)





de Bono JS, et al. *N Engl J Med*. 2011; 364:1995-2005;
Ryan CJ, et al. *N Engl J Med*. 2013;368:138-148;

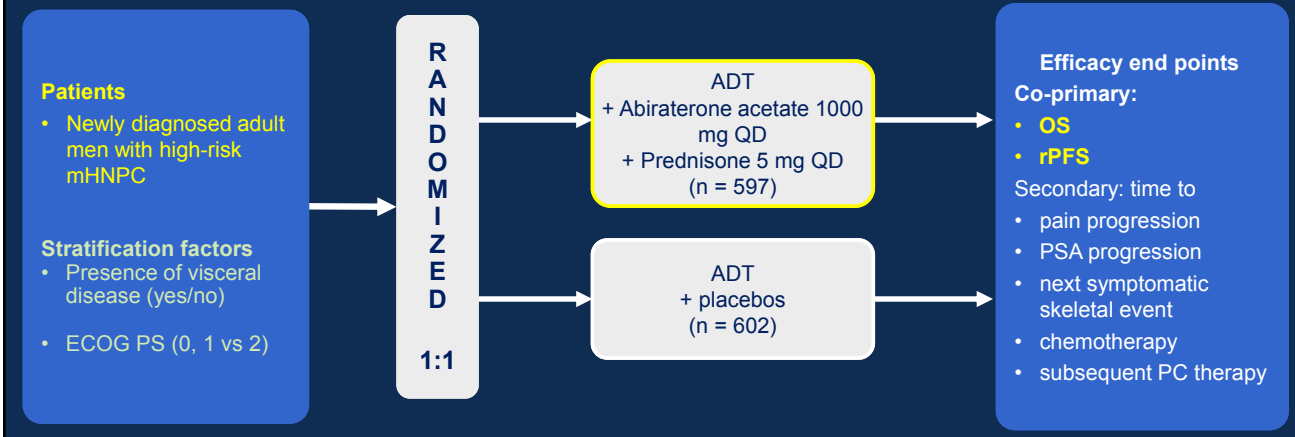
LATITUDE: Objective

To evaluate the addition of AA + P to ADT on clinical benefit in men with newly diagnosed, high-risk, mCNPC

High-risk defined as meeting at least 2 of 3 high-risk criteria:
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

Presented by: Karim Fizazi

Overall study design of LATITUDE

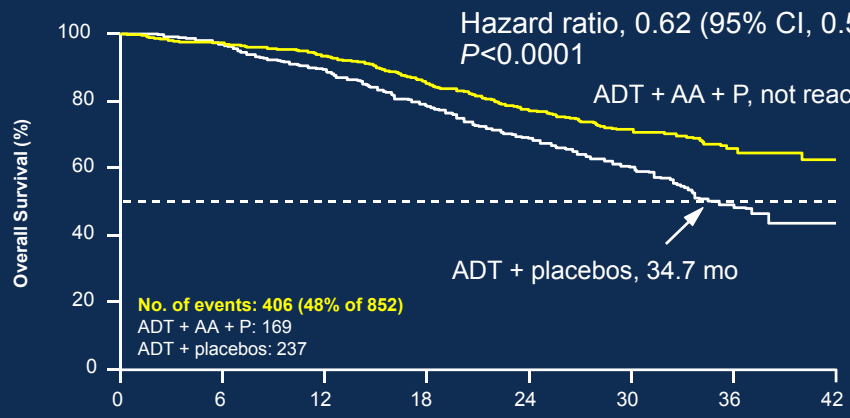


- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results**

LATITUDE Treatment arms were well balanced

	ADT + AA + P (n = 597)	ADT + Placebos (n = 602)
Median age, years (range)	68.0 (38-89)	67.0 (33-92)
Gleason score ≥ 8 at initial diagnosis	98%	97%
Patients with ≥ 3 bone metastases at screening	98%	97%
Extent of disease Bone Liver Lungs Node	97% 5% 12% 47%	98% 5% 12% 48%
Baseline pain score (BPI-SF Item 3) 0-1 2-3 ≥ 4	50% 22% 29%	50% 24% 27%

LATITUDE: Statistically significant 38% risk reduction of death



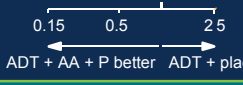
OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

Median follow-up: 30.4 months

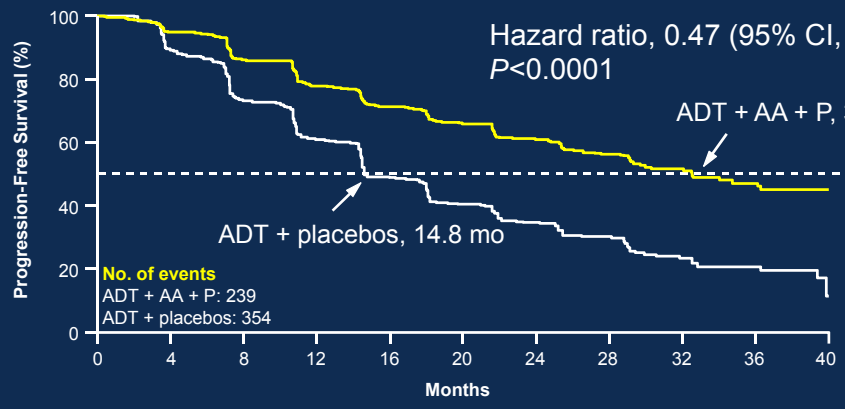
No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

LATITUDE: OS benefit consistently across subgroups

Subgroup	ADT + AA + P	ADT + placebos	Hazard ratio (95% CI)
	Median (mo)		
All patients	NR	34.7	0.63 (0.51-0.76)
ECOG			
0	NR	38.2	0.64 (0.48-0.86)
1-2	NR	31.3	0.61 (0.46-0.79)
Visceral disease			
Yes	NR	32.3	0.51 (0.33-0.79)
No	NR	35.1	0.66 (0.53-0.83)
Gleason score			
< 8	NR	NR	0.62 (0.18-2.11)
≥ 8	NR	34.7	0.63 (0.51-0.77)
Bone lesions			
≤ 10	NR	NR	0.65 (0.45-0.96)
> 10	NR	31.3	0.60 (0.47-0.75)
Region			
Asia	NR	NR	0.73 (0.42-1.27)
East Europe	NR	30.5	0.50 (0.36-0.69)
West Europe	NR	38.1	0.75 (0.51-1.09)
Rest of world	NR	31	0.70 (0.45-1.09)



LATITUDE:
Significant 53% risk reduction of radiographic progression or death



No. at risk											
ADT + AA + P	597	533	464	400	353	316	251	177	102	51	21
ADT + placebos	602	488	367	289	214	168	127	81	41	17	7

LATITUDE: Significant improvement in all secondary end points

Secondary End Points	ADT + AA + P (n = 597) Median (months)	ADT + placebos (n = 602) Median (months)	HR (95% CI)	*P* Value
Time to PSA progression	33.2	7.4	0.30 (0.26-0.35)	<0.0001
Time to pain progression	NR	16.6	0.70 (0.58-0.83)	<0.0001
Time to next symptomatic skeletal event	NR	NR	0.70 (0.54-0.92)	0.0086
Time to chemotherapy	NR	38.9	0.44 (0.35-0.56)	<0.0001
Time to subsequent prostate cancer therapy	NR	21.6	0.42 (0.35-0.50)	<0.0001

NR = not reached.

LATITUDE: Subsequent life-prolonging therapy

	ADT + AA + P (n = 597)	ADT + placebos (n = 602)
	n (%)	n (%)
Patients eligible*	n = 314 (53%)	n = 469 (78%)
Patients who received life-prolonging therapy	125 (40)	246 (52)
Docetaxel	106 (34)	187 (40)
Enzalutamide	30 (10)	76 (16)
AA-P	10 (3)	53 (11)
Cabazitaxel	11 (4)	30 (6)
Radium-223	11 (4)	27 (6)

*Patients who discontinued treatment and were eligible for subsequent therapy.

LATITUDE: Summary of adverse events

	ADT + AA + P (n = 597)	ADT + placebos (n = 602)
Adverse Events (AE)	n (%)	n (%)
Any AE	558 (93)	557 (93)
Grade 3 or 4 AE	374 (63)	287 (48)
Any Serious AE	165 (28)	146 (24)
Any AE leading to treatment discontinuation	73 (12)	61 (10)
AE leading to death	28 (5)	24 (4)

LATITUDE: Adverse events of special interest

Adverse Events	ADT + AA + P (n = 597)		ADT + placebos (n = 602)	
	Grade 3	Grade 4	Grade 3	Grade 4
	%		%	
Hypertension	20	0	10	0.2
Hypokalemia	10	0.8	1	0.2
ALT increased	5	0.3	1	0
AST increased	4	0.2	1	0
Hyperglycemia	4	0.2	3	0
Bone pain	3	0	3	0
Cardiac disorder	3	0.8	1	0
Anemia	2	0.5	4	0.2
Back pain	2	0	3	0
Fatigue	2	0	2	0
Spinal cord compression	2	0	1	0.5

LATITUDE: Safety

- Hypertension
  - Only rarely required treatment discontinuation
- Hypokalemia
  - Only 2 patients discontinued treatment due to hypokalemia
  - No hypokalemia-related deaths
- Cardiovascular events
  - 2 patients in each group died of cerebrovascular events;
  - 10 (ADT + AA + P) versus 6 (ADT + placebos) died of cardiac disorders

LATITUDE: Conclusions

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
  - Significantly improved OS with a 38% reduction in the risk of death
  - Significantly prolonged rPFS (53% reduction) and all secondary end points
- The overall safety profile of ADT + AA + P was consistent with prior studies in patients with Mcrpc
- These findings indicate that the addition of AA + P to ADT can potentially be considered a new standard of care for patients with high-risk, newly diagnosed mCNPC

MRC Clinical Trials Unit | Smarter studies Global impact Better health | UNIVERSITY OF BIRMINGHAM | CANCER RESEARCH UK | UCL

Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

Nicholas James
University of Birmingham and Queen Elizabeth Hospital Birmingham
on behalf of

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators

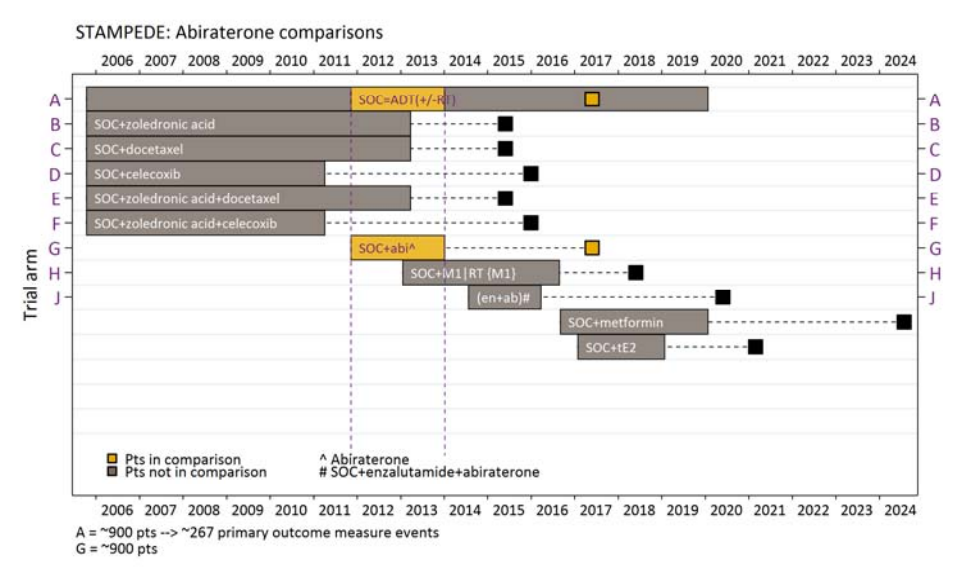
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

STAMPEDE: MULTI-ARM MULTI-STAGE PHASE III



STAMPEDE: Inclusion criteria

Newly-diagnosed
Any of:
- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:
- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

All patients
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampedetrial.org

STAMPEDE: Outcome measures

Primary outcome measure
- Overall survival

Secondary outcome measures
- Failure-free survival (FFS)
- Toxicity
- Quality of life
- Skeletal-related events
- Cost effectiveness

FFS definition
First of:
- PSA failure
- Local failure
- Lymph node failure
- Distant metastases
- Prostate cancer death

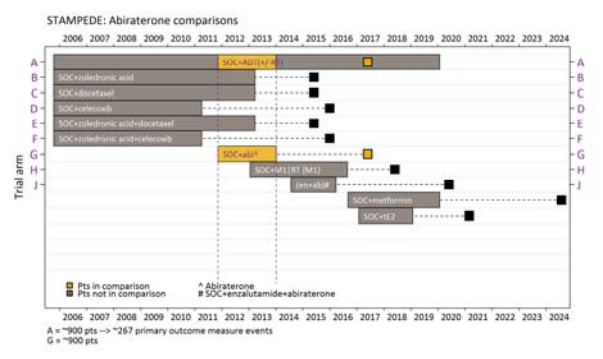
PSA failure definition
PSA fall >= 50%
→ 24wk nadir + 50% **and**
→ >4ng/ml

PSA fall of <50%
→ failure at t=0

STAMPEDE: Accrual

Comparison

Open: Nov-2011
Closed: Jan-2014
Accrual: 1917



Number of patients

957 **A** Standard-of-care* (SOC): ADT+/- XRT

960 **G** SOC + abiraterone acetate + prednisolone (SOC+AAP)

*SOC = ADT ± RT

STAMPEDE: Patient characteristics

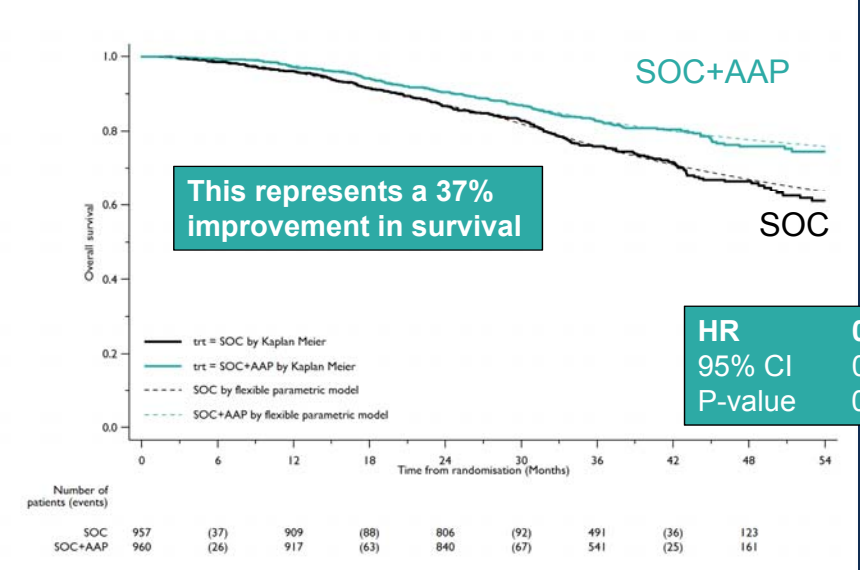
1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
67yr	Median age (min 39, max 85)	[s]
52%	Metastatic (88% Bony mets)	[s]
20%	N+M0	
28%	N0M0	
99%	LHRH analogues	[s]
41%	Planned for RT (96% of N0M0 pts; 62% of N+M0 pts)	[s]
5%	Previous local therapy	

Balanced by arm

[s] = Stratification factors

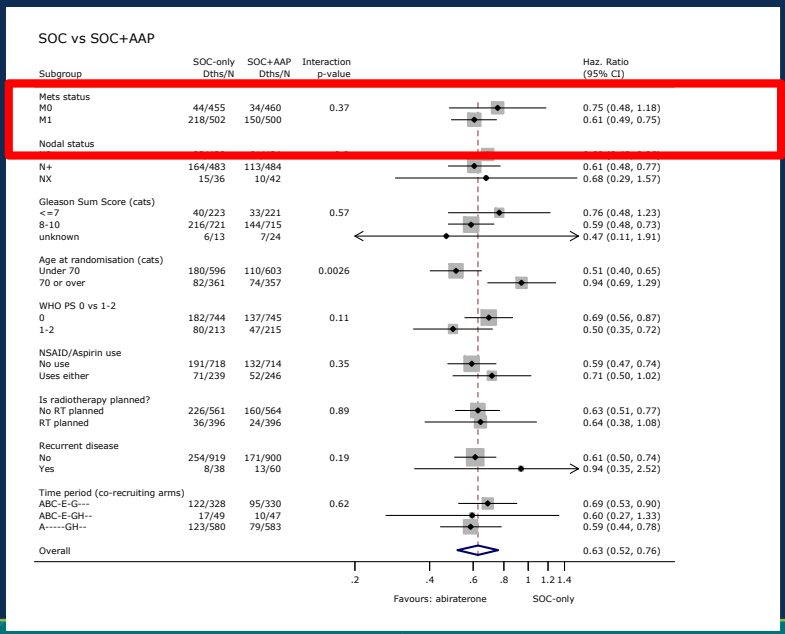
Also stratified on
:: hospital
:: NSAID/aspirin

STAMPEDE: Overall Survival



HR	**0.63**
95% CI	0.52 to 0.76
P-value	0.00000115

STAMPEDE: OS in subsets



No evidence of heterogeneity by stratification factors

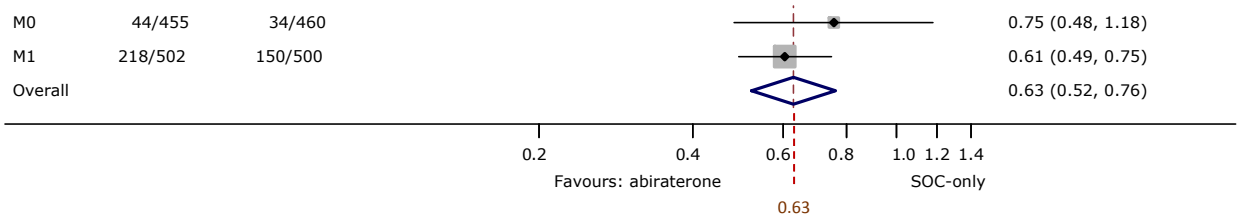
5

STAMPEDE: OS by metastatic status – pre-planned analysis

Mets * treatment interaction P-value = 0.37

SOC vs SOC+AAP

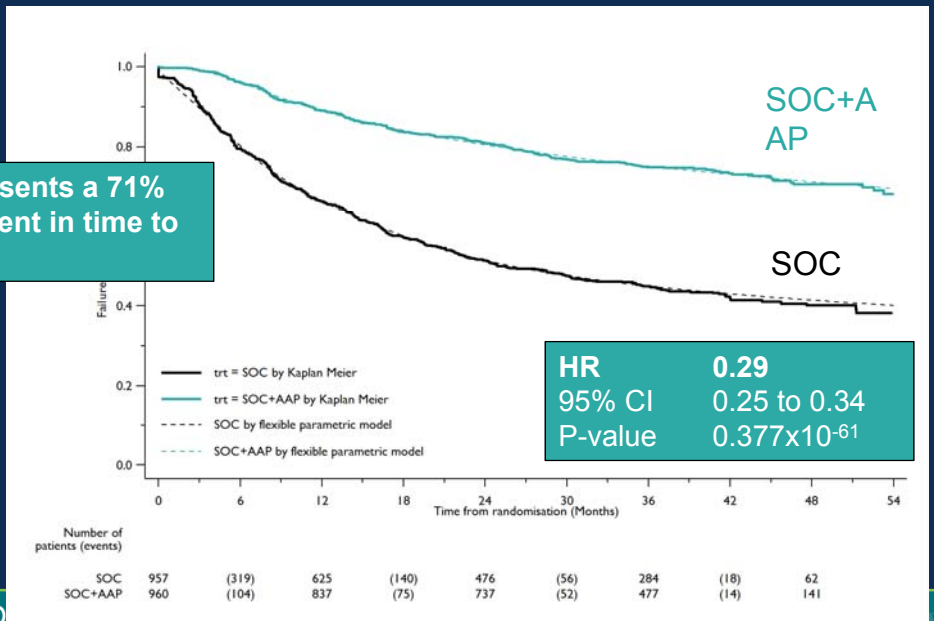
Mets status	SOC-only Dths/N	SOC+AAP Dths/N	Haz. Ratio (95% CI)
M0	44/455	34/460	0.75 (0.48, 1.18)
M1	218/502	150/500	0.61 (0.49, 0.75)
Overall			0.63 (0.52, 0.76)



No evidence of heterogeneity by metastatic status

STAMPEDE: FFS

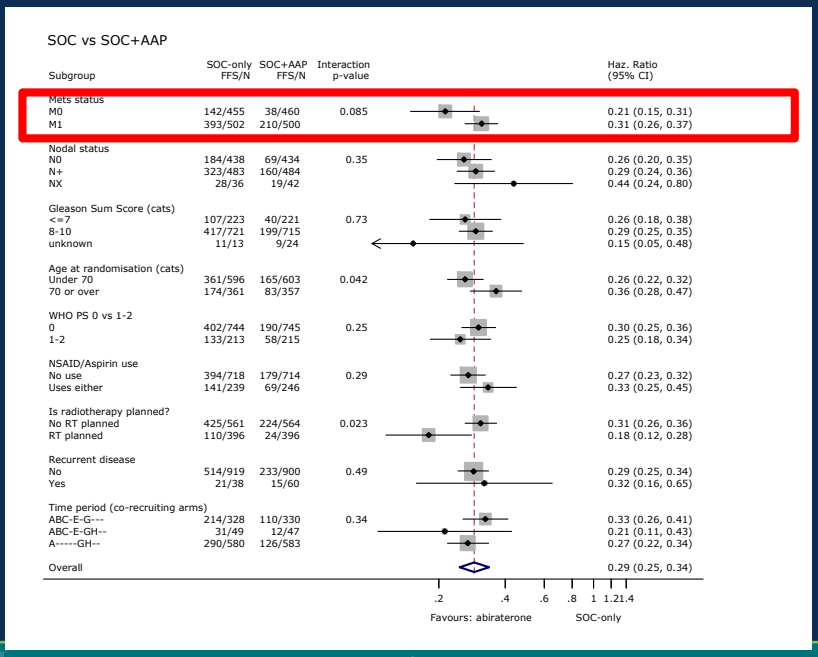
This represents a 71% improvement in time to failure



HR	**0.29**
95% CI	0.25 to 0.34
P-value	0.377×10^{-61}

Slide 29

5 Should there not be a p value for the interaction?
Nick James, 5/16/2017

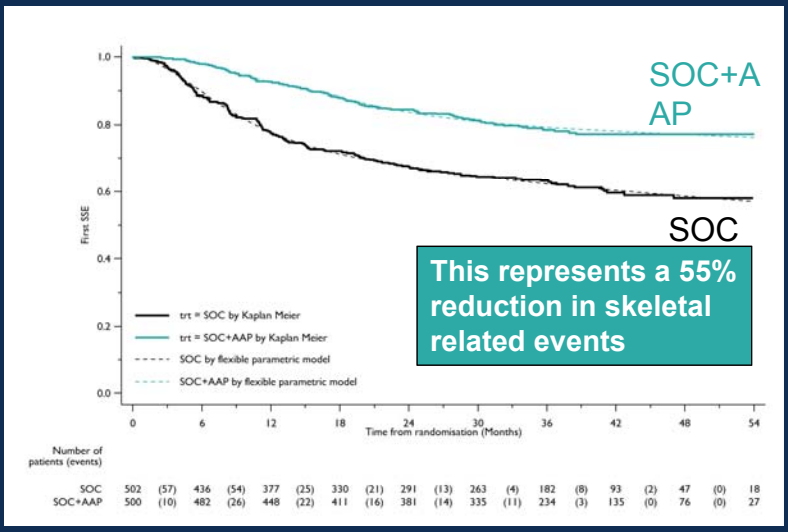


STAMPEDE: FFS subset analyses

Mets * treatment interaction P-value = 0.085

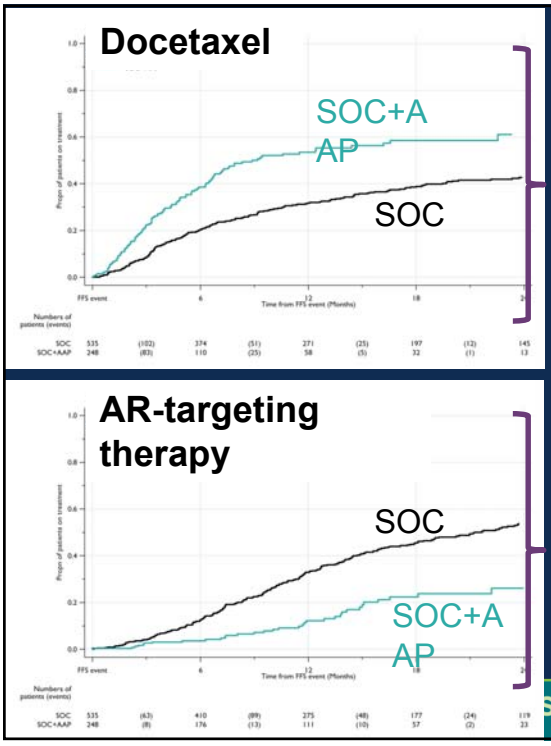
No evidence of heterogeneity by stratification factors

STAMPEDE: Skeletal related outcomes in M1 patients



This represents a 55% reduction in skeletal related events

HR	**0.45**
95% CI	0.36 to 0.58



STAMPEDE: Therapy for progression

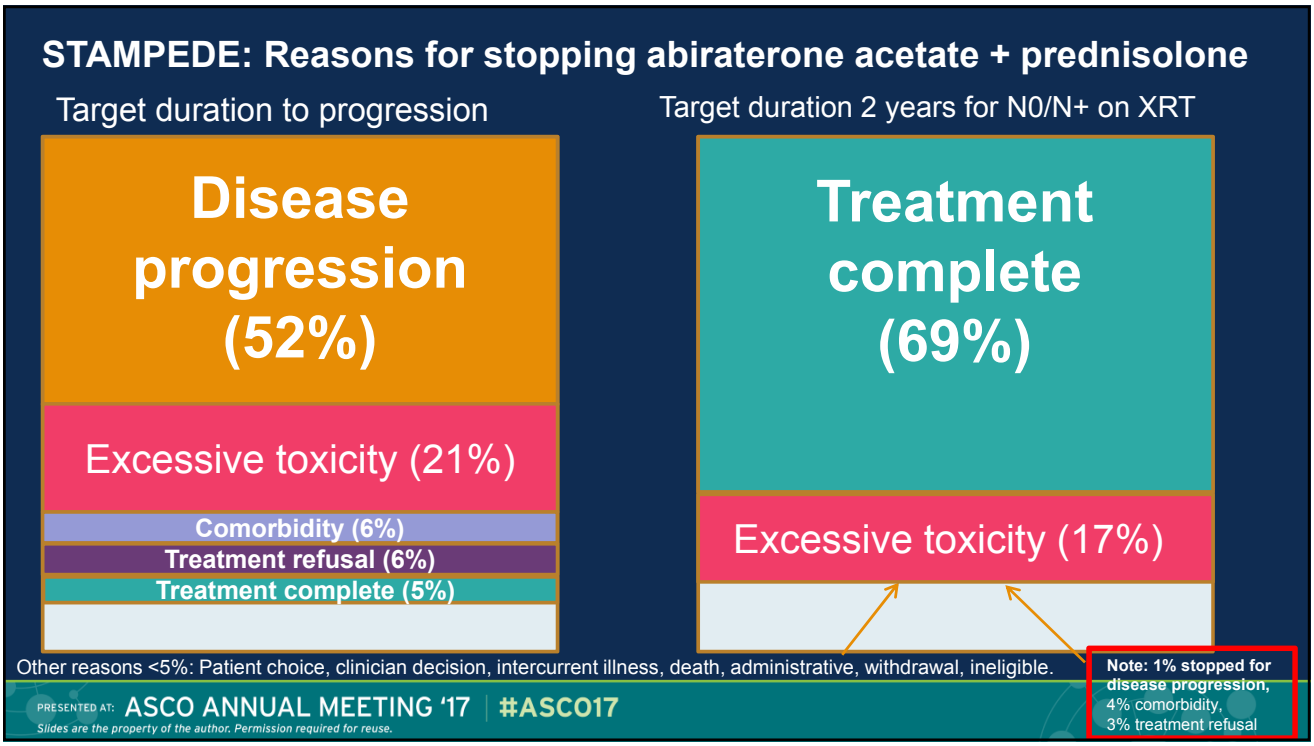
Treatment started since first progression	A *SOC*	G *SOC+abi*
Patients randomised	957	960
Patients with progression	535 (56%)	248 (26%)
Reported new treatment	477 (89%)	196 (79%)
Reported "life-prolonging" treatment	310 (58%)	131 (53%)
Docetaxel	200 (37%)	115 (46%)
Enzalutamide	138 (26%)	25 (10%)
Abiraterone	120 (22%)	8 (3%)
Radium-223	24 (5%)	19 (8%)
Cabazitaxel	28 (5%)	15 (6%)

Graph timed from first FFS event

STAMPEDE: Toxicities

	SOC-only	SOC+AAP
Safety population		
Patients included in adverse event analysis	960	948
Grade 1-5 AE	950 (99%)	943 (99%)
Grade 3-5 AE	315 (33%)	443 (47%)
Grade 5 AE	3	9
Grade 3-5 AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	133 (14%)	129 (14%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*):	41 (4%)	92 (10%)
Musculoskeletal disorder:	46 (5%)	68 (7%)
Gastrointestinal disorder:	40 (4%)	49 (5%)
Hepatic disorder (*incl. increased AST, increased ALT*):	12 (1%)	70 (7%)
General disorder (*incl. fatigue, oedema*):	29 (3%)	45 (5%)
Respiratory disorder (*incl. breathlessness*):	23 (2%)	44 (5%)
Lab abnormalities (*incl. hypokalaemia*):	21 (2%)	34 (4%)

STAMPEDE: Reasons for stopping abiraterone acetate + prednisolone



STAMPEDE: Conclusions

- In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
  - Overall survival by 37%
  - Failure free survival by 71%
  - Symptomatic skeletal events by 55%
- Treatment was well tolerated
- **Abiraterone acetate + prednisolone should be part of the standard of care for men starting long term androgen deprivation therapy**

Ongoing phase III trials of combinations for advanced prostate cancer

Trial	Standard arm	Experimental arm
Metastatic castration-sensitive		
ENZAMET	ADT + Bicalutamide (or similar) (+/- Docetaxel)	ADT + Enzalutamide (+/- Docetaxel)
STAMPEDE[1]	ADT + Abiraterone	ADT + Abiraterone+Enzalutamide
ARASENS	ADT + Docetaxel	ADT + Docetaxel+Darolutamide (ODM201)
ARCHES	ADT + Placebo (+/- Docetaxel)	ADT + Enzalutamide (+/- Docetaxel)
TITAN	ADT + Placebo (+/- Docetaxel)	ADT + Apalutamide (ARN509) (+/- Docetaxel)
SWOG-1216	ADT + Bicalutamide	ADT + Orteronel (TAK700)
PEACE-1	ADT (+/- Docetaxel +/-Local XRT)	ADT (+/- Docetaxel +/-Local XRT) +Abiraterone
Metastatic castration-resistant		
JANSSEN sponsor	Abiraterone	Abiraterone + Enzalutamide
US Intergroup	Enalutamide	Enzalutamide + Abiraterone
BAYER sponsor[2]	Abiraterone	Abiraterone + Radium223

[1]Non-metastatic high-risk disease allowed; [2]Requires asymptomatic/minimally symptomatic bone metastasis

A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

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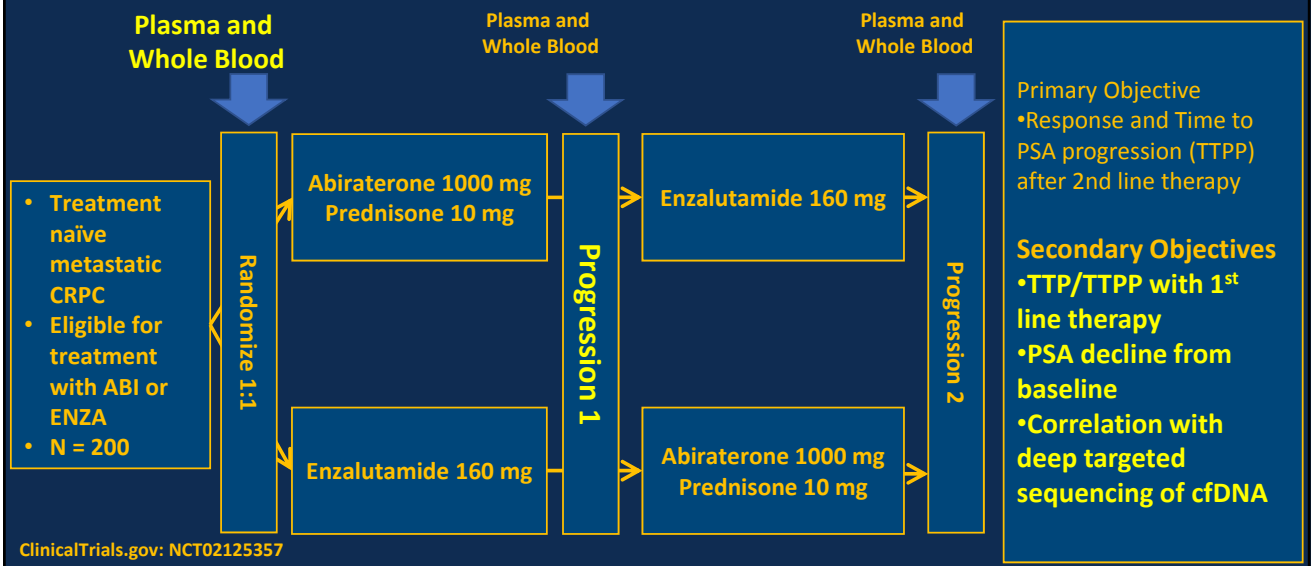
mCRPC Randomized II Abi→Enza vs. Enza→Abi: Background

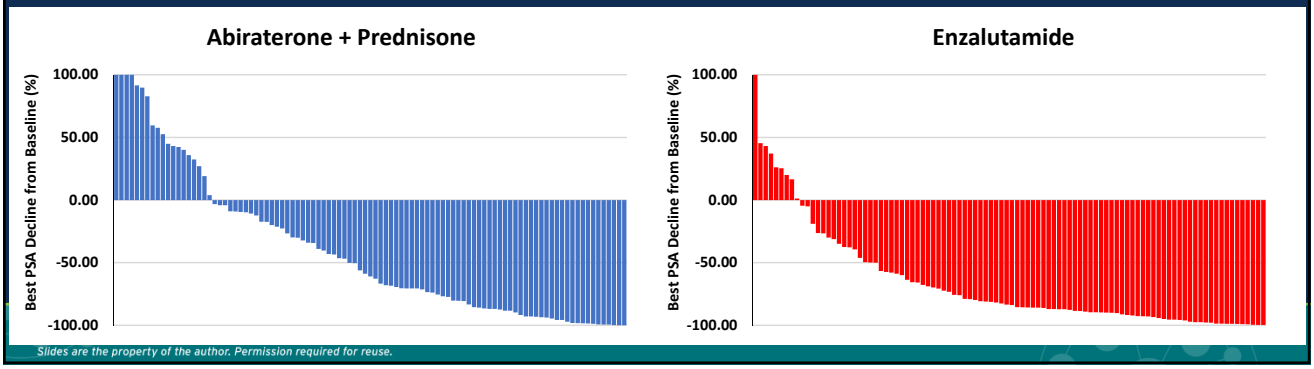
- Abiraterone + prednisone and enzalutamide are indicated as first-line therapy for mCRPC
  - Have not been directly compared
  - Optimal treatment sequencing not evaluated prospectively
  - Need for predictive biomarkers

mCRPC Randomized II Abi→Enza vs. Enza→Abi Study Schema

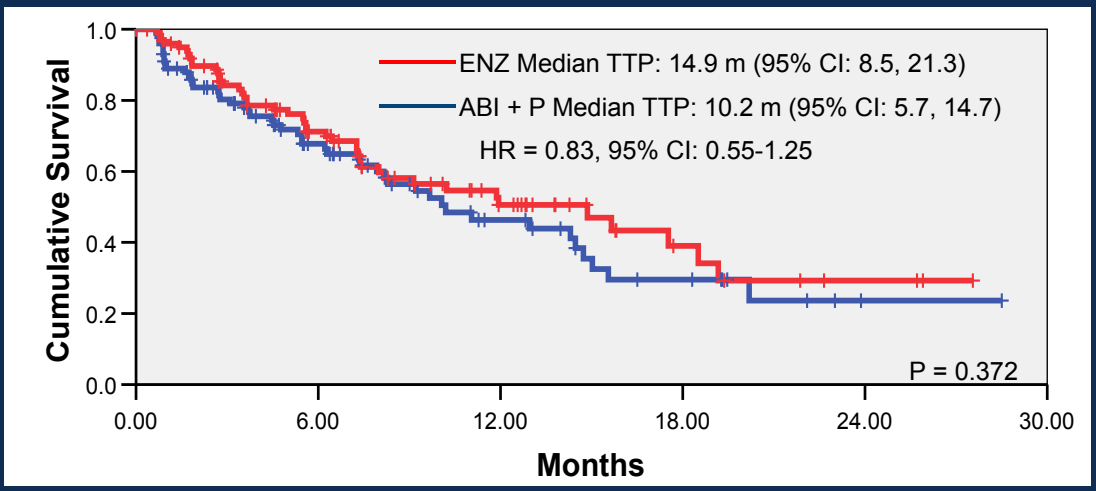


mCRPC Randomized II Abi→Enza vs. Enza→Abi: Best 1st Line PSA decline at 12 weeks

	Abiraterone + P N=99	Enzalutamide N=98	P-value
PSA Decline ≥ 30%	64 (65%)	83 (85%)	0.0012
PSA Decline ≥ 50%	54 (55%)	75 (77%)	0.0012
No PSA Decline	20 (20%)	10 (10%)	0.0501

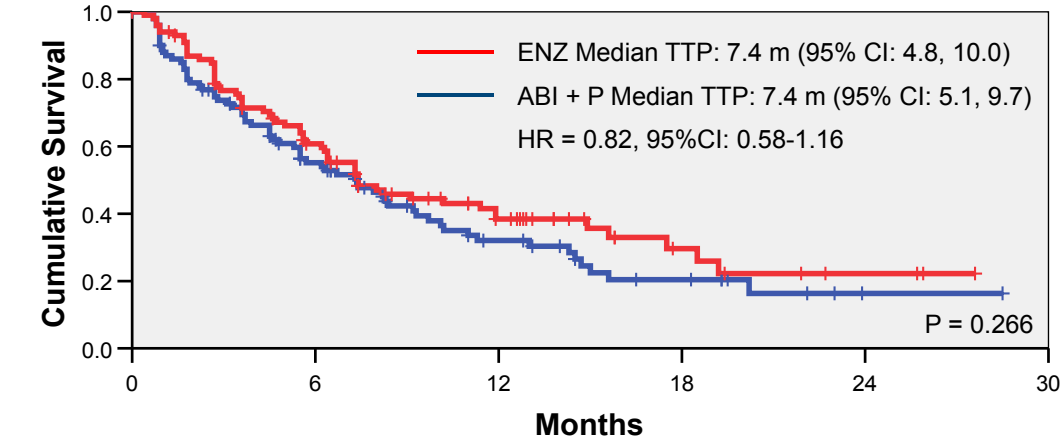


mCRPC Randomized II Abi→Enza vs. Enza→Abi: Time to PSA Progression (Confirmed)



*PCWG3: ≥ 25% and ≥ 2 ng/mL above nadir/baseline

mCRPC Randomized II Abi→Enza vs. Enza→Abi: Time to Radiographic/clinical Progression



*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease

mCRPC Randomized II Abi→Enza vs. Enza→Abi: Conclusions

- Higher PSA response with enzalutamide compared to abiraterone + prednisone
- No difference in time to progression or time to PSA progression

PLATO: A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study of Continued Enzalutamide Post Prostate-Specific Antigen Progression in Men With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

Gerhardt Attard,[1] Michael Borre,[2] Howard Gurney,[3] Yohann Loriot,[4] Corina Andresen-Daniil,[5] Ranjith Kalleda,[5] Trinh Pham,[5] Mary-Ellen Taplin[6]

[1]The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Macquarie University, Sydney, Australia; [4]Institut Gustave Roussy, University of Paris Sud, Villejuif, France; [5]Medivation, Inc. (Medivation was acquired by Pfizer Inc in September 2016), San Francisco, CA; [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Continued enza post progression for mCRPC: Background

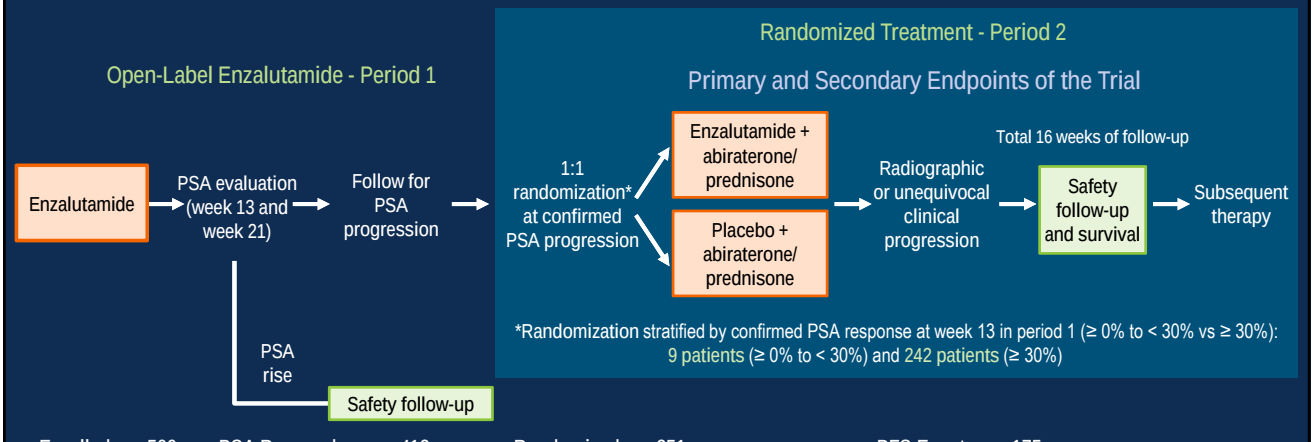
- Enzalutamide and abiraterone acetate (abiraterone) have distinct mechanisms of action[1,2]
- A standard of care for chemotherapy-naïve mCRPC is enzalutamide followed by abiraterone[3]
- Androgens have been reported to rise in patients treated with enzalutamide[4,5]

Hypotheses

- Cross-resistance occurs between abiraterone and enzalutamide
- In the setting of a rise in androgens on enzalutamide, targeting androgen synthesis whilst maintaining AR antagonism could re-induce sensitivity

1. Tran C et al. *Science*. 2009;324(5928):787-790. 2. Attard G et al. *J Clin Oncol*. 2008;26(28):4563-4571.
3. NCCN Guidelines – Prostate Cancer Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed May 15, 2017.
4. Richards J et al. *Cancer Res*. 2012;72(9):2176-2182. 5. Efstathiou E et al. *Eur Urol*. 2015;67(1):53-60.

PLATO: Novel Trial Design



Enrolled n = 509 (Target n = 500)

PSA Responders n = 412 (Target n = 415)

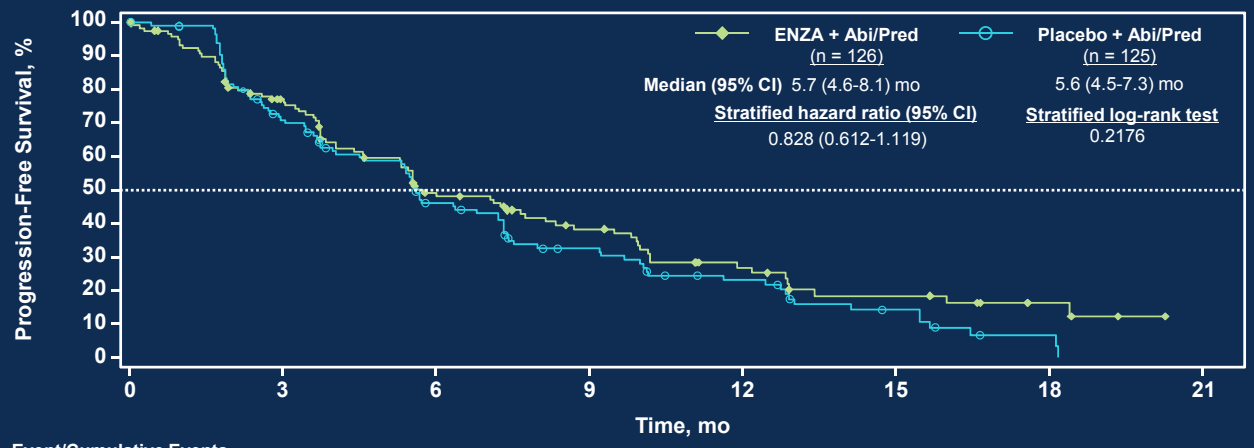
Randomized n = 251 (Target n = 250)

PFS Events n = 175 (Target n = 175)

Period 1 results presented by Attard G et al, at the European Cancer Congress; September 25-29, 2015; Vienna, Austria.

Patients enrolled in 51 study centers in North America, Europe, and Australia.
Abbreviation: PFS, progression-free survival.
NCT01995513; https://clinicaltrials.gov/show/NCT01995513.

PLATO: Primary Endpoint: PFS

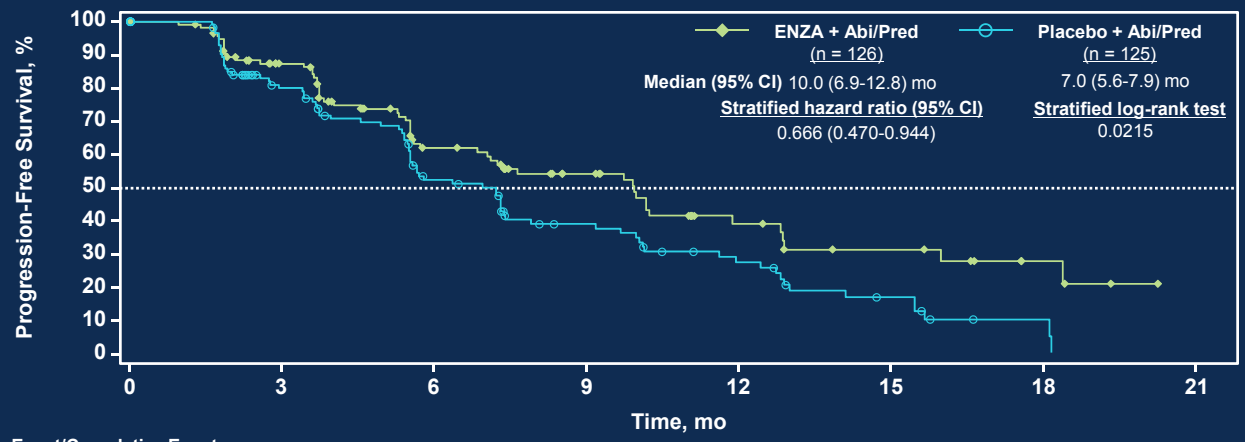


Event/Cumulative Events

ENZA + Abi/Pred	27/27	30/57	10/67	9/76	5/81	1/82	1/83
Placebo + Abi/Pred	33/33	26/59	13/72	8/80	6/86	4/90	2/92

Abbreviations: CI, confidence interval; mo, months.

PLATO: Prespecified rPFS Analysis



Event/Cumulative Events

ENZA + Abi/Pred	14/14	23/37	6/43	8/51	3/54	1/55	1/56
Placebo + Abi/Pred	22/22	26/48	11/59	8/67	6/73	3/76	2/78

*Analysis not adjusted for multiplicity.

PLATO: Conclusions

- Continuing enzalutamide after addition of abiraterone + prednisone, post PSA progression on enzalutamide alone, did not result in a statistically significant improvement in PFS
- An increased risk of hypertension and hepatic impairment was reported in the combination arm; abiraterone + prednisone alone or in combination with enzalutamide in patients progressing on enzalutamide alone was generally well tolerated
- Sensitivity analysis for rPFS showed a nominally significant difference but this may be subject to multiple biases
- Ongoing exploratory biomarker analysis in PLATO aims to identify distinct patient groups who might benefit from continuing enzalutamide with abiraterone + prednisone

UROTHELIAL CARCINOMA

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Updated Survival Analysis From KEYNOTE-045: Phase 3, Open-Label Study of Pembrolizumab Versus Paclitaxel, Docetaxel, or Vinflunine in Recurrent, Advanced Urothelial Cancer

Dean F. Bajorin,[1] Ronald de Wit,[2] David J. Vaughn,[3] Yves Fradet,[4] Jae Lyun Lee,[5] Lawrence Fong,[6] Nicholas J. Vogelzang,[7] Miguel A. Climent,[8] Daniel P. Petrylak,[9] Toni K. Choueiri,[10] Andrea Necchi,[11] Winald Gerritsen,[12] Howard Gurney,[13] David I. Quinn,[14] Stéphane Culine,[15] Cora N. Sternberg,[16] Yabing Mai,[17] Markus Puhlmann,[17] Rodolfo F. Perini,[17] Joaquim Bellmunt[10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [4]CHU de Québec-Université Laval, Québec City, QC, Canada; [5]Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; [6]University of California, San Francisco, San Francisco, CA, USA; [7]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [8]Fundación Instituto Valenciano de Oncología, Valencia, Spain; [9]Smilow Cancer Hospital at Yale University, New Haven, CT, USA; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [12]Radboud University Medical Center, Nijmegen, Netherlands; [13]Westmead Hospital and Macquarie University, Sydney, NSW, Australia; [14]University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA; [15]Hôpital Saint-Louis, Paris, France; [16]San Camillo Forlanini Hospital, Rome, Italy; [17]Merck & Co., Inc., Kenilworth, NJ, USA

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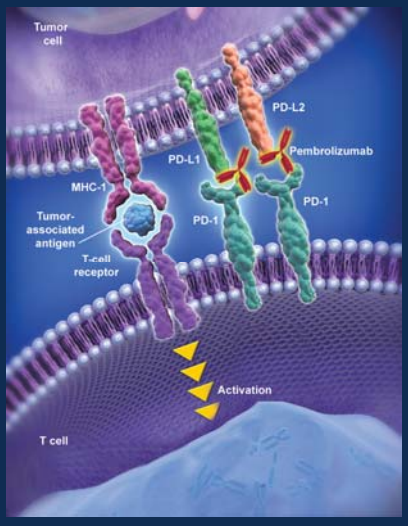
Challenges of Treating Recurrent Urothelial Carcinoma After Platinum Therapy

- Currently no universally accepted second-line therapy
  - Vinflunine: approved, commonly used in European Union[1]
  - Taxanes: supported by consensus guidelines[2]
  - Checkpoint inhibitors (atezolizumab, nivolumab, durvalumab, avelumab) received accelerated approvals in United States based on durable response rates
- Level 1 evidence for enhanced survival and safety over chemotherapy is of critical importance in advancing the treatment of urothelial cancer

1. Houede N et al. *BMC Cancer*. 2016;16:752.
2. NCCN Guidelines. Bladder cancer. 2017:version 1.2017.

Pembrolizumab Is Active and Safe in Recurrent Urothelial Cancer



- Phase 2 KEYNOTE-052
  - Data to be presented next (Abstr 4502)
- Phase 3 KEYNOTE-045
  - Survival superior to chemotherapy (median follow-up, 14 mo)[1]

FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Certain Patients with Locally Advanced or Metastatic Urothelial Carcinoma, a Type of Bladder Cancer

MAY 18, 2017

Now Approved for First-Line Treatment in Patients Ineligible for Cisplatin-Containing Chemotherapy and Second-Line Treatment in Patients Who Have Disease Progression During or Following Platinum-Containing Chemotherapy or Within 12 Months of Neoadjuvant or Adjuvant Treatment with Platinum-Containing Chemotherapy

KEYTRUDA is the Only Anti-PD-1 Therapy to Demonstrate Superior Overall Survival Versus Chemotherapy in Patients With Advanced Urothelial Carcinoma Post-Platinum Failure

1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-26.

KEYNOTE-045 Study Design (NCT02256436)

Key Eligibility Criteria

- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemotherapy or recurrence <12 mo after perioperative platinum-based therapy
- ECOG performance status 0-2
- Provision of tumor sample for biomarker assessment

R 1:1

- Pembrolizumab 200 mg IV Q3W
- Paclitaxel 175 mg/m² Q3W OR Docetaxel 75 mg/m² Q3W OR Vinflunine 320 mg/m² Q3W

Stratification Factors

- ECOG performance status (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

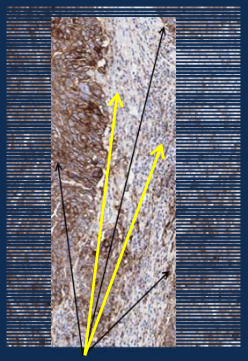
- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

[a]In total ITT population and in patients with combined positive score ≥10%.

KEYNOTE-045: Assessments

- Tumor imaging: week 9, then every 6 weeks for year 1, and every 12 weeks thereafter
- Data cutoff date for updated analysis: January 18, 2017
  - Actual OS events[a]: 366 (334 in prior analysis)
  - Median follow-up: 18.5 mo (range, 14.2-26.5) (median, 14.1 mo previously)
- PD-L1: assessed centrally using PD-L1 IHC 22C3 pharmDx (Dako)
  - Expression scored using combined positive score (CPS)

$$\text{CPS} = \frac{\text{\# PD-L1–staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$



PD-L1–positive cells (tumor cells, macrophages, lymphocytes)

[a]Planned final analysis to be performed after 370 events.

KEYNOTE-045: Baseline Characteristics

n (%)	Pembro (n = 270)	Chemo (n = 272)
Age, median (range), y	67 (29-88)	65 (26-84)
Men	200 (74.1)	202 (74.3)
Upper tract disease	38 (14.1)	37 (13.6)
Lower tract disease	232 (85.9)	235 (86.4)
ECOG PS[a]		
0	120 (44.4)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Visceral disease	241 (89.3)	234 (86.0)
Disease in lymph node only	28 (10.4)	38 (14.0)

n (%)	Pembro (n = 270)	Chemo (n = 272)
Liver metastases	91 (33.7)	95 (34.9)
Hemoglobin <10 g/dL[b]	43 (15.9)	44 (16.2)
Time since completion of most recent prior therapy		
≥3 months	167 (61.9)	168 (61.8)
<3 months	103 (38.1)	104 (38.2)
Setting of most recent prior therapy[c]		
Neoadjuvant	19 (7.0)	22 (8.1)
Adjuvant	12 (4.4)	31 (11.4)
First line	184 (68.1)	158 (58.1)
Second line	55 (20.4)	59 (21.7)
Third line	0	2 (0.7)

[a]Missing for 5 patients in the pembro arm and 4 patients in the chemo arm. [b]Missing for 8 patients in the pembro arm and 4 patients in the chemo arm. [c]Setting and time from completion were missing for 1 patient in each arm.
Data cutoff date: January 18, 2017.

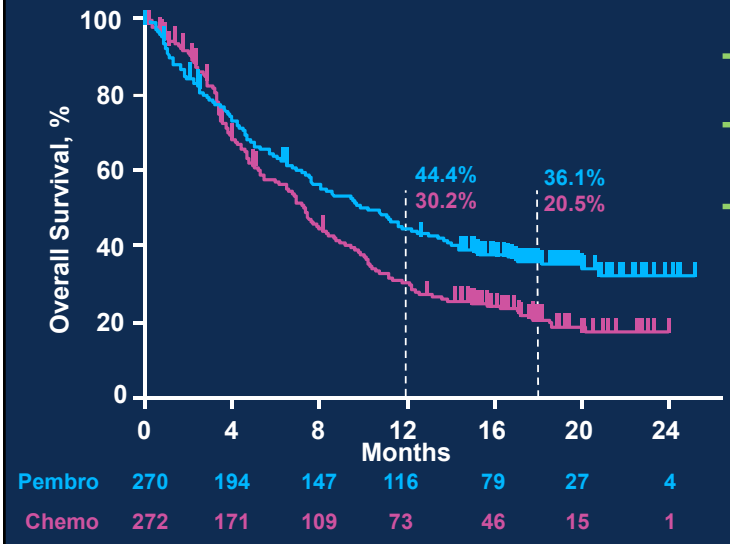
KEYNOTE-045: Baseline Characteristics

n (%)	Pembro (n = 270)	Chemo (n = 272)
Prior platinum therapy		
Cisplatin	199 (73.7)	214 (78.7)
Carboplatin	70 (25.9)	56 (20.6)
Other[a]	1 (0.4)	2 (0.7)
Smoking status[b]		
Never	104 (38.5)	83 (30.5)
Former	136 (50.4)	148 (54.4)
Current	29 (10.7)	38 (14.0)
PD-L1 CPS ≥10%	74 (27.4)	90 (33.1)

n (%)	Pembro (n = 270)	Chemo (n = 272)
Risk Factors[c]		
0	54 (20.0)	45 (16.5)
1	96 (35.6)	97 (35.7)
2	66 (24.4)	80 (29.4)
3-4	45 (16.7)	45 (16.5)

[a]Oxaliplatin, nedaplatin. [b]Missing for 1 patient in the pembro arm and 3 patients in the chemo arm. [c]Includes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol.* 2010;27:1850-1855) + time from prior chemotherapy <3 mo (*Eur Urol.* 2013;63:717-723). Missing for 9 patients in the pembro arm and 5 patients in the chemo arm.
Data cutoff date: January 18, 2017.

KEYNOTE-045: Overall Survival

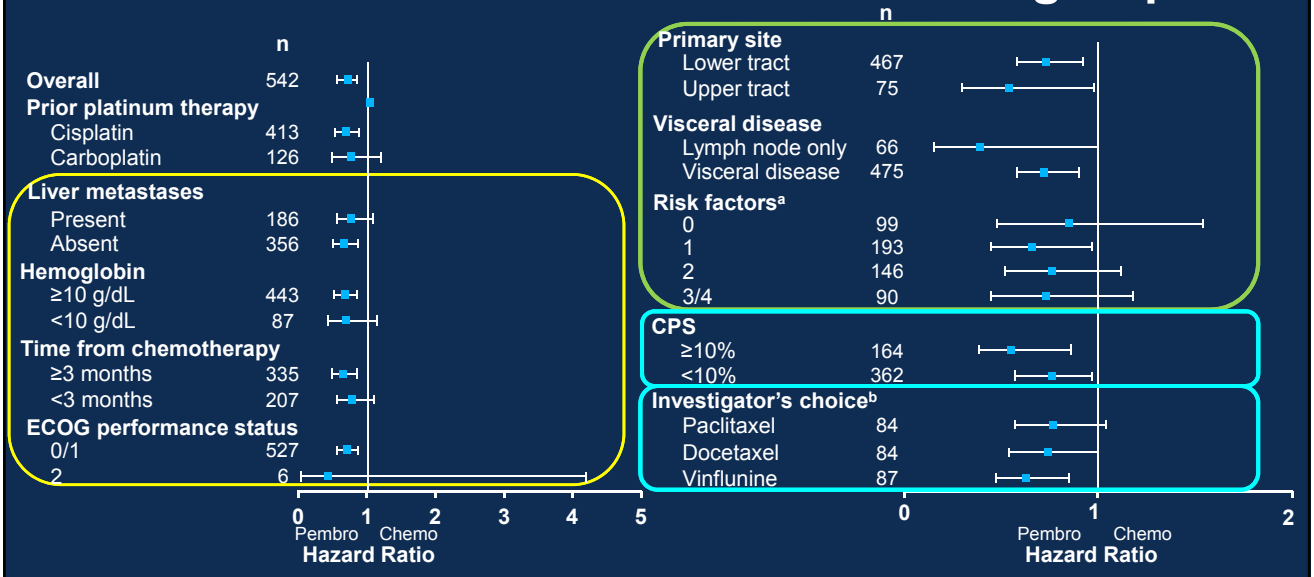


	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	170	0.70 (0.57-0.86)	0.0004
Chemo	196		

Median (95% CI):
10.3 mo (8.0-12.3)
7.4 mo (6.1-8.1)

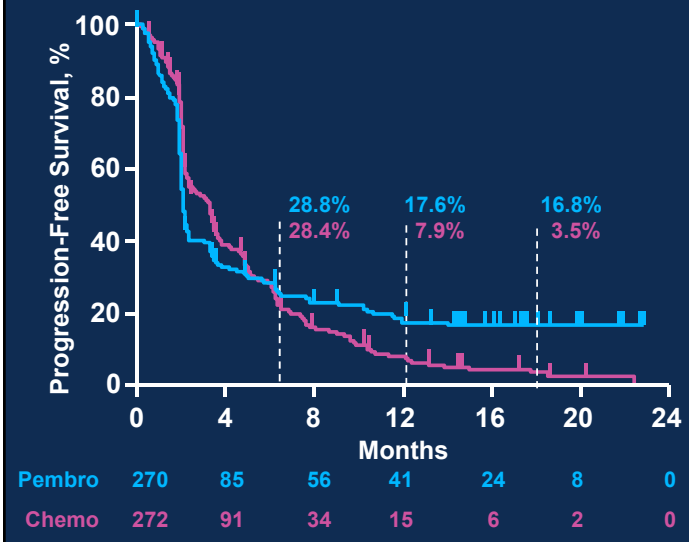
[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: January 18, 2017.

KEYNOTE-045: Overall Survival in Subgroups



[a]Includes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol.* 2010;27:1850-1855) + time from prior chemotherapy <3 mo (*Eur Urol.* 2013;63:717-723). [b]N is shown for the chemotherapy arm only. All comparisons were to all patients in the pembrolizumab arm.
Data cutoff date: January 18, 2017.

KEYNOTE-045: Progression-Free Survival

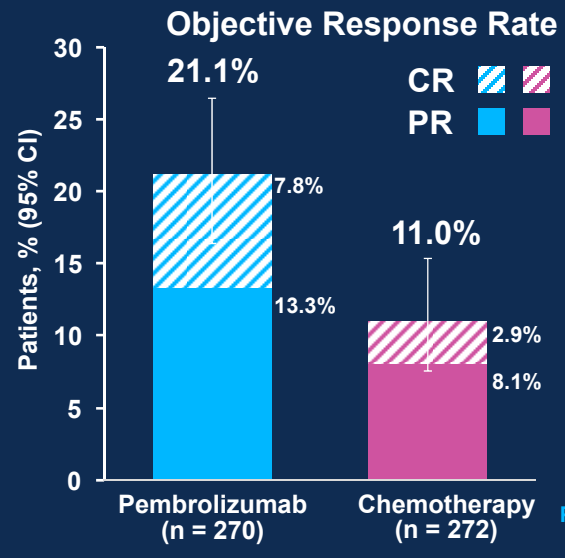


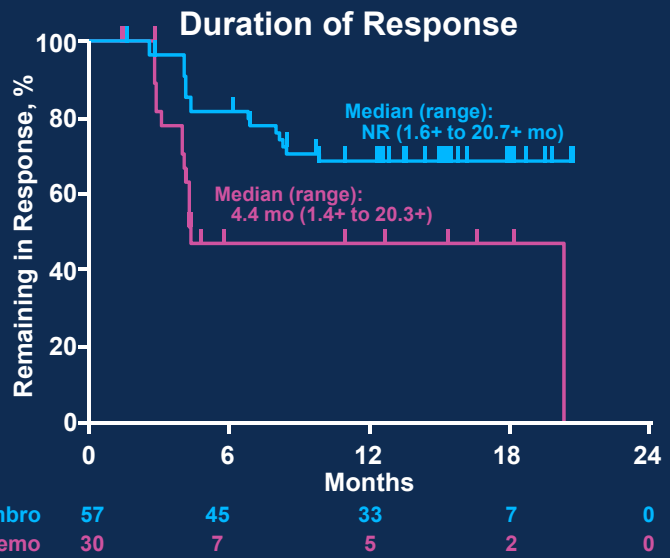
	Events, n	HR (95% CI)	*P*
Pembro	270	0.96 (0.79-1.16)	0.32
Chemo	272		

Median (95% CI):
2.1 mo (2.0-2.2)
3.3 mo (2.4-3.5)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: January 18, 2017.

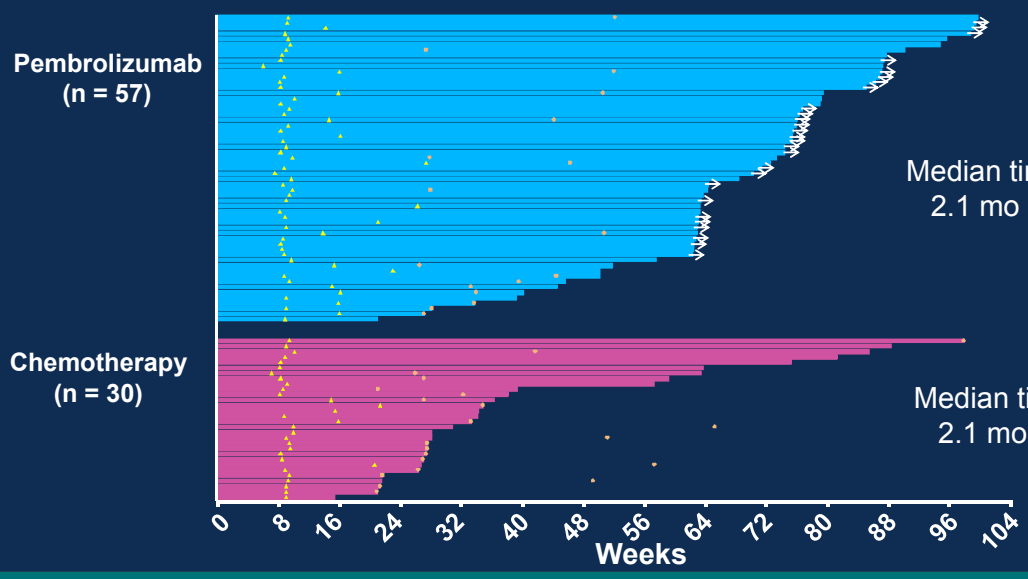
KEYNOTE-045: Response and Response Duration





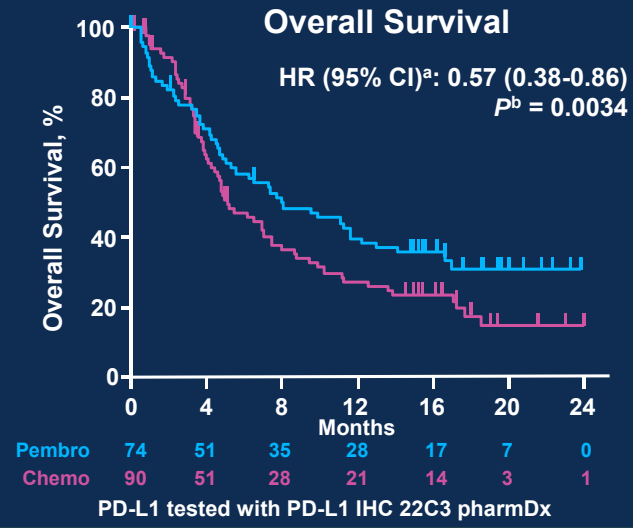
Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: January 18, 2017.

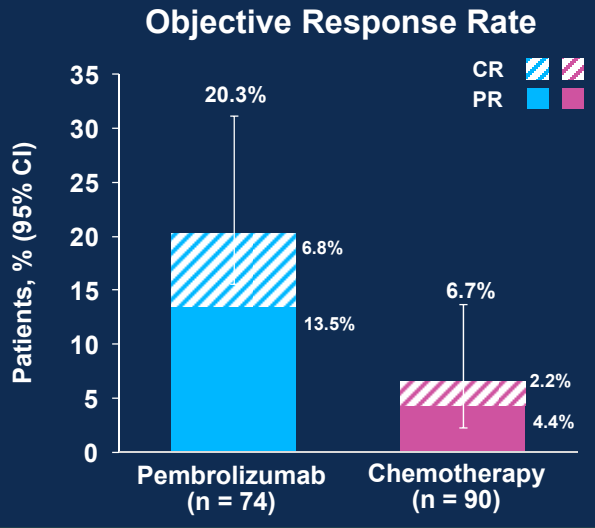
KEYNOTE-045: Time to Response[a]



[a]For patients who achieved a complete or partial response.
Data cutoff date: January 18, 2017.

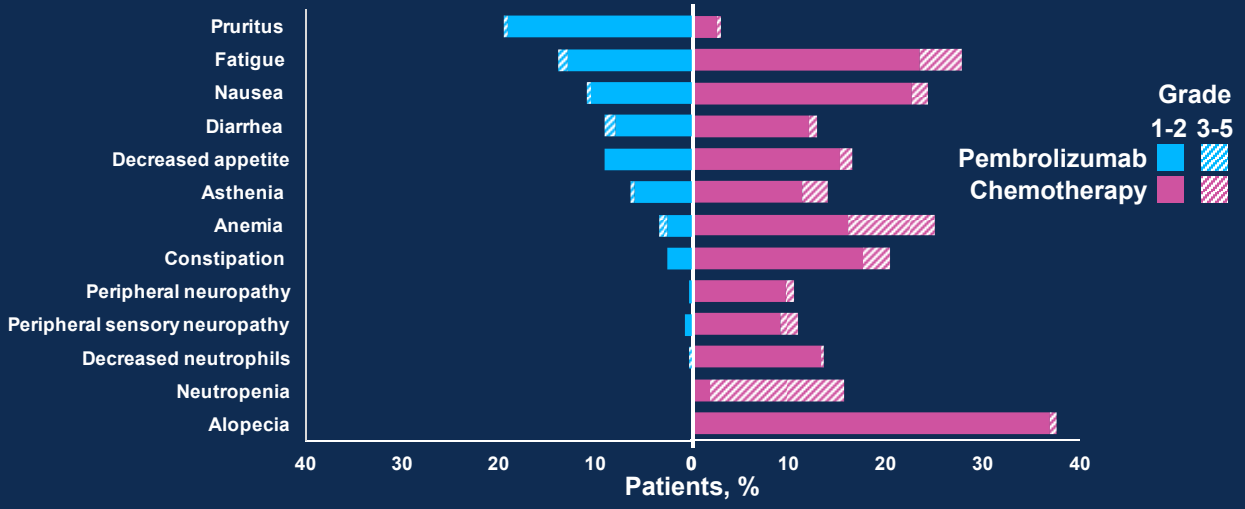
KEYNOTE-045: Efficacy by PD-L1 CPS ≥10%





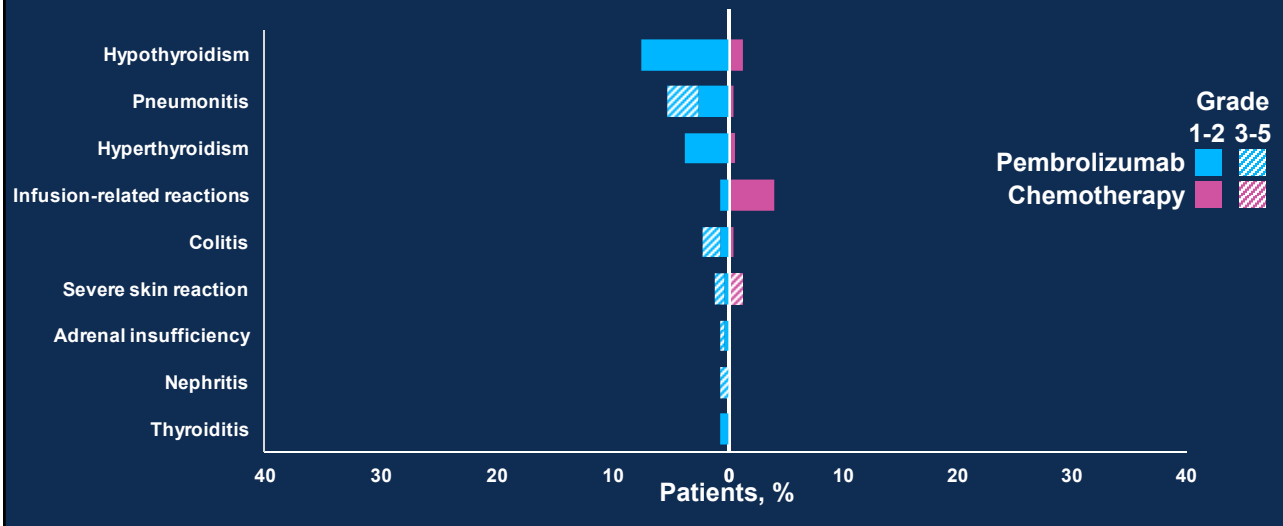
[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: January 18, 2017.

KEYNOTE-045: Treatment-Related AEs in ≥10% Patients[a]



[a]Of patients in either treatment arm.
7.5% febrile neutropenia in the chemotherapy arm.
Data cutoff date: January 18, 2017.

KEYNOTE-045: AEs of Interest[a] in ≥2 Patients[b]



[a]Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included. [b]In either treatment arm.
Data cutoff date: January 18, 2017.

KEYNOTE-045: Summary

- Pembrolizumab survival benefit maintained with longer follow-up
  - Median OS, 10.3 versus 7.4 mo; HR, 0.70; *P* = 0.0004; median follow-up, 18.5 mo
  - OS at 12 months (44.4% vs 30.2%) and 18 months (36.1% vs 20.5%)
- Continued higher ORR with pembrolizumab versus chemotherapy
- Responses more durable with pembrolizumab versus chemotherapy
  - Median duration of response: Not reached versus 4.4 mo
  - Responses lasting ≥12 months: 69% versus 36%
- Better safety profile with pembrolizumab versus chemotherapy
  - Treatment-related AEs: 61.3% versus 90.2%
  - Grade ≥3 treatment-related AEs: 16.5% versus 49.8%

KEYNOTE-045: Conclusions

- Pembrolizumab is the first immunotherapy to demonstrate superior survival over chemotherapy in patients with advanced urothelial carcinoma after failure of platinum-based therapy
- Pembrolizumab should be considered a standard of care for these patients, supported by level 1 evidence
- Based on these data, the FDA provided full approval of pembrolizumab in May 2017 for the treatment of advanced urothelial carcinoma after failure of platinum-based therapy without the need for PD-L1 staining

Biomarker Findings and Mature Clinical Results From KEYNOTE-052: First-Line Pembrolizumab in Cisplatin-ineligible Advanced Urothelial Cancer

Peter H. O'Donnell,[1] Petros Grivas,[2] Arjun V. Balar,[3] Joaquim Bellmunt,[4] Jaqueline Vuky,[5] Thomas Powles,[6] Elizabeth Plimack,[7] Noah Hahn,[8] Ronald de Wit,[9] Lei Pang,[10] Mary J. Savage,[10] Jared Lunceford,[10] Stephen M. Keefe,[10] Dean Bajorin,[11] Daniel Castellano[12]

[1]The University of Chicago Medical Center, Chicago, IL, USA; [2]Cleveland Clinic, Cleveland, OH, USA; [3]Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Oregon Health & Science University, Portland, OR, USA; [6]Barts Cancer Institute, Queen Mary University of London, London, UK; [7]Fox Chase Cancer Center, Philadelphia, PA, USA; [8]Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [9]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Hospital Universitario 12 de Octubre, Madrid, Spain

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First-Line Advanced Urothelial Cancer Treatment

- Advanced UC most often afflicts older patients with comorbidities and poor performance status[1]
- First-line cisplatin-based chemotherapy improves survival[2]
- Age-related complications (eg, renal dysfunction, poor ECOG) preclude ~50% of patients from receiving standard first-line cisplatin treatment[1]
- Alternative first-line options have inferior outcomes and substantial toxicity[3,4]
  - Best supportive care is considered a reasonable option[1]
- Anti–PD-1/PD-L1 antibodies have shown antitumor activity as first-line treatment
  - Atezolizumab: ORR is 23% in cisplatin-ineligible patients (single-arm, phase 2 IMvigor210 study, N = 119)[5]
    - Median follow-up = 17 months (range, 0.2-24 months)

1. Galsky MD et al. *J Clin Oncol.* 2011;29:2432-2438. 2. Harshman LC et al. *Br J Cancer.* 2013;109:2548-2553.
3. Galsky MD et al. *Ann Oncol.* 2012;23:406-410. 4. De Santis M et al. *J Clin Oncol.* 2012;30:191-199.
5. Balar AV et al. *Lancet.* 2017;389:67-76.

KEYNOTE-052 (NCT02335424): First-Line Pembrolizumab for Cisplatin-Ineligible Advanced Urothelial Cancer

Patients

- Advanced urothelial cancer
- No prior chemotherapy for metastatic disease
- ECOG PS 0-2
- Ineligible for cisplatin:
  - CrCl <60 mL/min
  - ECOG PS 2
  - Grade ≥2 neuropathy or hearing loss
  - NYHA class III heart failure

Pembrolizumab 200 mg Q3W
N = 370

Pretreatment sample collection for biomarker analyses

Continue until

- 24 months of treatment
- Confirmed PD
- Intolerable toxicity
- Patient withdrawal

- **Primary end points:** ORR
- **Secondary end points:** DOR, PFS, OS, safety; identification of cut point for high PD-L1 expression
- **Exploratory objective:** Relationship between candidate biomarkers and response
- **Data cutoff date:** March 9, 2017
  - Median follow-up: 9.5 months (range, 0.1-23 months)

KEYNOTE-052: Baseline Characteristics

Characteristic, n (%)	N = 370
Age, median (range), y	74 (34-94)
≥80 years	107 (29)
Men	286 (77)
ECOG performance status[a]	
0	80 (22)
1	134 (36)
2	155 (42)
Primary tumor location[b]	
Upper tract	69 (19)
Lower tract	300 (81)
Liver metastases	77 (21)

Characteristic, n (%)	N = 370
Metastases location[c]	
Lymph node only	51 (14)
Visceral disease	315 (85)
Prior adjuvant/neoadjuvant platinum-based chemotherapy[d]	37 (10)
Reasons for cisplatin ineligibility	
Renal dysfunction[e]	183 (50)
ECOG performance status 2	120 (32)
ECOG performance status 2 and renal dysfunction	34 (9)
Other reasons[f]	33 (9)

Data cutoff: March 9, 2017.

[a]1 patient had an ECOG PS 3. [b]Unknown for 1 patient. [c]Unknown for 4 patients. [d]Adjuvant platinum-based chemotherapy following radical cystectomy or neoadjuvant platinum-based chemotherapy with recurrence >12 months from completion of therapy was allowed. [e]Renal dysfunction defined as creatinine clearance <60 mL/min. [f]Other reasons include NYHA class III heart failure, grade ≥2 peripheral neuropathy, and grade ≥2 hearing loss.

KEYNOTE-052: Objective Response Rate

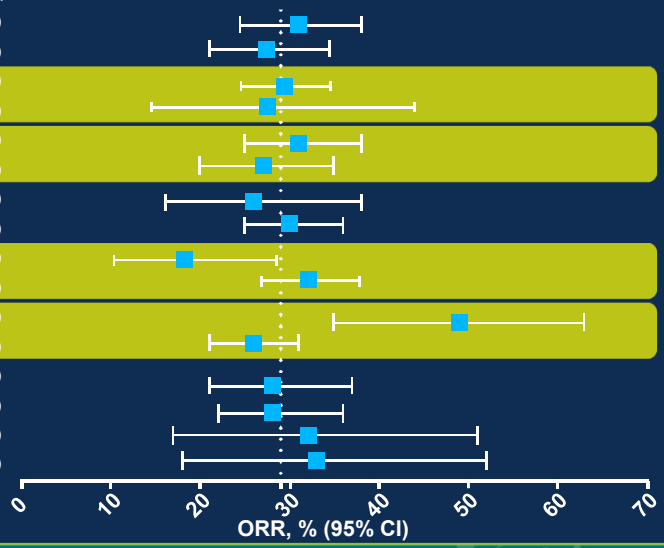
	Total Population N = 370		
	n	%	95% CI
Objective response rate	108	**29**	25-34
Complete response	27	7	5-10
Partial response	81	22	18-27
Stable disease	67	18	14-22
Progressive disease	155	42	37-47

With longer follow-up[a]:
- 5% increase in ORR
- 10 additional complete responses
- 9 additional partial responses

Data cutoff: March 9, 2017. Assessed per RECIST v1.1 by central imaging vendor review. An additional 31 patients had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy, and 9 patients had ≥1 postbaseline tumor assessment, none of which were evaluable.
[a]Compared with September 1, 2016, data cutoff.

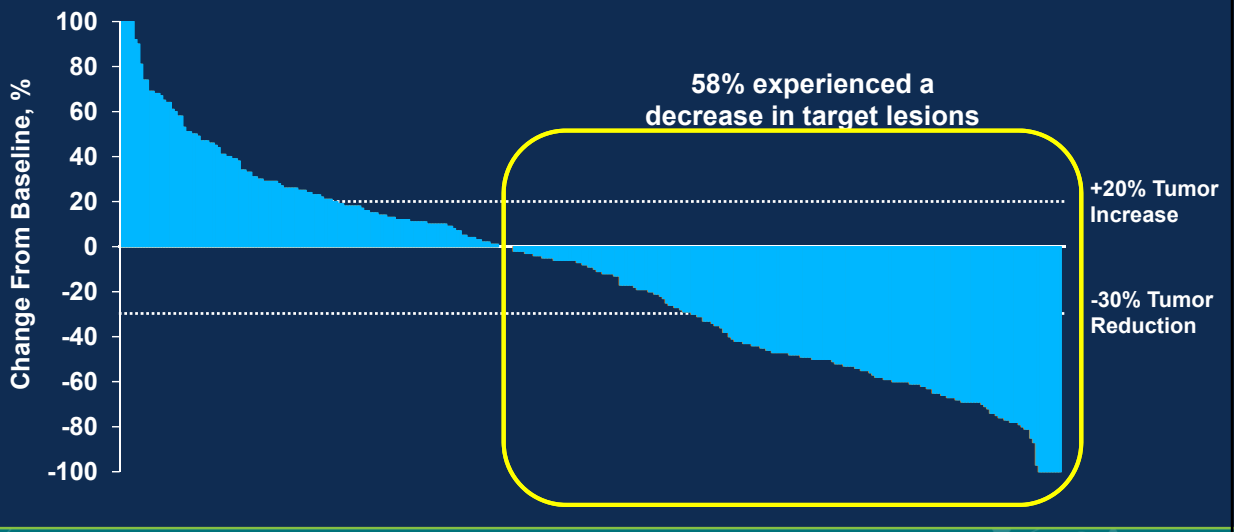
KEYNOTE-052: Objective Response Rate by Subgroup

		n/N	% (95% CI)
Age	<75 years	59/191	31 (24-38)
	≥75 years	49/179	27 (21-35)
	<85 years	97/330	29 (25-35)
	≥85 years	11/40	28 (15-44)
ECOG PS	0/1	66/214	31 (25-38)
	2	42/156	27 (20-35)
Disease location	Upper tract	18/69	26 (16-38)
	Lower tract	90/300	30 (25-36)
Liver metastases	Present	14/77	18 (10-29)
	Absent	94/293	32 (27-38)
Metastases location	Lymph node only	25/51	49 (35-63)
	Visceral disease	81/315	26 (21-31)
Reason for cisplatin ineligibility	ECOG PS 2	34/120	28 (21-37)
	Renal dysfunction	52/183	28 (22-36)
	ECOG PS 2/renal dysfunction	11/34	32 (17-51)
	Other[a]	11/33	33 (18-52)



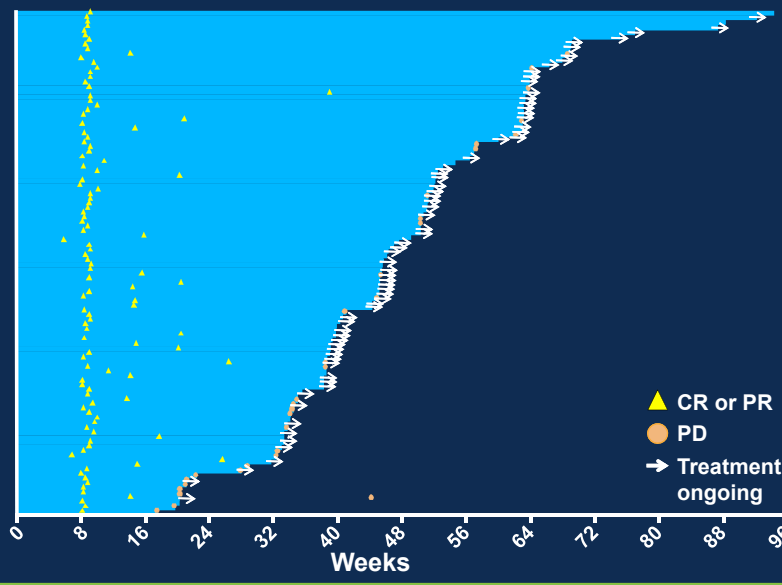
Data cutoff: March 9, 2017.
Assessed per RECIST v1.1 by central imaging vendor review.
[a]1 patient had an ECOG performance status of 3. [b]Other reasons include NYHA class III heart failure, grade ≥2 peripheral neuropathy, and grade ≥2 hearing loss.

KEYNOTE-052: Best size Change



Data cutoff: March 9, 2017.
Assessed per RECIST v1.1 by central imaging vendor review.
Includes patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a postbaseline assessment (n = 332).

KEYNOTE-052: Treatment Exposure and Response Duration[a]



Median time to response[a]

- 2 months (range, 1-9 months)

Median duration of response[a]

- Not reached (95% CI, 12 months-NR)[b]
- 82% of responses lasted ≥6 months[b]
- At data cutoff, 67% of responses were ongoing

Data cutoff: March 9, 2017. Median follow-up: 9.5 months (range, 0.1-23 months).
[a]Includes patients who achieved a confirmed PR or better per RECIST v1.1 by central imaging vendor review.
[b]Kaplan-Meier estimate.

KEYNOTE-052: Objective Response Rate by PD-L1: Training Set

	CPS <10% n = 66			CPS ≥10% n = 30		
	n	%	95% CI	n	%	95% CI
Objective response rate	11	**17**	9-28	11	**37**	20-56
Complete response	3	5	1-13	4	13	4-31
Partial response	8	12	5-23	7	23	10-42
Stable disease	9	13	6-24	7	23	10-42
Progressive disease	35	53	40-65	11	37	20-56

Data cutoff: March 9, 2017.

Assessed per RECIST v1.1 by central imaging vendor review. 361/370 patients had CPS and ORR data. For CPS <10%, 7 additional patients had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy, and 4 patients had ≥1 postbaseline tumor assessment, none of which were evaluable. For CPS ≥10%, 1 additional patient did not have a postbaseline imaging assessment.

KEYNOTE-052: Objective Response Rate: Validation Set

	CPS <10% n = 185			CPS ≥10% n = 80		
	n	%	95% CI	n	%	95% CI
Objective response rate	42	**23**	17-29	41	**51**	40-63
Complete response	5	3	1-6	14	18	10-28
Partial response	37	20	15-27	27	34	24-45
Stable disease	35	19	14-25	15	19	11-29
Progressive disease	86	47	37-54	19	24	15-35

Data cutoff: March 9, 2017.

Assessed per RECIST v1.1 by central imaging vendor review. 361/370 patients had CPS and ORR data. For CPS <10%, 17 additional patients had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy, and 5 patients had ≥1 postbaseline tumor assessment, none of which were evaluable. For CPS ≥10%, 5 additional patients did not have a postbaseline imaging assessment.

KEYNOTE-052: Treatment-Related Adverse Events

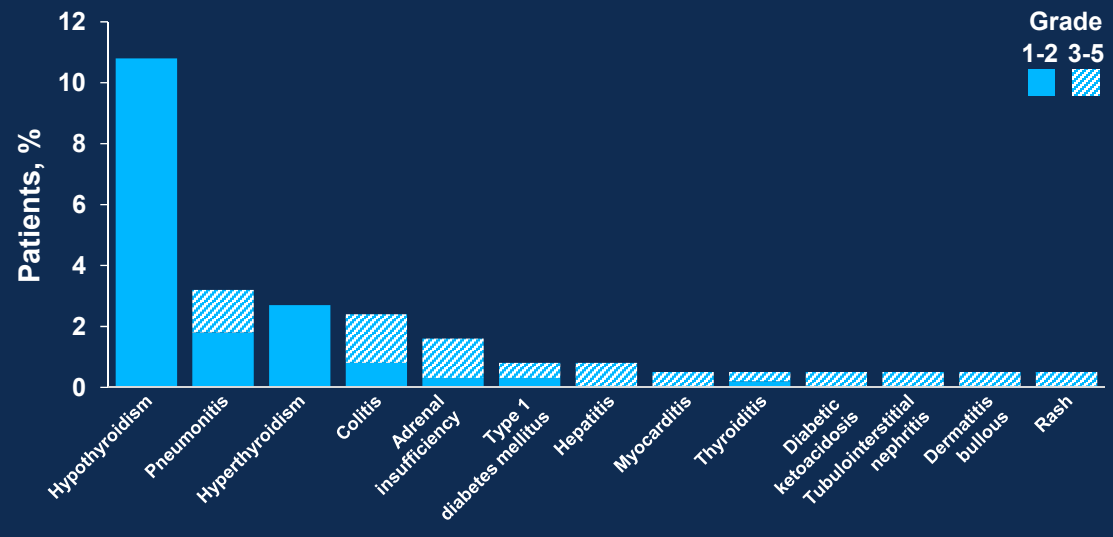
n (%) N = 370	Any Grade (≥5% of pts)
Any	243 (66)
Fatigue	67 (18)
Pruritus	62 (17)
Rash	44 (12)
Decreased appetite	37 (10)
Hypothyroidism	35 (10)
Diarrhea	32 (9)
Nausea	31 (8)

n (%) N = 370	Grade 3-5 (≥3 pts)
Any	70 (19)
Fatigue	8 (2)
Colitis	6 (2)
Muscle weakness	5 (1)
Alkaline phosphatase increase	5 (1)
Diarrhea	4 (1)
Pneumonitis	4 (1)
AST increase	4 (1)
Asthenia	3 (1)
Hepatitis	3 (1)
ALT increase	3 (1)

- 7% discontinued because of a treatment-related AE
- 1 death attributed to a treatment-related AE (myositis in an 83-year-old woman)

Data cutoff: March 9, 2017.

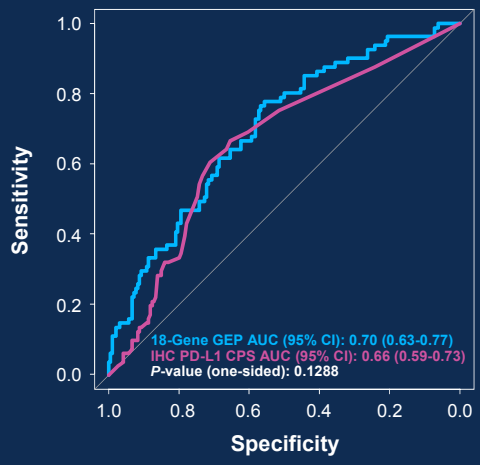
KEYNOTE-052: Immune-Mediated Adverse Events[a]

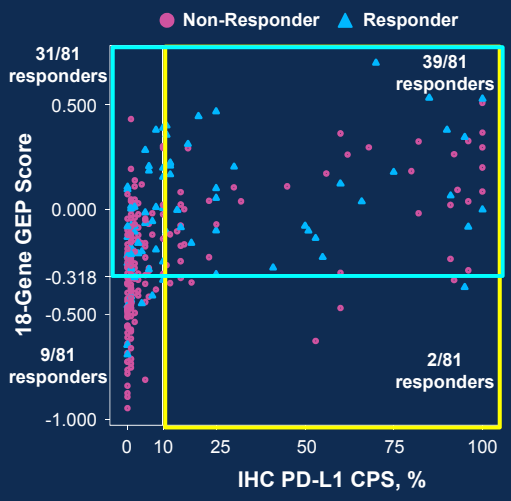


Data cutoff: March 9, 2017.

[a]Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included.

KEYNOTE-052: PD-L1 and 18-Gene T-Cell Inflamed GEP and Response





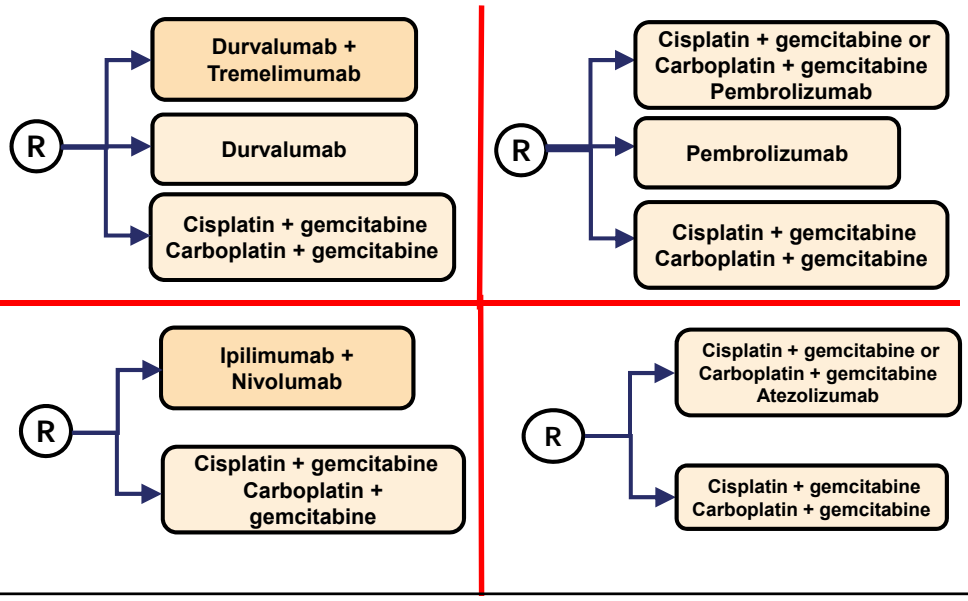
Data cutoff: March 9, 2017.
n = 275. Response assessed per RECIST v1.1 by central imaging vendor review.
-0.318 is cutoff on Merck discovery platform, an equivalent cutoff on a clinical grade assay is under evaluation in some Merck trials.

KEYNOTE-052: Conclusions

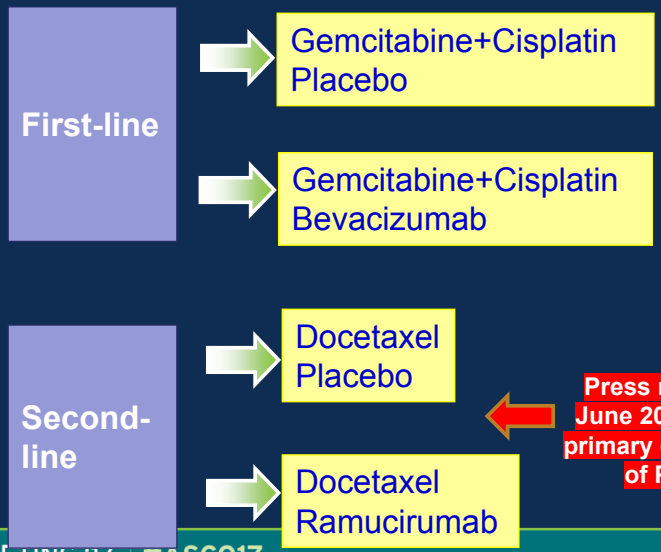
- First-line pembrolizumab elicits clinically meaningful, durable antitumor activity in cisplatin-ineligible patients with advanced urothelial cancer
  - **29% ORR** in all patients
  - Response observed across subgroups
  - Median duration of response not yet reached
- No new safety signals identified
- In the PD-L1 expression analysis, CPS ≥10% determined to be optimal enrichment cutoff for predicting response
  - **51% ORR** for CPS ≥10% (validation set)
- Appreciable number of additional responders were captured using the T-cell inflamed GEP as compared with the PD-L1 IHC biomarker
- Accelerated approval for first-line cisplatin-ineligible urothelial carcinoma (May 2017)

PD1/PD-L1 inhibitors in first-line phase III trials

Cisplatin-eligible and ineligible patients in same trials



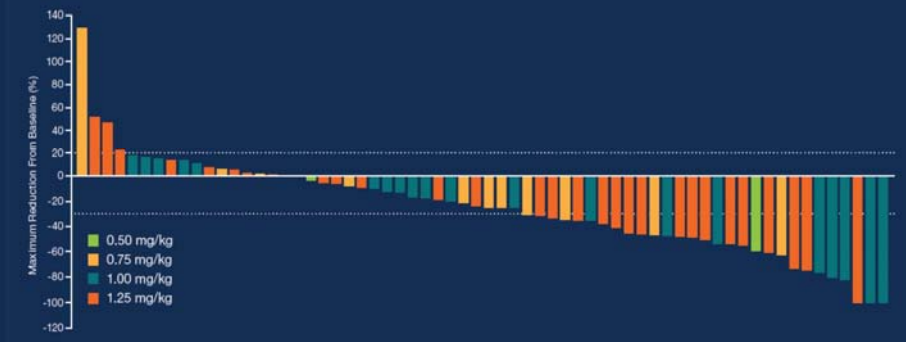
VEGF inhibitors in phase III trials of advanced UC



Enfortumab Vedotin (anti-Nectin-4 ADC) as salvage therapy for UC

Petrylak et al, ASCO 2017

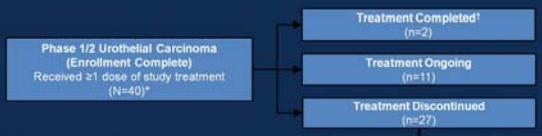
Maximum Reduction from Baseline in Total Tumor Burden in Patients with mUC on Enfortumab Vedotin



Pembrolizumab + Epacadostat as salvage therapy for UC

Smith D, et al, ASCO 2017

Epacadostat Plus Pembrolizumab: Phase 1/2



Median (range) follow-up: 33.8+ (3.6 to 131+) weeks

Median (range) epacadostat exposure: 20.1 (1 to 132+) weeks

- Disease progression (n=18)
- Adverse events (n=5)
- Patient decision (n=3)
- Death (n=1)

CR, complete response.
* 1 additional patient was enrolled but data were not yet available at the time of data cutoff. † Patients received 24 months of study treatment or achieved CR and elected to discontinue treatment following the protocol-defined minimum amount of treatment (≥24 weeks before discontinuation and ≥2 cycles of combination treatment beyond the date of initial CR).

Best Objective Response

Patients, n (%)	Total (N=40)	No. Prior Lines of Treatment		PD-L1 Expression†	
		0*–1 (n=32)	≥2 (n=8)	Positive (n=11)	Negative (n=8)
ORR (CR+PR)	14 (35)	12 (38)	2 (25)	7 (64)	1 (13)
CR	3 (8)	3 (9)	0	0	0
PR	11 (28)	9 (28)	2 (25)	7 (64)	1 (13)
SD	7 (18)	7 (22)	0	1 (9)	1 (13)
DCR (CR+PR+SD)	21 (53)	19 (59)	2 (25)	8 (73)	2 (25)
PD	14 (35)	10 (31)	4 (50)	2 (18)	6 (75)
Not evaluable	5 (13)	3 (9)	2 (25)	1 (9)	0

Based on irRECIST: ORR=38% (4 CR, 11 PR); DCR=60% (9 SD)

CR, complete response; DCR, disease control rate; irRECIST, immune-related RECIST; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
* Enrolled patients who had no prior treatment for advanced urothelial carcinoma received platinum-based treatment in adjuvant/neoadjuvant setting. † Of 21 patients with unknown PD-L1 expression, there were 3 CR, 3 PR, 5 SD, 8 PD, and 4 not evaluable by RECIST.

RENAL CELL CARCINOMA

Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT)

Robert Motzer, Naomi Haas, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae-Lyun Lee, Bohuslav Melichar, Brian Rini, Toni Choueiri, Milada Zemanova, Lori Wood, Dirk Fahlenkamp, Martin Reaume, Arnulf Stenzl, Weichao Bao, Paola Aimone, Christian Doehn, Paul Russo, Cora Sternberg for the PROTECT investigators

Abstract 4507

PROTECT, **P**azopanib as adjuvant the**R**apy in l**O**calized/locally advanced RCC af**T**er n**E**phre**CT**omy (VEG113387).

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17
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Adjuvant therapy for RCC: Introduction

- About 75% of patients with RCC have localized disease and 30% to 40% with high-risk localized RCC relapse following nephrectomy
- Adjuvant VEGFR-TKI therapy is being investigated to improve disease-free survival (DFS)
- ASSURE trial did not meet the primary end point; S-TRAC met the primary end point for sunitinib[1,2]

TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
1. Haas NB, et al. *Lancet*. 2016;387:2008. **2.** Ravaud A, et al. *N Engl J Med*. 2016;375:2246-2254.

Rationale and Initial Primary Objective

- A randomized, double-blind phase III trial of pazopanib vs placebo was conducted in patients with high-risk, locally advanced RCC following nephrectomy

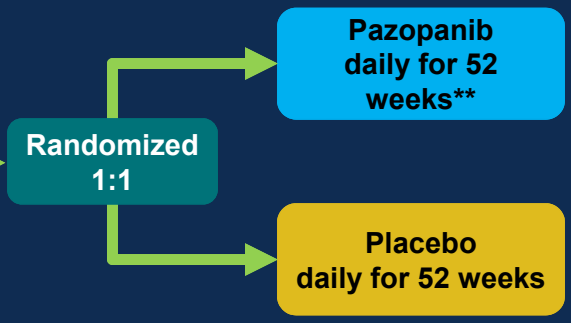
Initial primary objective was DFS for pazopanib 800 mg vs placebo → **Amended primary objective was DFS for pazopanib 600 mg vs placebo**

- In August 2011, the primary objective of the study was amended based on high treatment discontinuation rate due to adverse events (AEs)

PROTECT: Study Design

Key eligibility criteria

- Resected non-metastatic clear-cell RCC histology and pathologic staging*
  - –pT2, G3 or G4, N0
  - –pT3, G_{any}, N0
  - –pT4, G_{any}, N0
  - –pT_{any}, G_{any}, N1
- Baseline imaging assessment by independent radiologist review that excluded metastasis
- Adequate PS and organ function



Stratification: partial vs radical nephrectomy; pathologic staging

**Starting dose 600 mg assessed for safety at 8-12 weeks and could be escalated to 800 mg or maintained at 600 mg based on patient's tolerability

*Staging based on TNM classification per the American Joint Committee on Cancer (AJCC) 2010 version and Fuhrman nuclear grades

PROTECT: Study Assessments

- Tumor imaging at baseline, weeks 20, 36, and 52 during year 1, every 6 months during years 2-5, and yearly thereafter
  - Baseline imaging assessment by independent radiologist and investigator; all subsequent imaging studies assessed by investigator only
- Safety evaluations at regular intervals
- Quality of life using FKSI-19

FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index-19.

PROTECT: Baseline Characteristics (n=1538)

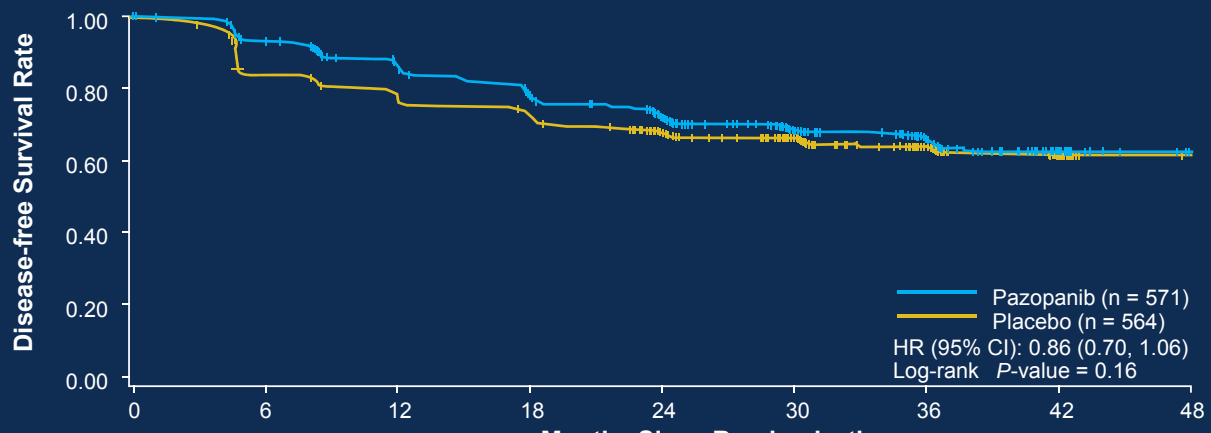
	ITT_{600mg} (n=1135)		ITT_{800mg} (n=403)	
	Pazopanib n = 571	Placebo n = 564	Pazopanib n = 198	Placebo n = 205
Age, years, median (range)	58 (22–83)	58 (21–82)	56 (29–80)	60 (30–79)
Gender, %				
• Male	70	71	70	75
• Female	30	29	30	25
KPS,* %				
• 100	67	69	66	72
• 80 or 90	33	31	34	28
Nephrectomy, %				
• Partial	7	7	4	5
• Radical	93	93	96	95
Fuhrman grade,** %				
• High (Grade 3 or 4)	69	63	71	63
• Low (Grade 1 or 2)	31	37	29	37

*KPS was unknown for one patient in the ITT_{600mg} placebo group; **Fuhrman grade was missing for two patients in the ITT_{600mg} placebo group.

PROTECT: Baseline Characteristics

	ITT_{600mg}		ITT_{800mg}	
	Pazopanib n = 571	Placebo n = 564	Pazopanib n = 198	Placebo n = 205
Primary tumor stage, %				
• T1	<1	<1	1	<1
• T2	15	15	14	15
• T3	82	82	83	82
• T4	2	3	3	3
Regional lymph node status, %				
• N0	94	95	93	95
• N1	6	5	7	5
Tumor staging and grade, %				
• pT2G3–G4N0	14	14	14	14
• $pT3G_{any}N0$	78	78	77	79
• $pT4G_{any}N0$ and $pT_{any}G_{any}N1$	8	8	9	7

PROTECT: Primary Analysis of DFS in ITT$_{600mg}$

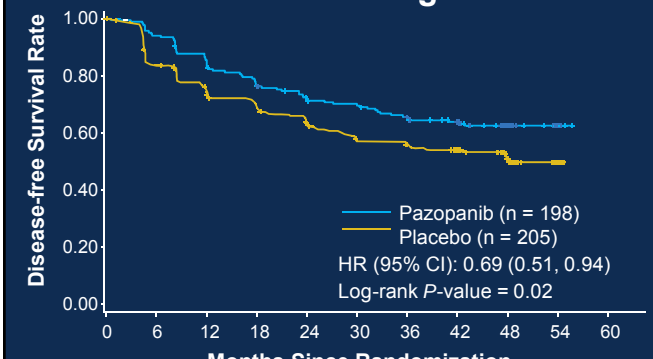


Patients at risk									
Pazopanib	571	482	423	382	308	209	118	29	0
Placebo	564	443	394	372	300	213	118	37	0

The median duration of follow up was 30.4 months and 30.7 months for the pazopanib and placebo arms, respectively.

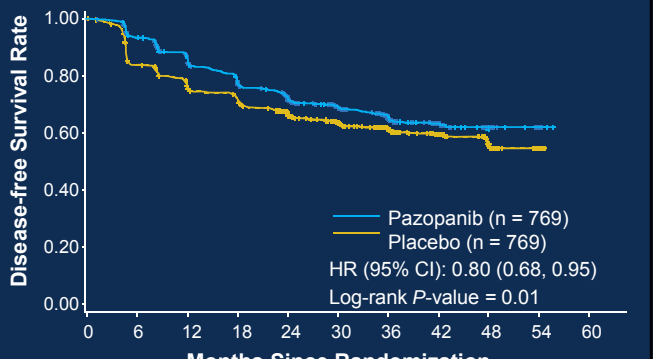
PROTECT: Secondary Analyses of DFS

ITT$_{800mg}$



Patients at risk											
Pazopanib	198	176	156	140	128	123	113	102	48	8	0
Placebo	205	169	144	134	119	106	97	85	46	3	0

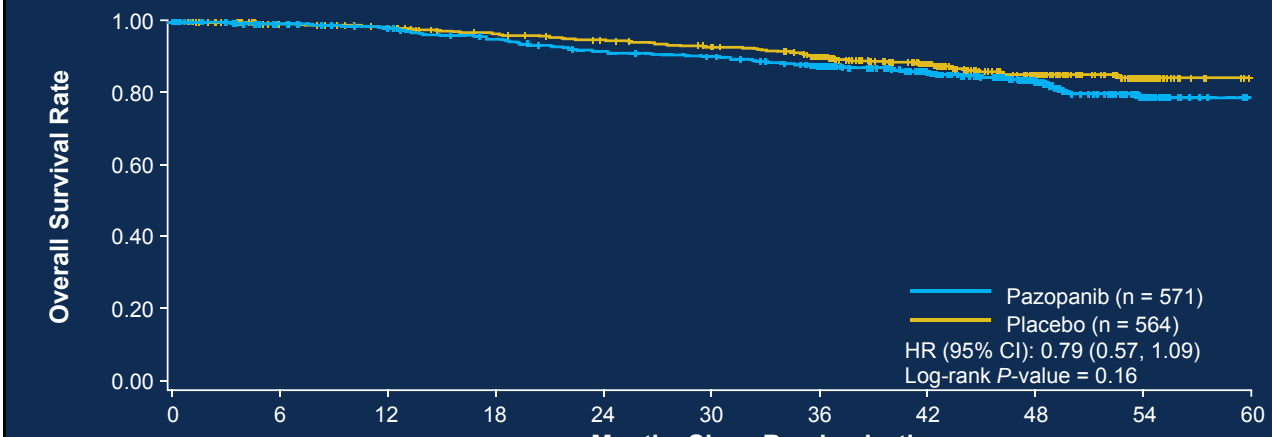
ITT$_{All}$



Patients at risk											
Pazopanib	769	658	579	522	436	332	231	131	48	8	0
Placebo	769	612	538	506	419	319	215	122	46	3	0

The median duration of follow up for both treatment arms in the ITT$_{800mg}$ group was 47.9 months, the median duration of follow up for the pazopanib and placebo arms was 35.5 and 35.9 months, respectively.

PROTECT: Overall Survival in ITT$_{600mg}$



Patients at risk

Pazopanib	571	529	517	498	484	468	428	315	178	58	0
Placebo	564	539	525	504	484	476	427	310	176	63	0

Interim analysis was based on 65 and 83 events in the pazopanib and placebo arms, respectively and performed on data cut-off October 15, 2016 as part of DFS follow-up.

PROTECT: Adverse Events

Adverse event,* %	Pazopanib 600 mg, n = 568		Placebo, n = 558	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any	98	60	90	21
Diarrhea	64	7	25	<1
Hypertension	52	25	19	7
Hair color changes	41	0	5	0
Nausea	40	<1	16	0
Fatigue	39	2	26	<1
Increased alanine aminotransferase	35	16	5	<1
Dysgeusia	30	<1	3	0
Increased aspartate aminotransferase	25	6	4	<1
Headache	24	<1	14	<1
Decreased appetite	20	<1	14	<1

*≥20%, any Grade.
There were no study treatment-related deaths according to investigator in the pazopanib 600 mg group.

PROTECT: Treatment Administered

	Pazopanib 600 mg n = 568	Placebo n = 558	Pazopanib 800 mg n = 198	Placebo n = 204
Median months on treatment*	10.6	11.9	10.2	12.0
AE-related dose reductions, %	48	9	53	11
Treatment discontinued, % Disease recurrence AEs Other**	85 6 35 11	5< 19 5 5	84 9 6< 9	5; 54 9 4
Dose escalation to 800 mg, %	21	73	NA	NA

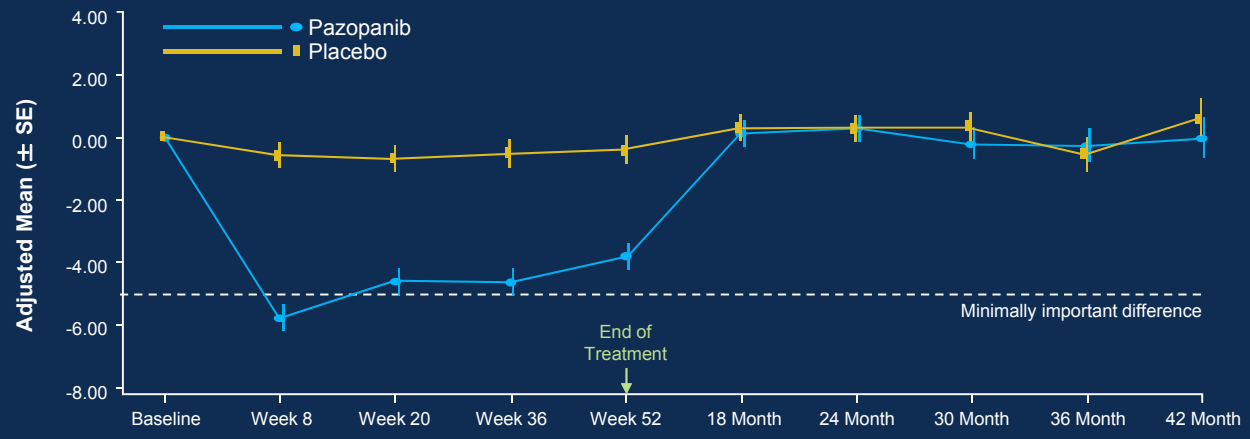
*Does not exclude dose interruptions; **Includes decision by patient or proxy, lost to follow up, physician decision, and protocol deviation.
NA, not applicable.

PROTECT: Treatment Administered and Hepatic-Related AEs

	Pazopanib 600 mg n = 568	Pazopanib 800 mg n = 198
Median time on study drug,* months	10.6	10.2
AEs leading to dose reduction, % Hepatic-related AEs requiring dose reduction/interruption	48 19	53 19
Treatment discontinued, % Hepatic-related AEs leading to discontinuation	85 53	84 54
Hepatic transaminase elevations*		
ALT >5x ULN, %	19	18
ALT >8x ULN, %	10	10

*Does not exclude dose interruptions.

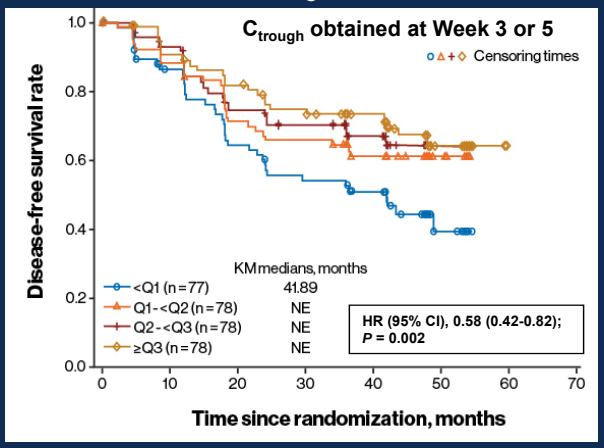
Quality-of-Life Assessment by FKSI-19 for ITT_{600mg} vs Placebo



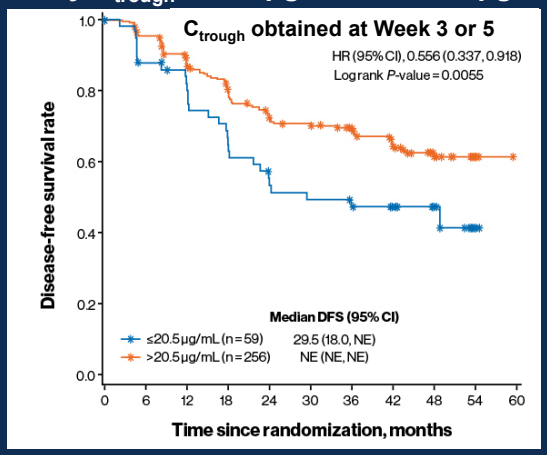
Evaluable patients (n)										
Pazopanib	558	435	485	451	423	364	335	253	161	71
Placebo	547	513	493	432	401	359	340	252	153	74

PROTECT: Pazopanib Concentrations for 600 mg Dose

DFS by C_{trough} Quartiles



DFS by C_{trough} >20.5 µg/mL or ≤20.5 µg/mL



- Longer DFS was observed in patients achieving higher C_{trough} quartiles and those achieving C_{trough} >20.5 µg/mL

PROTECT: Conclusions

- Pazopanib 600 mg daily dose as adjuvant therapy did not prolong DFS
- Pazopanib 800 mg starting dose resulted in a 31% decrease in the risk of recurrence or death, but this was a secondary objective of the study
- The safety profile was similar between 600 mg and 800 mg dose cohorts, and consistent with prior experience in advanced RCC
- Pazopanib is not recommended for adjuvant therapy following resection of locally advanced RCC

Differences in patient population between ASSURE, PROTECT and S-TRAC

	ASSURE	PROTECT	S-TRAC
Stage	≥T1b high grade and/or N1	≥T2 high grade and/or N1 (~85% were ≥T3 and/or N1)	≥T3 and/or N1
Required Clear Cell	No	Yes	Yes
Dose of sunitinib / Pazopanib	37.5 mg/d →25 mg/d	600 mg/d → escalate or de-escsalate	50 mg/d → 37.5 mg/d
Early Discontinuation	34-44%	35%	28.1%
Institutions	More community participation	Academic and community	Academic and major institution dominated
Radiology central review	No	Baseline only	Yes

RCC Adjuvant therapy: ongoing phase III trials of VEGF and mTOR inhibitors

Trial	Only clear cell RCC allowed	Stage	Therapy
ATLAS	Yes (>50% clear cell)	≥pT2 or N+	Axitinib x 3 years
SORCE	No	Intermediate or High risk by Leibovich score 3 to 11 (pT1b high grade or N+)	Sorafenib x 1 year Sorafenib x 3 years
EVEREST	No	pT1b high grade or N+	Everolimus x 1 year

RCC adjuvant therapy: Ongoing phase III trials of PD1/PD-L1 inhibitors

Trial	Only clear cell RCC allowed	Stage	Placebo controlled	Therapy
Immotion-010	Yes (sarcomatoid allowed)	≥pT2 or N+	Yes	Atezolizumab x 1 yr
KEYNOTE-564	Yes (sarcomatoid allowed)	≥pT2 or N+	Yes	Pembrolizumab x 1 yr
PROSPER	No	≥T2 or N+	No	Nivolumab x 1 mo → Sx → Nivolumab x 9 mo

GU: KEY TAKE HOME MESSAGES

- Addition of Abiraterone Acetate + Prednisone to ADT for metastatic castration-sensitive prostate cancer is a new standard (competes with docetaxel x 6 in the same space)
- Pembrolizumab demonstrated extension of survival compared to taxane/vinflunine salvage therapy for advanced urothelial carcinoma in a phase III trial (?preferred standard).
- Adjuvant therapy of RCC remains a field in evolution (1 POSITIVE trial [S-TRAC] and 2 NEGATIVE trials [ASSURE, PROTECT])