2011 GASCO Highlights GI Oncology

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Discussion Points

- GIST
  - Plenary session highlights
- Hepatocellular
- Colorectal
  - Metastatic colorectal cancer
    - Novel agents
  - Rectal
    - Radiosensitization
- Gastric CA
- Neuroendocrine
- Pancreatic

- Courtesy C. Eng

GIST Tumors: Adjuvant Therapy

Twelve vs. 36 months of adjuvant imatinib as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO)

H. Joensuu, M. Eriksson, J.Hartmann, K. Sundby Hall, J. Schütte, A. Reichardt, M. Schlemmer, E. Wardelmann, G. Ramadori, S. Al-Batran, B.E.Nilsson, O. Monge, R. Kallio, M. Sarlomo-Rikala, P. Bono, M. Leinonen, P. Hohenberger, T.Alvegård, P. Reichardt

Courtesy of Dr. Joensuu

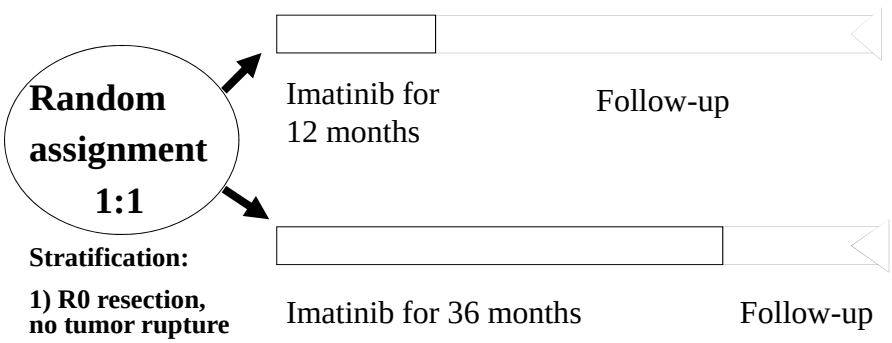
Gastrointestinal stromal tumor (GIST)

- Most common mesenchymal tumor of the GI-tract
  - Incidence ~10 cases/million/year
- GISTs have variable malignancy potential
- High-risk GIST
  - Consist of large (>5 cm) tumors with a high cell proliferation rate
  - Associated with ≥50% 5-year risk of recurrence after surgery[1-3]
- 75% of GIST have mutations of cKIT and 10% with mutations of PDGFR
- One year of adjuvant imatinib improved RFS compared to placebo in the ACOSOG Z9001 trial, but relapse rate increased occured after 1 year[4]

[1]Nilsson B et al. Cancer 2005; 103:821-9; [2]Hassan I et al. Ann Surg Oncol 2008; 15:52-9; [3]Rutkowski P et al. Ann Surg Oncol 2007; 14:2018-27, [1]DeMatteo RP et al. Lancet 2009; 373:1097-104

SSGXVIII: Study design

An open-label Phase III study



Stratification:

1) R0 resection, no tumor rupture

2) R1 resection *or* tumor rupture

Primary objective: RFS

SSGXVIII: Objectives

- Hypothesis
  - Three years of adjuvant imatinib may result in longer RFS as compared to 1 year of imatinib
- **Primary: RFS**
  - Time from randomization to GIST recurrence or death
- **Secondary objectives included:**
  - Safety
  - Overall survival

SSGXIII: Key criteria

- Inclusion criteria
  - Histologically confirmed GIST, KIT-positive
  - High risk of recurrence according to the modified Consensus Criteria*:
    - Tumor diameter >10 cm *or*
    - Tumor mitosis count >10/50 HPF** *or*
    - Size >5 cm and mitosis count >5/50 HPFs *or*
    - Tumor rupture spontaneously or at surgery
- Exclusion Criteria
- Inoperable, recurrent or metastatic GIST*
- Age <18
- ECOG** performance status >2
- >12 weeks between the date of surgery and study entry
- Clinically significant cardiac, hepatic, renal or bone marrow disease

*Fletcher CD et al. Hum Pathol 2002; 33:459-65

**HPF, High Power Field of the microscope

Patients with operable metastases were allowed to enter until protocol amendment in October 2006; **Eastern Cooperative Oncology Group

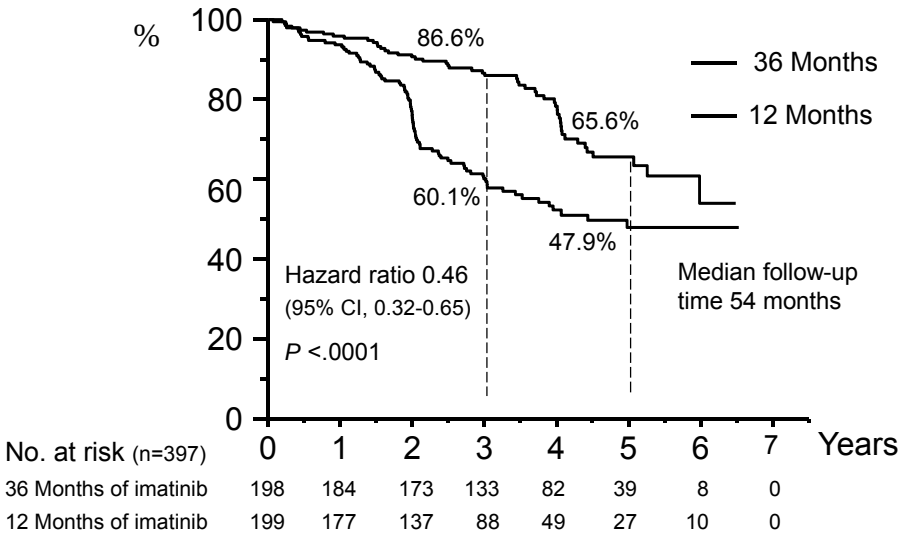
Courtesy of Dr. Joensuu

Baseline characteristics (ITT)

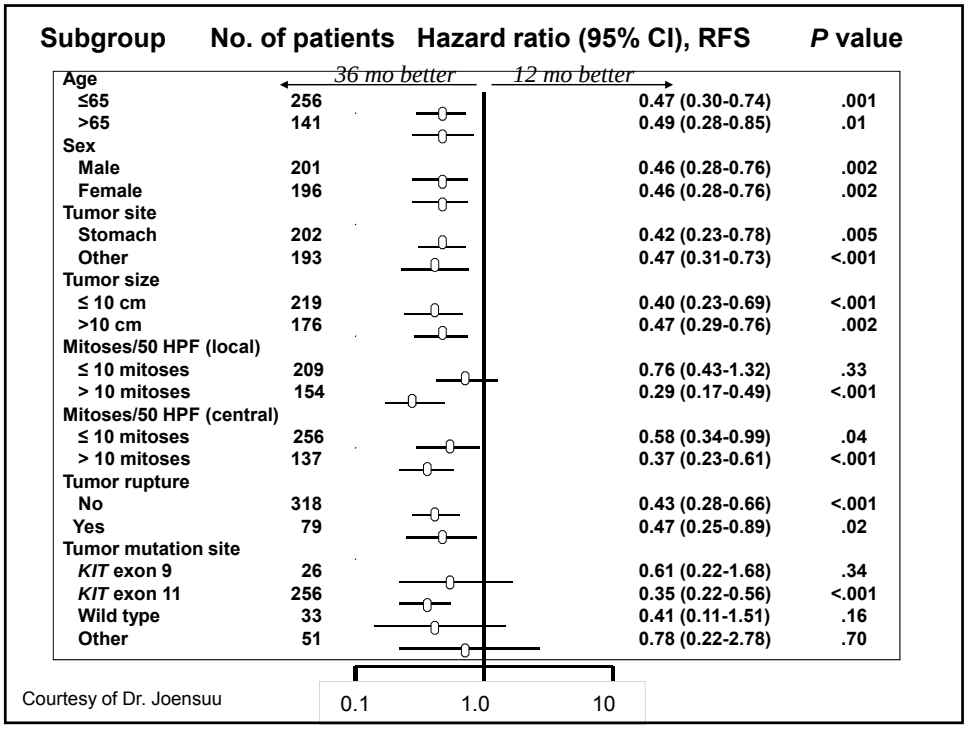
Characteristic	12-Mo group	36-Mo group
Median age (range) - years	62 (23-84)	60 (22-81)
Male - (%)	52	49
ECOG performance status 0 - (%)	85	86
Gastric primary tumor - (%)	49	53
Median tumor size (range) - cm	9 (2-35)	10 (2-40)
Median mitosis count - /50 HPFs	10 (0-250)	8 (0-165)
Tumor rupture - (%)	18	22
GIST gene mutation site - (%)*		
- *KIT* exon 9	6	7
- *KIT* exon 11	69	71
- *KIT* exon 13	2	1
- *PDGFRA* (D842V)	13 (10)	12 (8)
- wild type	10	8

*Available for 366 (92%) out of the 397 tumors

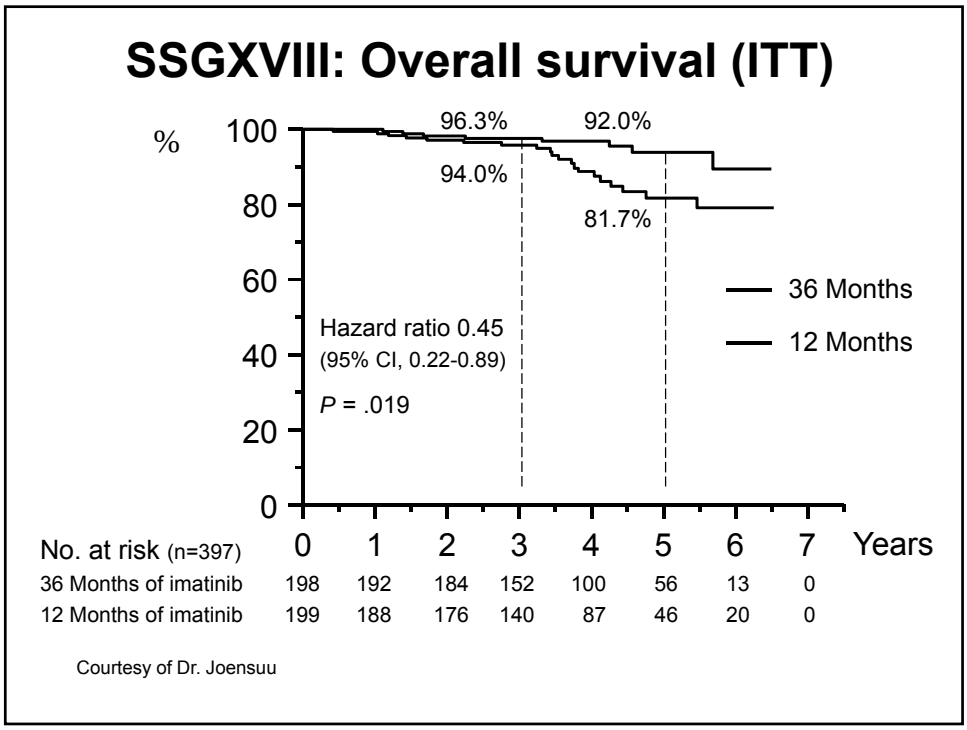
SSGXVIII: Recurrence-free survival (ITT)



Courtesy of Dr. Joensuu



Courtesy of Dr. Joensuu



Courtesy of Dr. Joensuu

Treatment safety

Category	12-month group (n=194) No. (%)	36-month group (n=198) No. (%)	*P*
Any adverse event	192 (99)	198 (100)	.24
Grade 3 or 4 event	39 (20)	65 (33)	.006
Cardiac event	8 (4)	4 (2)	.26
Second cancer	14 (7)	13 (7)	.84
Death, possibly imatinib-related	1* (1)	0 (0)	.49
Discontinued imatinib, no GIST recurrence	25 (13)	51 (26)	.001

*Lung injury

Courtesy of Dr. Joensuu

Most frequent adverse events

Adverse event	Any Grade		*P*	Grade 3 or 4		*P*
	12 Mo %	36 Mo %		12 Mo %	36 Mo %	
Anemia	72	80	.08	1	1	1.00
Periorbital edema	59	74	.002	1	1	1.00
Elevated LDH*	43	60	.001	0	0	-
Fatigue	48	48	1.00	1	1	.62
Nausea	45	51	.23	2	1	.37
Diarrhea	44	54	.044	1	2	.37
Leukopenia	35	47	.014	2	3	.75
Muscle cramps	31	49	<0.001	1	1	1.00

*LDH, lactate dehydrogenase

Courtesy of Dr. Joensuu

Conclusions

- Compared to 1 year of adjuvant imatinib,3 years of imatinib improves
  - RFS
  - Overall survival
  - As treatment of GIST patients who have a high estimated risk of recurrence after surgery.
- Adjuvant imatinib is relatively well tolerated; severe adverse events are infrequent.

Hepatocellular Carcinoma

Abstract 4000

Phase 3 Trial of Sunitinib versus Sorafenib in Advanced Hepatocellular Carcinoma

A-L Cheng,[1] Y-K Kang,[2] D-Y Lin,[3] J-W Park,[4] M Kudo,[5] S Qin,[6] M Omata,[7] S Pitman Lowenthal,[8] S Lanzalone,[9] L Yang,[8] MJ Lechuga,[9] E Raymond[10] for the SUN1170 HCC Study Group

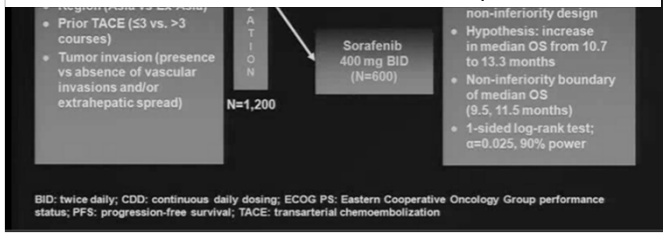
[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Asan Medical Center, Seoul, Republic of Korea; [3]Chang Gung Memorial Hospital, Chang Gung University, Taiwan; [4]Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea; [5]Kinki University Hospital, Osaka, Japan; [6]Nanjing Bayi Hospital, Nanjing, Jiangsu, China; [7]Yamanashi Prefecture Central Hospital, Kofu, Yamanashi, Japan; [8]Pfizer Oncology, La Jolla, California, USA; [9]Pfizer Italia Srl, Milan, Italy; [10]Service Inter Hospitalier de Cancerologie Bichat-Beaujon, Clichy, France

SUN1170 HCC – Study Design

Enrollment Criteria
- Advanced histologically confirmed HCC
- No prior systemic
- Prior TACE (≤3 vs. >3 courses)
- Tumor invasion (presence vs absence of vascular invasions and/or extrahepatic spread)

Endpoints
- Primary: OS
- Secondary

The study was stopped after a planned safety analysis by an IDMC (events = 457 deaths). Higher incidence of SAE's with sunitinib. Enrollment halted after 1,074 pts



- non-inferiority design
- Hypothesis: increase in median OS from 10.7 to 13.3 months
- Non-inferiority boundary of median OS (9.5, 11.5 months)
- 1-sided log-rank test; α=0.025, 90% power

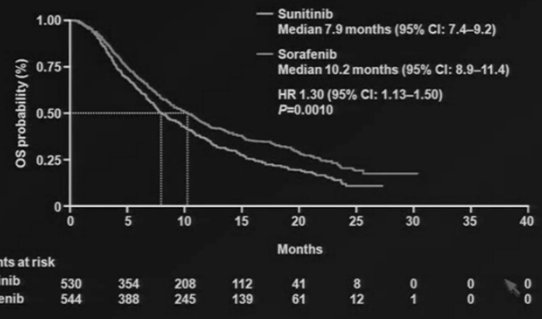
BID: twice daily; CDD: continuous daily dosing; ECOG PS: Eastern Cooperative Oncology Group performance status; PFS: progression-free survival; TACE: transarterial chemoembolization

Baseline Patient Characteristics
(ITT Population)

Characteristic	Sunitinib (N=530)	Sorafenib (N=544)
Median age (range), years	59 (18–85)	59 (18–84)
Male gender (%)	82	84
Geographical region of Asia* (%)	76	75
Vascular invasion and/or extrahepatic spread* (%)	79	76
Prior TACE* (%)		
≤3 courses	84	83
>3 courses	15	17
ECOG PS of 1 (%)	47†	47
HBV/HCV infection (%)	55/21	53/22
CLIP score (%)		
0	9	13
1/2	58	57
≥3	29	28
BCLC stage B/C (%)‡	13§/87§	16/83

*Stratification factor; †includes 1 patient with ECOG performance status of 2; ‡staging assigned retrospectively
§Percentage of 529 patients
BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of the Liver Italian Program; ITT: intent-to-treat

OS – Primary Endpoint
(ITT Population)



Patients at risk

Sunitinib	530	354	208	112	41	8	0	0	0
Sorafenib	544	388	245	139	61	12	1	0	0

P value based on stratified log-rank test; CI: confidence interval; HR: hazard ratio

Conclusions

- Sunitinib did not demonstrate superiority or non-inferiority in OS, compared with sorafenib in patients with advanced HCC
- PFS, TTP, and ORR were comparable between treatment arms
- Frequency and severity of AEs were higher with sunitinib than sorafenib
- In patients with HBV infection, OS was similar between arms. In patients with HCV infection, OS was shorter with sunitinib

GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma [HCC] and Of its treatment with sorafeNib) second interim analysis in >1500 patients: clinical findings in patients with liver dysfunction

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R. Lencioni, M. Kudo, S. L. Ye, K. Nakajima, F. Cihon, A. Venook

The GIDEON study

GIDEON study design and objectives

- GIDEON is a non-interventional study
  - **Primary objective**: to evaluate safety of sorafenib in patients with uHCC who are candidates for systemic therapy and for whom the decision to treat with sorafenib was made in clinical practice
  - **Secondary objectives**: efficacy, duration of therapy, methods of patient evaluation, diagnosis and follow-up, co-morbidities and practice patterns
- GIDEON will also provide information in patient subgroups where data are currently limited
  - Including patients with Child-Pugh B status who were generally excluded from sorafenib Phase III trials in uHCC

Conclusions (1)

- Based on the second interim analysis, there is no evidence suggesting that treating physicians use a different dosing strategy for Child-Pugh B patients compared with Child-Pugh A patients
- Duration of sorafenib therapy was shorter in Child-Pugh B patients than in Child-Pugh A patients
- Compared with Child-Pugh A patients, Child-Pugh B patients did not have a higher incidence of drug-related AEs, but had a higher incidence of liver-associated AEs
- In patients with moderate liver dysfunction, no unexpected AEs were observed

AEs, adverse events; SAEs, serious adverse events

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Conclusions (2)

- The vast majority of deaths were due to HCC or underlying liver disorders
- The differences in patient outcomes across Child-Pugh groups likely reflect differences in prognosis
- Consistent with previously reported studies, these preliminary data indicate that Child-Pugh status appears to be a useful prognostic factor for overall survival
- The GIDEON study is ongoing, and the safety, tolerability, and efficacy of sorafenib in HCC patients will continue to be evaluated

HCC, hepatocellular carcinoma; GIDEON, Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib

Colon Cancer

Adjuvant

The efficacy of oxaliplatin (Ox) when added to 5-fluorouracil/leucovorin (FU/L) in stage II colon cancer. (Abst 3507)

Background

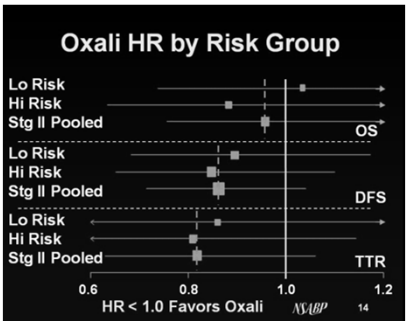
- Use of Oxali for stage II colon cancer is controversial, particularly for patients who lack "high risk" features
- In this study, high risk defined as:
  - Perforation
  - T4 penetration
  - Less than 12 nodes examined

-NCCN Guidelines v3.2011
-Benson AB, et al. *J Clin Oncol* 2004;22:3408-19 NSABP 3

Methods

- Examine pooled data from recent NSABP colon trials to gain power for Stage II as well as High and Low risk subsets within Stage II
- NSABP Trials Included:
  - C-05 5-FU/Lv or similar
  - C-06 5-FU/Lv or similar
  - C-07: Rand to 5-FU/Lv +/- Oxali
  - C-08: 5-FU/Lv + Oxali or similar

NSABP 4



Observed 5 year Adjusted* Kaplan-Meier Estimates by Risk Group

Endpoint – Risk Group	5-FU/Lv	5-FU/Lv + Oxali	Increase with Oxali
OS – HiRisk	86.7	90.2	+ 3.5
– LoRisk	89.2	91.7	+ 2.5
DFS – HiRisk	76.3	80.7	+ 4.4
– LoRisk	80.6	83.6	+ 3.0
TTR – HiRisk	84.0	89.2	+ 5.2
– LoRisk	89.2	91.6	+ 2.9

*Adjusted for age, gender, and race

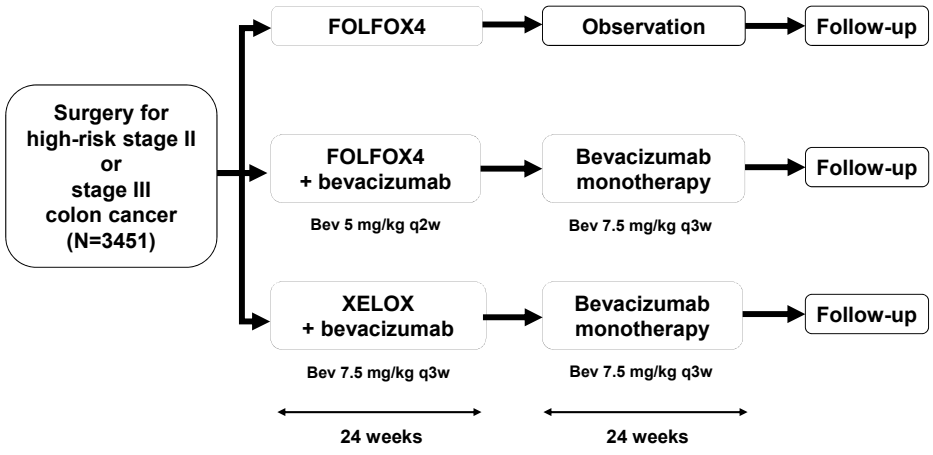
NSABP 15

Discussion

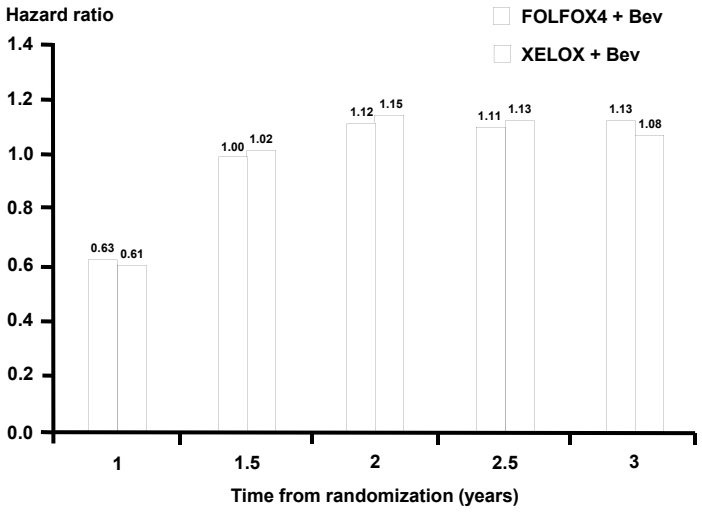
- The observed HR & KM estimates suggest a trend for benefit from Oxali in stage II (particularly for DFS & TTR)
  - Effect smaller in St II than St III
- Smaller relative benefit observed in stage II combined with lower overall event rates imply small absolute benefit in stage II
  - Observed absolute benefit ≈ 3% OS, 5% TTR
  - Number needed to treat ≈ 33 OS, 20 TTR

NSABP 18

Adjuvant therapy with bevacizumab: AVANT Study Design (Andre et al)



DFS: Cumulative Hazard Ratio (ITT Stage III)



Summary of Results For DFS (ITT Stage III)

	FOLFOX4 (N=955)	FOLFOX4 + Bev (N=960)	XELOX + Bev (N=952)
Lost to follow-up, n (%)	62 (7)	52 (5)	52 (6)
Patients with event, n (%)	237 (25)	280 (29)	253 (27)
P-value for global hypothesis		p=0.2024	
3-year DFS rate, %	76	73	75

Summary and Conclusions

- **Addition of bevacizumab to FOLFOX4 or XELOX did not prolong DFS in adjuvant treatment of stage III colon cancer**
  - **chemotherapy alone arm was favoured numerically**
- **Bevacizumab treatment effect was not constant over time**
  - **transient favourable effect can be seen within 1 year, which is in-line with NSABP C-08**
  - **although transient favourable effect is more dominant in N2 subgroup, overall treatment effect is lost**
- **Further subgroup analysis results for DFS were consistent with those seen in overall stage III colon cancer population**
- **Immature OS data suggest a potential detriment. Follow up will continue until at least June 2012, for 5 years minimum follow up for analysis of OS**
- **Biomarker programme might help us to understand results seen with bevacizumab in the adjuvant setting**

Final results from PRIME: Randomized ph 3 study of panitumumab (pmab) + FOLFOX4 for 1st-line met colorectal cancer (mCRC). (#3510)

WT *KRAS* mCRC (n = 656)	FOLFOX+pmab (n = 325)	FOLFOX (n = 331)	HR (95% CI)	P value[a]
Median PFS - mos (95% CI)	10.0 (9.3 - 11.4)	8.6 (7.5 - 9.5)	0.80 (0.67 - 0.95)	0.009
Median OS - mos (95% CI)	23.9 (20.3 - 27.7)	19.7 (17.6 - 22.7)	0.88 (0.73 - 1.06)	0.17
ORR[b] - % (95% CI)	57 (51 - 63)	48 (42 - 53)		
Odds ratio (95% CI)	1.47 (1.07 - 2.04)			0.018
MT *KRAS* mCRC (n = 440)	**FOLFOX+pmab(n = 221)**	**FOLFOX (n = 219)**		
Median PFS - mos (95% CI)	7.4 (6.9 - 8.1)	9.2 (8.1 - 9.9)	1.27 (1.04 - 1.55)	0.02
Median OS - mos (95% CI)	15.5 (13.1 - 17.6)	19.2 (16.5 - 21.7)	1.17 (0.95 - 1.45)	0.15
ORR[b] - % (95% CI)	40 (33 - 47)	41 (34 - 48)		
Odds ratio (95% CI)	0.98 (0.65 - 1.47)			0.98

Colon Cancer

Metastatic

Selection of Anti-EGFR Antibodies: Are all KRAS Mutations in Colorectal Cancer Created Equal ?

KRAS status as a determinant of response to anti-EGFR antibodies

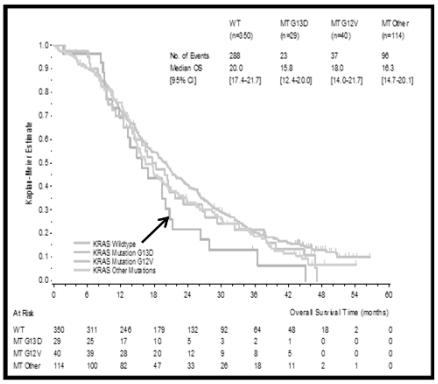
- Initial retrospective analyses of MCRC trials suggested that patients with KRAS-mutated (MT) tumors will not benefit from EGFR inhibitors
- Health Authorities in the US and EU recently indicated that patients with KRAS codon 12 or 13 MT tumors are not candidates for cetuximab or panitumumab

Allegra et al. J Clin Oncol. 2009;27(12):2091-2096
De Rook et al. JAMA. 2010;304(16): 1812-1820

Courtesy of T. Saab

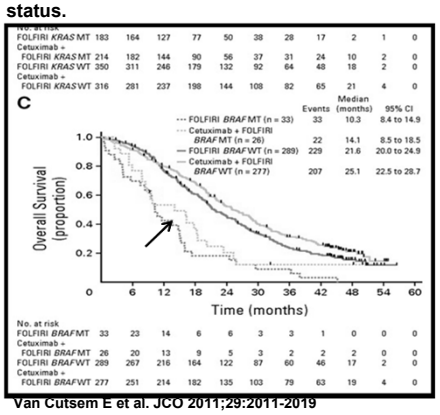
KRAS G13D and *BRAF* mutations are prognostic in MCRC

CRYSTAL (FOLFIRI Only): OS for patients according to tumor KRAS mutation status.



Tejpar et al . Abs 3511 ASCO 2011.

CRYSTAL : OS for patients with KRAS WT disease according to tumor BRAF mutation status.



Van Cutsem E et al. JCO 2011;29:2011-2019

Courtesy of T. Saab

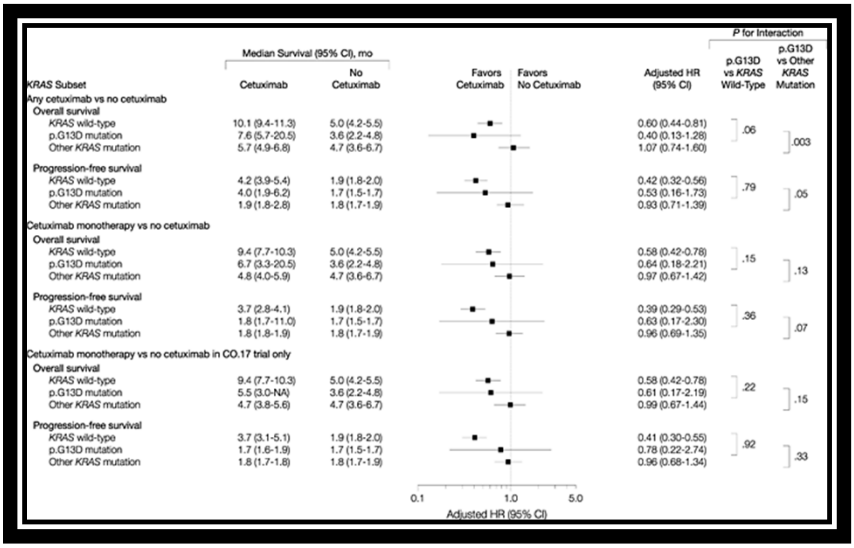
Influence of KRAS G13D mutations on outcome in pts with mCRC treated with First Line Chemotherapy +/- cetuximab

	N	Response %		PFS mo		OS mo	
		CT	CT+cet	CT	CT+cet	CT	CT+cet
KRAS wt	845	38.5	57.3	7.6	9.6	19.5	23.5
Odds ratio/HR*		2.17		0.66		0.81	
[95% CI]		[1.64-2.86]		[0.55-0.80]		[0.69-0.94]	
P value		<0.0001		<0.0001		0.0063	
KRAS G13D	83	22.0	40.5	6.0	7.4	14.7	15.4
Odds ratio/HR*		2.41		0.60		0.80	
[95% CI]		[0.90-6.45]		[0.32-1.12]		[0.49-1.30]	
P value		0.0748		0.1037		0.37	
KRAS other mutations	450	43.8	30.5	8.5	6.4	17.7	15.5
Odds ratio/HR*		0.56		1.42		1.14	
[95% CI]		[0.38-0.83]		[1.10-1.83]		[0.93-1.40]	
P value		0.0037		0.0069		0.1964	

Tejpar et al . Abs 3511 ASCO 2011.

Courtesy of T. Saab

Association of Various KRAS Mutations with Outcome in Patients with Chemorefractory Colorectal Cancer treated with Cetuximab



De Roock, W. et al. JAMA 2010;304:1812-1820

Courtesy of T. Saab

Conclusions and Future Directions

- *KRAS G13D* and *BRAF* mutations likely have an adverse prognostic effect in mCRC
  - Modest benefit with the addition of anti-EGFR antibodies
  - Cost/Benefit question may be difficult to address in a randomized trial
  - Prospective validation of results is needed
  - Future studies with anti-EGFR antibodies should include and stratify for *KRAS G13D* and *BRAF* mutations
- *KRAS G12* mutation is predictive of lack of response to anti-EGFR antibodies
  - *KRAS G12V* likely has no prognostic value in mCRC

Does primary = metastases in molecular changes ?

- **Abstract 10500 (YES)**
- Mutational analysis of 84 matched pairs of primary and met. CRC
- concordance rate of 98%, 98% and 95% for RAS/BRAF, PIK3CA and TP53 mutations
- Unsupervised clustering of array CGH data from 22 matched pairs of primary and metastatic CRC showed that all pairs clustered together.

- **Abstract 3535 (No)**
- Used targeted sequencing of primary and metastases
- 83 potentially relevant SNV (Single Nucleotide Variation) were gained in the mets
- 70 SNVs present in the primary tumor were lost.
- genetic variations affected several essential pathways.
- Conclusion: tumor evolution caused losses and gains of critical genes
- No selective pressure from chemotherapy

C-Met Inhibitors in Metastatic Colorectal Cancer

Primary Analysis and Biomarker Evaluation: Randomized Phase Ib/II Study of Rilotumumab (AMG 102) or Ganitumab (AMG 479) With Panitumumab Versus Panitumumab Alone in Patients With Metastatic Colorectal Cancer (mCRC)

Cathy Eng,[1] Elzbieta Nowara,[2] Anna Świeboda-Sadlej,[3] Niall C. Tebbutt,[4] Edith Mitchell,[5] Irina Davidenko,[6] Elena Elez,[7] Kelly S. Oliner,[8] Lisa Chen,[8] Jing Huang,[9] Ian McCaffery,[8] Elwyn Loh,[9] Dominic Smethurst,[10] Eric Van Cutsem[11]

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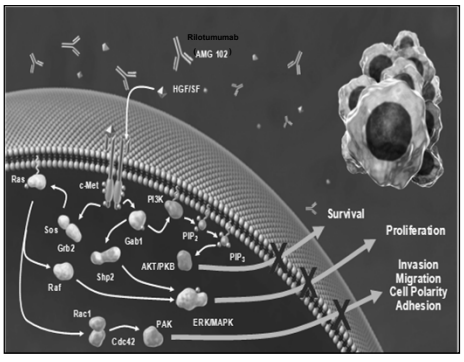
As presented at World GI Congress, Barcelona, 2011

Introduction

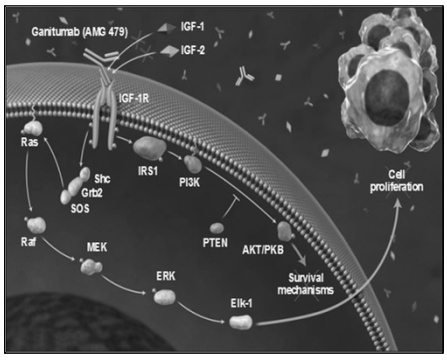
- Panitumumab, a fully human monoclonal antibody against the epidermal growth factor receptor (EGFR), has demonstrated efficacy in patients with wild-type (WT) *KRAS* mCRC in clinical trials[1-4]
- Rilotumumab (AMG 102) and ganitumab (AMG 479) are investigational, fully human monoclonal antibodies against the hepatocyte growth factor (HGF; ligand for c-Met receptor) and the insulin-like growth factor 1 receptor (IGF-1R), respectively
- Preclinical studies indicate that there is complex interdependence between the HGF/c-Met and IGF-1R and EGFR pathways[5-10]
- Combinations of agents that block these receptors are being investigated for their potential to generate additive/synergistic anticancer effects

1. Van Cutsem E, et al. *J Clin Oncol.* 2007;25:1658-1664.
2. Amado RG, et al. *J Clin Oncol.* 2008;26:1626-1634.
3. Peeters M, et al. *J Clin Oncol.* 2010;28:4706-4713.
4. Douillard JY, et al. *J Clin Oncol.* 2010;28:4697-4705.
5. Lesko E, et al. *Front Biosci.* 2008;13:1271-1280.
6. Hynes NE, et al. *Nat Rev Cancer.* 2005;5:341-354.
7. Jo M, et al. *J Biol Chem.* 2000;275:8806-8811.
8. Ahmad T, et al. *J Biol Chem.* 2004;279:1713-1719.
9. Roudabush FL, et al. *J Biol Chem.* 2000;275:22583-22589.
10. Swantek JL, et al. *Endocrinology.* 1999;140:3163-3169.

Rilotumumab (AMG 102) and Ganitumab (AMG 479) Mechanisms of Action



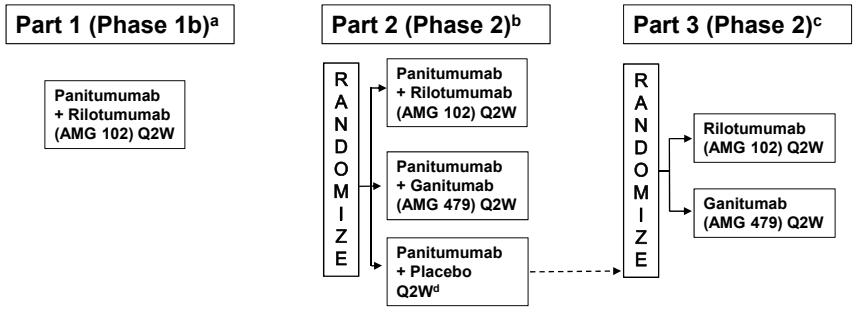
Rilotumumab (AMG 102) targets HGF, inhibiting downstream c-Met signaling



Ganitumab (AMG 479) targets IGF-1R, inhibiting downstream signaling through PI3K/AKT and MAPK pathways

Study Schema

- Amgen Trial 20060447; ClinicalTrials.gov identifier NCT00788957



[a]Panitumumab 6 mg/kg Q2W; rilotumumab (AMG 102) 10 mg/kg Q2W with dose de-escalation to 5 mg/kg as necessary; primary endpoint was incidence of dose-limiting toxicities
[b]Panitumumab 6 mg/kg Q2W; rilotumumab (AMG 102) dose based on phase 1b; ganitumab (AMG 479) 12 mg/kg Q2W; primary endpoint was ORR
[c]Rilotumumab 10 mg/kg Q2W; ganitumab (AMG 479) 12 mg/kg Q2W; primary endpoint was ORR
[d]Patients in the placebo arm of Part 2 with progressive disease or intolerance to treatment were eligible to participate in Part 3
DLT, dose-limiting toxicity; ORR, objective response rate; Q2W, every 2 weeks

- Tumor assessments were performed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0

Results for Part 2

- 142 patients enrolled from 37 sites in 11 countries
- The enrollment period was June 9, 2009 through February 5, 2010
- The date for data cut-off for this analysis was July 23, 2010
- Median follow-up is 6.9 months; follow-up is ongoing

Part 2: Patient Demographics and Disease Characteristics at Baseline

	Panitumumab + Placebo (n = 48)	Panitumumab + Rilotumumab (AMG 102) (n = 48)	Panitumumab + Ganitumab (AMG 479) (n = 46)
Men - n (%)	28 (58)	29 (60)	25 (54)
Age - mean years (range)	55.0 (19-75)	62.1 (45-78)	62.0 (33-81)
ECOG performance status - n (%)			
0	15 (31)	24 (50)	18 (39)
1	33 (69)	23 (48)[a]	28 (61)
Metastatic sites - n (%)			
Liver only	5 (10)	5 (10)	4 (9)
Liver + other sites	27 (56)	32 (67)	29 (63)
Prior therapies for mCRC - n (%)			
First-line therapy	46 (96)[b]	48 (100)	46 (100)
Second-line therapy	31 (65)	33 (69)	26 (57)
Third-line therapy and later	14 (29)	16 (33)	12 (26)
Prior chemotherapies for mCRC - n (%)			
Oxaliplatin	39 (81)	42 (88)	40 (87)
Irinotecan	30 (63)	32 (67)	26 (57)
Oxaliplatin and irinotecan	23 (48)	26 (54)	20 (44)

[a]One patient with ECOG performance score of 2 was enrolled in error; data from this patient were included in all efficacy and safety analyses
[b]Two patients had not received first-line therapy for mCRC; both patients had received oxaliplatin-based chemotherapy for non-metastatic CRC in the adjuvant setting and progressed on therapy before entering the study

Primary Endpoint: Objective Response Rate

	Panitumumab + Placebo (n = 48)	Panitumumab + Rilotumumab (AMG 102) (n = 48)	Panitumumab + Ganitumab (AMG 479) (n = 46)
Objective Response - n (%)	10 (21)	15 (31)	10 (22)
Complete Response (CR)	0 (0)	0 (0)	0 (0)
Partial Response (PR)	10 (21)	15 (31)	10 (22)
Stable Disease (SD)[a]	17 (35)	19 (40)	18 (39)
Progressive Disease (PD)	16 (33)	11 (23)	15 (33)
Unevaluable/Not done	5 (10)	3 (6)	3 (6)
Disease control rate[b] - % (95% CI)	56 (41-71)	71 (56-83)	61 (45-75)
Duration of response - median months (95% CI)	3.7 (3.6-NE)	5.1 (3.7-5.6)	3.7 (3.6-5.8)
Posterior probability of Odds Ratio > 1[c]		0.93	0.63

[a]The minimum assessment time must be at least 49 days from the first dosing date to be qualified as stable disease
[b]Disease control rate = CR + PR + SD
[c]OR is calculated based on ORR; an OR > 1 favors the combination arm over panitumumab alone
NE, not estimable

- Responses were required to be confirmed at least 4 weeks after response criteria were first met

Adverse Events
(Any Grade in ≥ 20% or Grade 3/4 in ≥ 2 Patients)

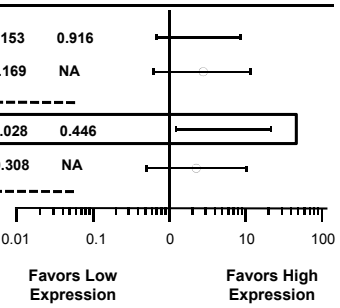
	Panitumumab + Placebo (n = 48)		Panitumumab + Rilotumumab (AMG 102) (n = 48)		Panitumumab + Ganitumab (AMG 479) (n = 46)	
AE (Preferred term) - %	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Any AE	94	52	98	71	100	63
Rash	52	8	58	29	48	13
Acneiform dermatitis	33	10	35	15	26	11
Pruritus	25	0	21	0	28	2
Skin fissures	17	0	15	2	26	0
Paronychia	15	2	31	4	20	2
Dry skin	15	0	23	2	22	0
Acne	0	0	8	4	11	0
Skin toxicity	0	0	2	2	4	4
Constipation	25	6	10	0	13	0
Decreased appetite	17	2	21	2	20	2
Abdominal pain	15	6	10	4	9	7
Diarrhea	10	0	15	4	26	2
Hypomagnesemia	21	2	29	4	41	15
Fatigue	21	2	10	4	17	2
Anemia	17	8	4	0	2	0
Asthenia	15	0	8	0	13	4

AE, adverse event

- There were 9 grade 5 AEs; 1 occurred in the panitumumab alone arm and 4 occurred each in the combination arms
  - All except 1 were due to disease progression; 1 fatal AE was due to staphylococcal sepsis (panitumumab + ganitumab [AMG 479] arm)
  - None were reported to be related to investigational product

Effect of Cytoplasmic c-Met IHC Staining on Objective Response Rate

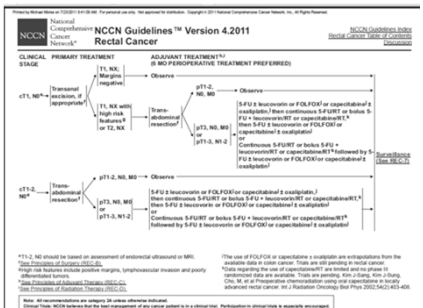
c-Met IHC Parameter	Treatment Group	# of Patients (# of Events) Low Expression	High Expression	OR (95% CI)	P-value	Interaction P-value
High = % Pos > 50%* Low = % Pos ≤ 50%	AMG 102 + Pmab	26 (6)	21 (9)	2.501 (0.712-8.789)	0.153	0.916
	Placebo + Pmab	26 (4)	18 (6)	2.777 (0.648-11.903)	0.169	NA
High = Max SI ≥ 2+ Low = Max SI < 2+	AMG 102 + Pmab	35 (8)	12 (7)	4.975 (1.194-20.729)	0.028	0.446
	Placebo + Pmab	32 (6)	12 (4)	2.187 (0.486-9.830)	0.308	NA



*Positive tumor cells are those with a staining intensity of at least 1

IHC, immunohistochemistry; OR, odds ratio; Pmab, panitumumab; SI, staining intensity; Pos, positive

Rectal Cancer



NCCN Guidelines™ Version 4.2011
Rectal Cancer

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CLINICAL STAGE | PRIMARY TREATMENT | ADJUVANT TREATMENT[h,j] (6 MO PERIOPERATIVE TREATMENT PREFERRED)

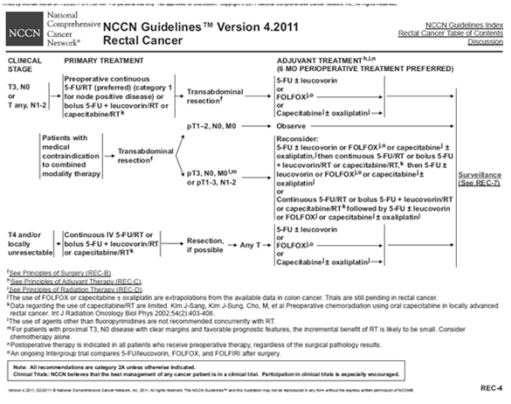
cT1, N0[a] → Transanal excision, if appropriate[b]
- T1, NX; Margins negative → Observe
- T1, NX with high risk features[a] or T2, NX → Trans-abdominal resection[f]
  - pT1-2, N0, M0 → Observe
  - pT3, N0, M0 or pT1-3, N1-2 → 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin.[i] then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT[k] then 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin[i] or Continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT[k] followed by 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin[i] → Surveillance (See REC-7)

cT1-2, N0[a] → Trans-abdominal resection[f]
- pT1-2, N0, M0 → Observe
- pT3, N0, M0 or pT1-3, N1-2 → 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin.[i] then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT,[k] then 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin[i] or Continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT[k] followed by 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin[i]

[a]T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.
[b]See Principles of Surgery (REC-B).
High risk features include positive margins, lymphovascular invasion and poorly differentiated tumors.
[c]See Principles of Adjuvant Therapy (REC-C).
[d]See Principles of Radiation Therapy (REC-D).
[f]The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer. Trials are still pending in rectal cancer.
[k]Data regarding the use of capecitabine/RT are limited. Kim J-Sang, Kim J-Sung, Cho, M, et al Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer: Int J Radiation Oncology Biol Phys 2002;54(2):403-408.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

REC-3



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Rectal Cancer

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CLINICAL STAGE | PRIMARY TREATMENT | ADJUVANT TREATMENT[h,j,m] (6 MO PERIOPERATIVE TREATMENT PREFERRED)

T3, N0 or T any, N1-2 → Preoperative continuous 5-FU/RT (preferred) (category 1 for node positive disease) or bolus 5-FU + leucovorin/RT or capecitabine/RT[k] → Transabdominal resection[f]
- pT1–2, N0, M0 → Observe
- pT3, N0, M0[l,m] or pT1-3, N1-2 → 5-FU ± leucovorin or FOLFOX[i,o] or Capecitabine[j] ± oxaliplatin[i]

Patients with medical contraindication to combined modality therapy → Transabdominal resection[f]
- pT1–2, N0, M0 → Observe
- pT3, N0, M0[l,m] or pT1-3, N1-2 → Reconsider: 5-FU ± leucovorin or FOLFOX[i,o] or capecitabine[j] ± oxaliplatin.[i] then continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT,[k] then 5-FU ± leucovorin or FOLFOX[i,o] or capecitabine[j] ± oxaliplatin[i] or Continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT[k] followed by 5-FU ± leucovorin or FOLFOX[i] or capecitabine[j] ± oxaliplatin[i] → Surveillance (See REC-7)

T4 and/or locally unresectable → Continuous IV 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT[k] → Resection, if possible → Any T → 5-FU ± leucovorin or FOLFOX[i,o] or Capecitabine[j] ± oxaliplatin[i]

[b]See Principles of Surgery (REC-B)
[c]See Principles of Adjuvant Therapy (REC-C)
[d]See Principles of Radiation Therapy (REC-D)
[f]The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer. Trials are still pending in rectal cancer.
[k]Data regarding the use of capecitabine/RT are limited. Kim J-Sang, Kim J-Sung, Cho, M, et al Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer: Int J Radiation Oncology Biol Phys 2002;54(2):403-408.
[l]The use of agents other than fluoropyrimidines are not recommended concurrently with RT.
[m]For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.
[o]Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[s]An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

REC-4

Capecitabine versus 5-fluorouracil-based (neo-)adjuvant chemo-radiotherapy for locally advanced rectal cancer:

Long term results of a randomized phase III trial

R. Hofheinz, F. Wenz, S. Post, A. Matzdorff, S. Laechelt, J. Hartmann, L. Müller, H. Link, M. H. Moehler, E. Kettner, E. Fritz, U. Hieber, H. W. Lindemann, M. Grunewald, S. Kremers, C. Constantin, M. Hipp, D. Gencer, I. Burkholder, A. Hochhaus, on behalf of the German MARGIT study group

Abstract 3504

Study Objectives

- **Primary aim**
  To determine whether 5-year overall survival rate (SR5) was non-inferior in arm A (Cape) vs. arm B (5-FU)

- 2 strata enrolled
  - Neoadjuvant
  - Adjuvant

Courtesy of R. Hofheinz

Inclusion/Exclusion and Demographics

- Histologically proven rectal ca(0 – 16 cm ab ano)
- No distant metastases

Adjuvant stratum

- TME performed (R0-resection)
- pT3/4 N_{any} M0 **or** pT_{any} N+ M0

Neoadjuvant stratumum

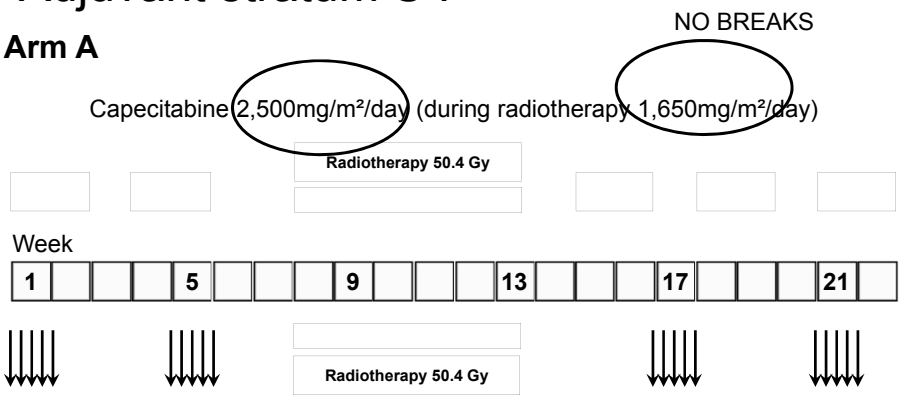
- uT3/4 uN_{any} M0 **or** uT_{any} uN+ M0 (staging with EUS)
- TME mandatory

Adapted from R. Hofheinz

	Capecitabine n = 197	5-FU n = 195
Age, years		
Median (Range)	64.6 (29.6 – 84.8)	64.0 (32.8 – 86.3)
Gender, n (%)		
Male	129 (65.5)	131 (67.2)
Female	68 (34.5)	64 (32.8)
Stratum, n (%)		
Adjuvant	116 (58.9)	115 (59.0)
Neoadjuvant	81 (41.1)	80 (41.0)
Tumor stage, n (%)		
T1 or T2	29 (14.7)	36 (18.5)
T3	150 (76.1)	140 (71.8)
T4	15 (7.7)	14 (7.2)
Missing data	3 (1.5)	5 (2.6)
Nodal, n (%)		
Node negative	78 (39.6)	69 (35.4)
Node positive	112 (56.9)	120 (61.5)
Missing data	7 (3.6)	6 (3.1)

Treatment regimen Adjuvant stratum S I

Arm A



5-FU 500mg/m² day 1 – 5 (during radiotherapy 225 mg/m²/day)

Arm B

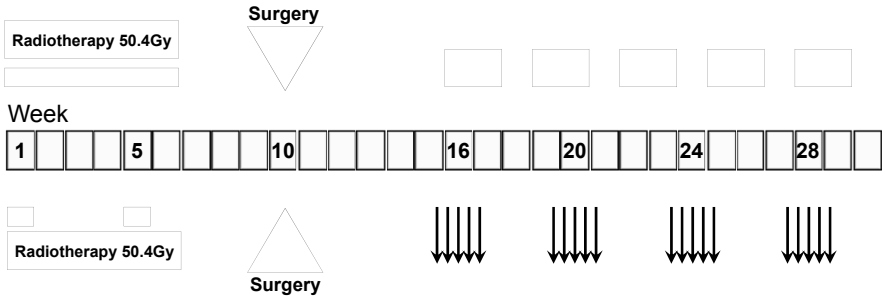
Courtesy of R. Hofheinz

Treatment: Neodjuvant stratum S II

(added after German neoadjuvant study results)

Arm A

Capecitabine 2,500mg/m²/day (during radiotherapy 1,650mg/m²/day)



5-FU 500mg/m² day 1 – 5 (during radiotherapy 1000 mg/m² d 1 – 5, d 29 – 33)

Arm B

Courtesy of R. Hofheinz

Gastrointestinal Toxicity – NCI-CTC grades (v. 2.0)

	Capecitabine n = 197			5-FU n = 195			p-value[2]
	Total[1]	1/2	3/4	Total[1]	1/2	3/4	
Nausea	36	33	2	32	30	–	0.69
Vomiting	14	11	1	9	8	1	0.39
Diarrhea	104	83	17	85	76	4	0.07
Mucositis	12	11	1	17	15	2	0.34
Stomatitis	8	8	–	12	11	–	0.37
Abdominal pain	23	19	1	14	11	–	0.17
Proctitis	31	26	1	10	9	1	< 0.001

[1] CTC-grade is missing in some pts.
[2] p-value resulted from Chi-Square test comparing the total number of events between both treatment arms.

More HFS and fatigue with capecitabine;
More leucopenia and alopecia with 5FU

Courtesy of R. Hofheinz

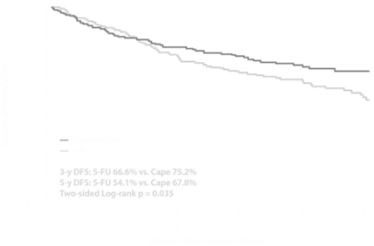
Results

In neoadjuvant: trend for better downstaging (including more pT0, less N+) with cape similar percentage of pts having LAR vs APR

Localization of recurrence and death	Capecitabine n = 197	5-FU n = 195	p-value χ^2 test
Local recurrence	12 (6.1)	14 (7.2)	p = 0.7795
Distant metastases	37 (18.8)	54 (27.7)	p = 0.0367
Deaths, n (%)	38 (19.3)	55 (28.2)	p = 0.0380
Disease related	26 (13.2)	37 (19.0)	
Other causes	12 (6.1)	15 (7.7)	
Unknown	0	3 (1.5)	

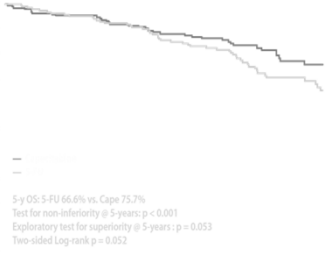
Courtesy of R. Hofheinz

DFS: Superior for capecitabine



Note: **Cape pts with HFS had better 3-y DFS (83.2%) and 5-y OS (91.4%)**

OS: Noninferior (trend for superiority)



Conclusion: Capecitabine may replace 5FU in peri-op tx

Courtesy of R. Hofheinz

The Impact of Capecitabine and Oxaliplatin in the Preoperative Multimodality Treatment of Patients with Carcinoma of the Rectum: NSABP R-04 (Abstr 3503)

MS Roh, GA Yothers, MJ O'Connell, RW Beart, HC Pitot, AF Shields, DS Parda, S Sharif, CJ Allegra, NJ Petrelli, JC Landry, DP Ryan, A Arora, TL Evans, GS Soori, L Chu, RV Landes, M Mohiuddin, S Lopa, N Wolmark

Courtesy of M. Roh

NSABP R-04

Primary Aims

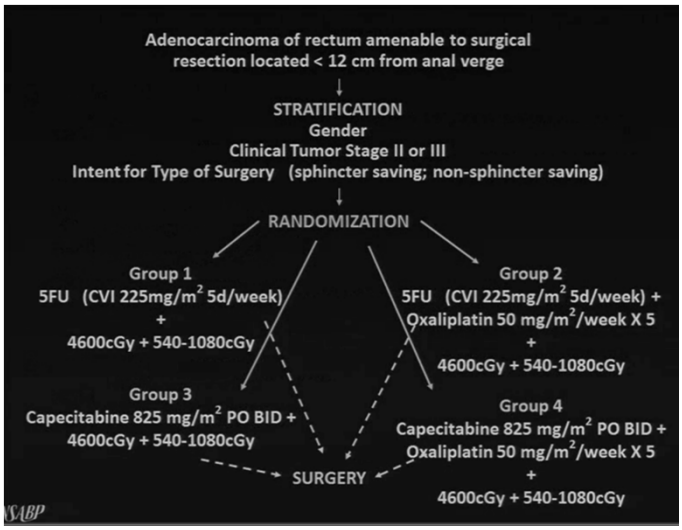
1. Compare the rate of local-regional relapse in patients receiving preoperative capecitabine with RT to patients receiving preoperative CVI 5-FU with RT
2. Compare the rate of local-regional relapse in patients receiving preoperative oxaliplatin with those not receiving preoperative oxaliplatin

Surgical Goals

- Determine if capecitabine given consurrently with pre-op RT is similar to CI 5FUgiven with pre-op RT in attaining
  - Locoregional diseasecontrol
  - Sphincter preservation

Courtesy of M. Roh

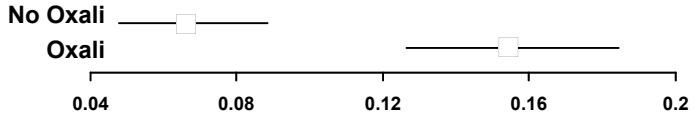
Inclusion: Patients with clinical stage II or III rectal cancer undergoing pre-op RT



Gastrointestinal Toxicity
5-FU or CAPE vs addition of Oxaliplatin

GI Toxicity**	No Oxali	Oxali	Total
< Grade 3 diarrhea	581	534	1115
Grade 3/4 diarrhea	41	97	138
Total Patients	622	631	1253
Incidence (%)	6.6	15.4	P-value 0.0001

**CTCAE Version 3.0



Courtesy of M. Roh

Surgical outcomes

- No increase in surgical complication rates in any group
- No difference in surgical downstaging rate for cape vs 5FU and with or without oxaliplatin
- No difference in sphincter-sparing rate for cape vs 5FU and with or without oxaliplatin
- No difference in pCR rate for cape vs 5FU and with or without oxaliplatin

NSABP R-04 Conclusions

- Administration of capecitabine with preoperative RT achieved rates similar to continuous infusion 5-FU for
  - Surgical downstaging
  - Sphincter saving surgery
  - Pathologic complete response
- Addition of oxaliplatin did not improve outcomes and added significant toxicity
- Longer follow up will be needed to assess local-regional tumor relapse, DFS and OS

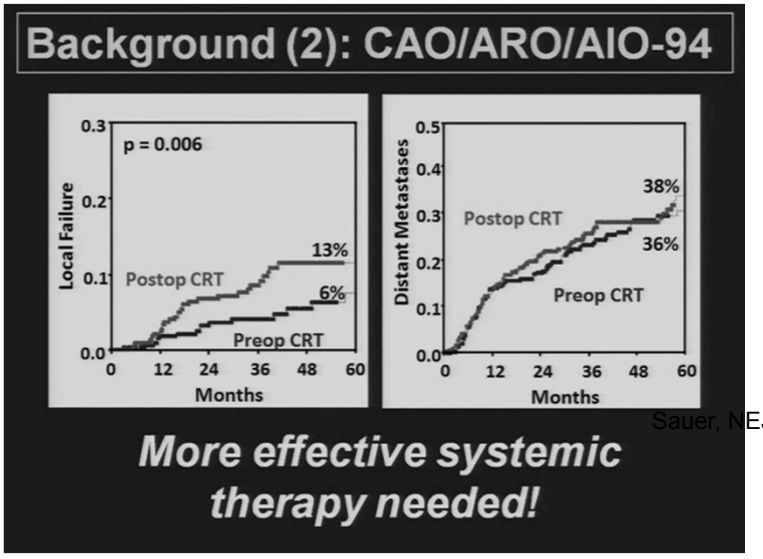
Preoperative chemoradiotherapy and postoperative chemotherapy with 5-FU and oxaliplatin versus 5-FU alone in locally advanced rectal cancer: First results of CAO/ARO/AIO-04 (LBA3505)

C. Rödel, H. Becker, R. Fietkau, U. Graeven,
W. Hohenberger, C. Hess, T. Hothorn, M. Lang-Welzenbach,
T. Liersch, L. Staib, C. Wittekind, R. Sauer

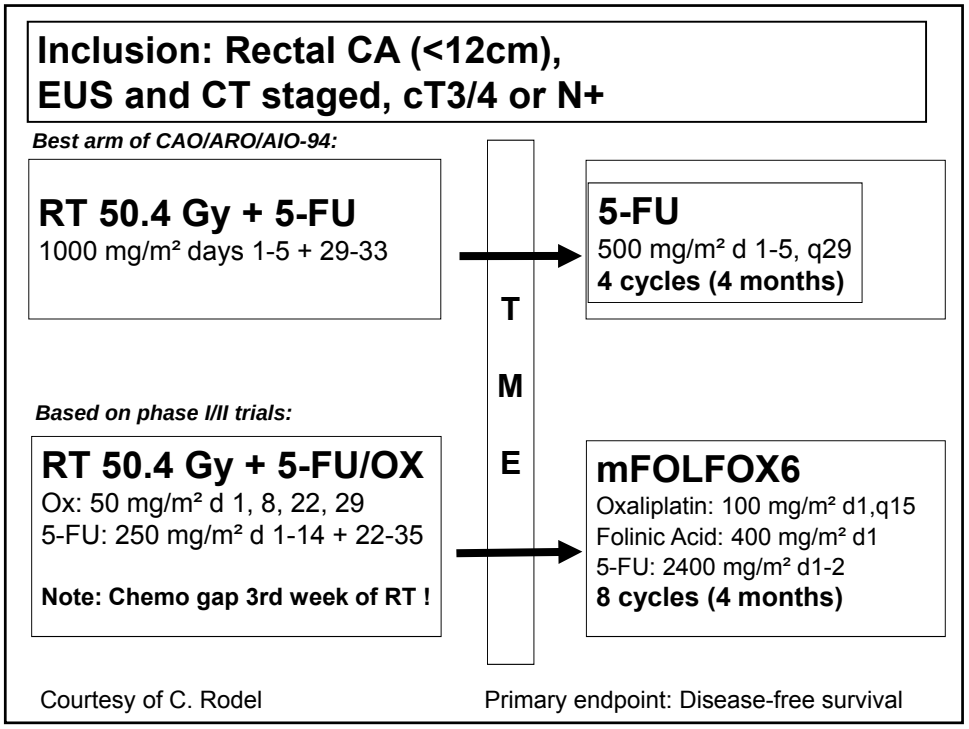
German Rectal Cancer Study Group

Courtesy of C. Rodel

Purpose for study



Sauer, NEJM 2004



Demographics and surgical outcomes

- Similar percentage of T3 and N+ tumors in each arm
- Toxicity similar except slightlymore GI tox with oxaliplatin arm
- Similar LAR and APR rates
- Similar R0 rate
- Numerically slightly more pCR with oxali(16.5 vs 12.8%)
- Similar rates of post-op chemotherapy
- DFS and other outcome measures not reported yet

Summary/ Comparison (1)	STAR-01[1]	ACCORD 12/0405[2]	CAO/ARO/ AIO-04
Number of pts	747	598	1265
Primary Endpoint	OS	pCR	DFS
Preop CRT	5-FU 225 mg/m² + 50.4 Gy vs 5-FU 225 mg/m² Ox 60 mg/m² weekly + 50.4 Gy	Cape 1600 mg/m² 5d/wk + 45 Gy vs Cape 1600 mg/m² 5d/wk Ox 50 mg/m² weekly + 50 Gy	5-FU + 50.4 Gy vs 5-FU/Ox + 50.4 Gy
Cum OX preop	360 mg/m²	250 mg/m²	200 mg/m²
Adjuvant Chemo	FU/LV	Center choice	mFOLFOX6

[1]Aschele et al., J Clin Oncol 2009;27:170s abstr CRA4008; [2]Gérard. et al., J Clin Oncol 2010;28:1638-44

Summary/ Comparison (2)	STAR-01[1]	ACCORD 12/0405[2]	CAO/ARO/ AIO-04
Main (first) results	pCR not improved (16% both arms) More tox with Ox	pCR n.s. improved (14% vs 19%) More tox with Ox	pCR improved No more tox
Compliance OX preop	66% received all 6 OX-cycles	Dose modification required in 59%	80% vs. 85% full dose
Full dose RT	97% vs 90%	100% vs 87%	95% vs 94%

[1]Aschele et al., J Clin Oncol 2009;27:170s abstr CRA4008; [2]Gérard. et al., J Clin Oncol 2010;28:1638-44

Courtesy of C. Rodel

Rectal cancer summary

- Xeloda is noninferior and may be superior to 5FU with RT
- Oxaliplatin does not improve outcome (further follow-up from AIO-04 pending)

Gastric Cancer

LBA 4002, abstracts 4003, 4004

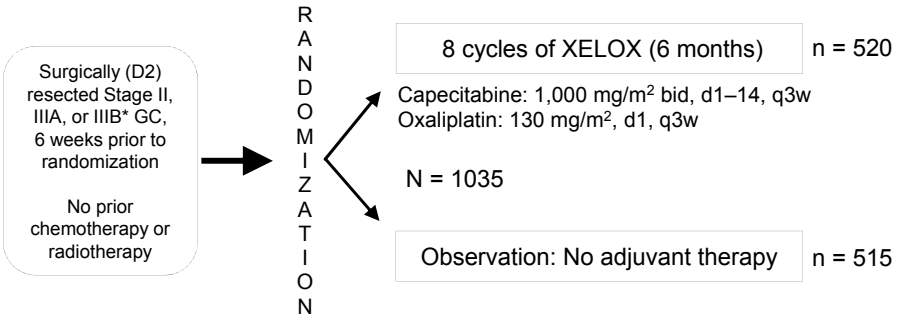
Courtesy: **Florian Lordick, MD**

What we know about adjuvant therapy of gastric cancer

- **Pre-op+ post-op chemo improves survival (MAGIC) but EORTC 40954 was negative**
- **Post-op chemo/RT improves DFS and OS (INT-0116)**
- **Post-op chemo alone improves RFS and OS (ACTS-GC of S-1)**
- **There is no randomized data for pre-op chemo/rt vs chemo for GASTRIC (but it is in NCCN guidelines based on phase II)**

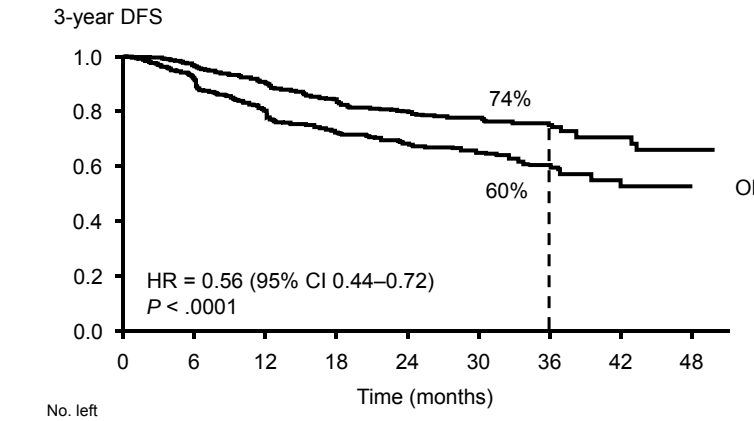
Yung-Jue Bang et al. LBA 4002 CLASSIC – Adjuvant Chemotherapy

- Asia: Korea, China, Taiwan
- Surgical technique: D2 resection



- Primary endpoint: 3-year DFS‡
- Secondary endpoints: overall survival and safety profile

CLASSIC – Primary Endpoint Met (3-year DFS at Interim Analysis)

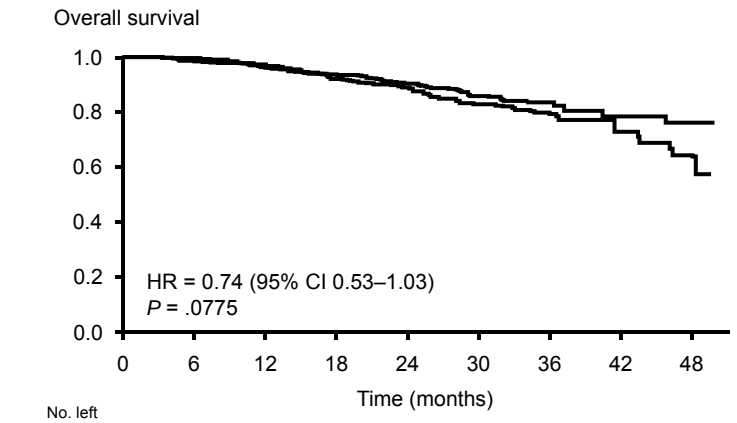


No. left

XELOX	520	443	410	333	246	166	74	30	10
Observation	515	414	352	286	209	147	58	22	6

ITT population
Median follow-up 34.4 months (range 16–51)

CLASSIC – Overall Survival



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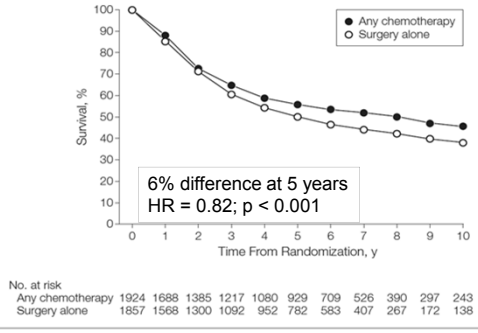
XELOX	520	468	451	395	304	216	120	35	16
Observation	515	458	441	378	286	203	112	34	12

ITT population
Median follow-up 34.4 months (range 16–51)

CLASSIC – Discussion

GASTRIC Group Meta-analysis

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



No. at risk

Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery alone	1857	1568	1300	1092	952	782	583	407	267	172	138

The Gastric Group. *JAMA* 2010; 303: 1729-1737

Role of more aggressive chemotherapy with adjuvant chemoradiation ? (*Fuchs et al. # 4003)*

Background

- INT 0116 demonstrated improved survival with post-operative adjuvant 5-FU/LV/RT compared to surgery alone*
  - Post-op 5-FU/LV/RT was associated with reduction in local-regional recurrences
  - Reductions in distant relapse were less apparent
- MAGIC trial found improved outcome with perioperative ECF**
- Could the benefit associated with post-op 5-FU/LV/RT be improved with a potentially more active systemic regimen (ECF) than 5-FU/LV?

*(N Eng J Med 2001) **(N Engl J Med. 2006)

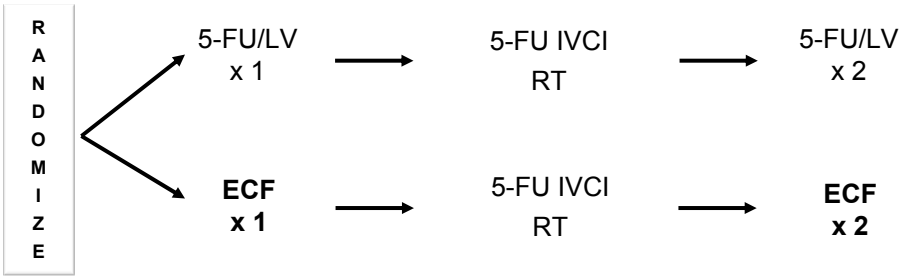
CALGB 80101

Eligibility Criteria

- GE junction or gastric adenocarcinoma
- En bloc resection; negative resection margins
- Extension beyond muscularis propria or nodal involvement; M1 disease excluded
- No prior chemo or radiotherapy
- ECOG PS: 0-2

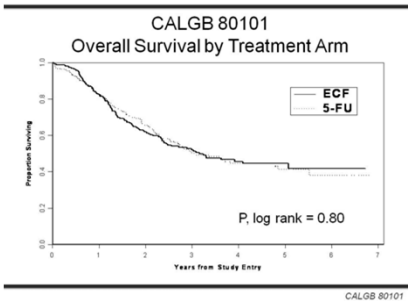
CALGB 80101

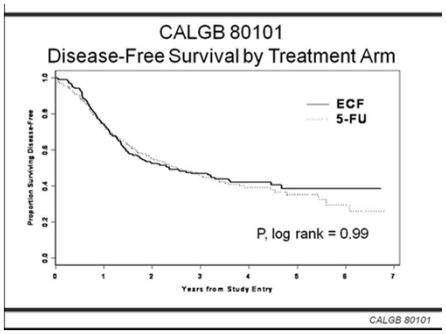
Schema: CALGB 80101



N = 540
Stratification by T stage, N stage, < or ≥ 7 examined lymph nodes
Primary endpoint: improvement in overall survival

CALGB 80101 – DFS/OS





Following curative resection of gastric or GEJ adenocarcinoma,
postoperative chemoRT using ECF before & after 5-FU/RT
does not improve survival when compared to bolus 5-FU/LV before & after 5-FU/RT.

Advanced Gastric Cancer

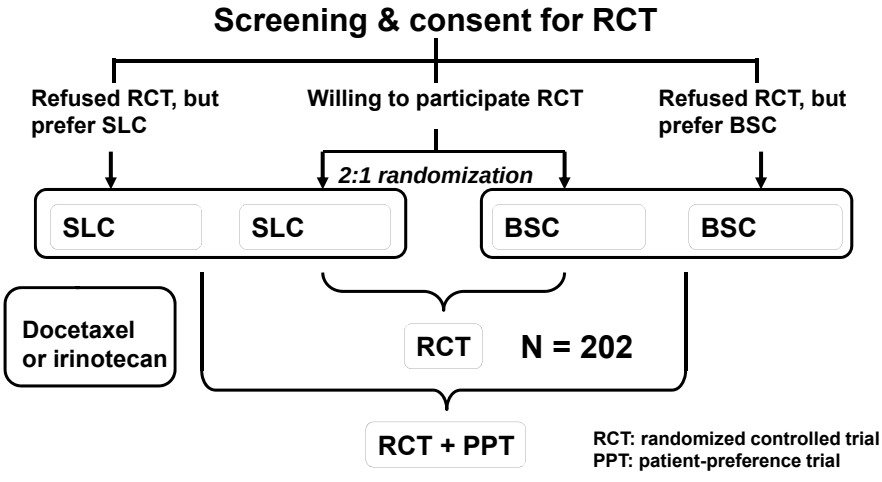
- 1st line chemotherapy prolongs survival
- 1st line chemotherapy improves symptom control

Wagner et al. *J Clin Oncol* 2006; 24: 2903-9

Established standard 1st line:
Platin-fluoropyrimidine-combinations

Park et al. # 4004
Is there a role for second-line chemotherapy?

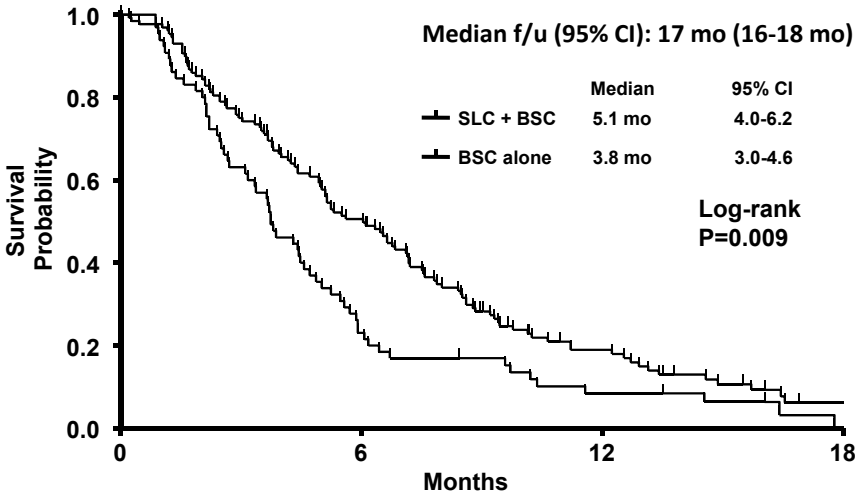
2nd line Chemotherapy (SLC) Park et al. #4004



RCT: randomized controlled trial
PPT: patient-preference trial

ClinicalTrials.gov, NCT00821990

Survival (Park et al. #4004)



Park et al. #4004 Conclusion

2nd line chemotherapy has a proven benefit in advanced gastric cancer and should be offered to patients

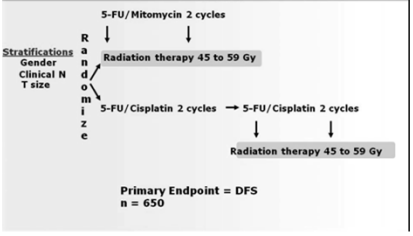
with an acceptable Karnofksy PS
and
motivation to receive further chemotherapy

ANAL CANCER

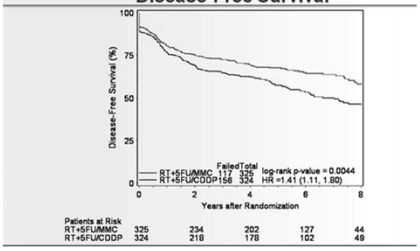
U.S. GI Intergroup RTOG 98-11
Eligibility and Stratifications

- Eligibility
  - Histologic proof of anal canal carcinoma
  - ≥ 18 years of age
  - KPS ≥ 60
  - T stage 2 to 4
  - Any N stage (pelvic or inguinal)
  - Adequate organ function
  - Written consent
- Stratification Factors
  - Male vs. Female
  - Clinical N+ vs. N0
  - Primary size: >2 to 5 cm vs. > 5 cm

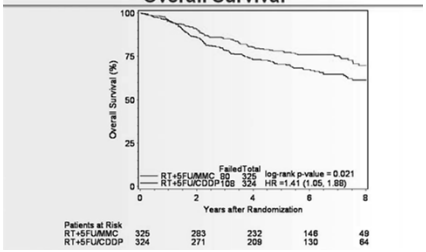
U.S. GI Intergroup RTOG 98-11
Schema



U.S. GI Intergroup RTOG 9811
Disease-Free Survival

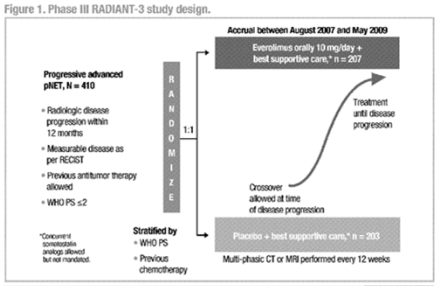


U.S. GI Intergroup RTOG 9811
Overall Survival



NEUROENDOCRINE TUMORS

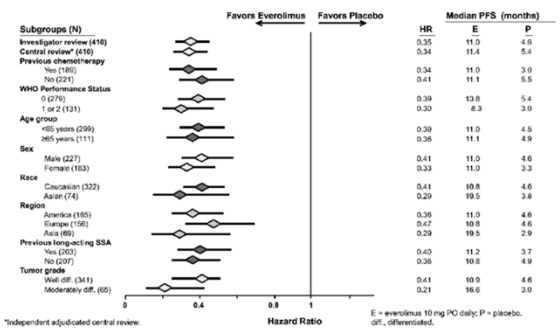
Figure 1. Phase III RADIANT-3 study design.

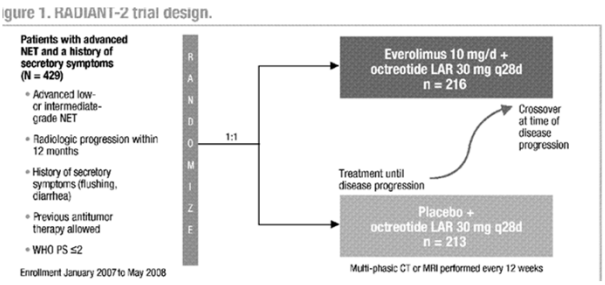


Everolimus in patients with advanced pNET: RADIANT-3
Strosberg et al., #4009
Shah et al, #4010

Better PFS for everolimus vs placebo in pts who received on-study SSA (11.4 mo vs 3.9) and those without on-study SSA (10.8 mo vs 4.6) and regardless of prior chemotherapy

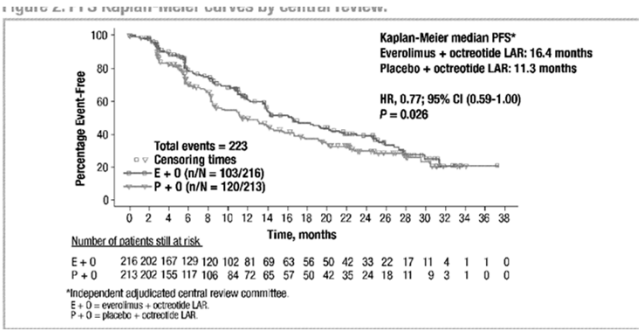
igure 4. Subgroup PFS analysis.

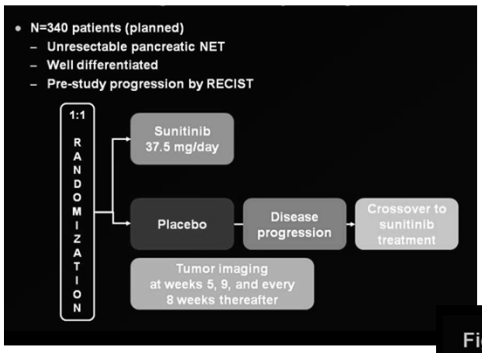




Everolimus + octreotide LAR v. placebo + octreotide LAR in advanced neuroendocrine tumors (NET): RADIANT-2.
Yao et al, #4011

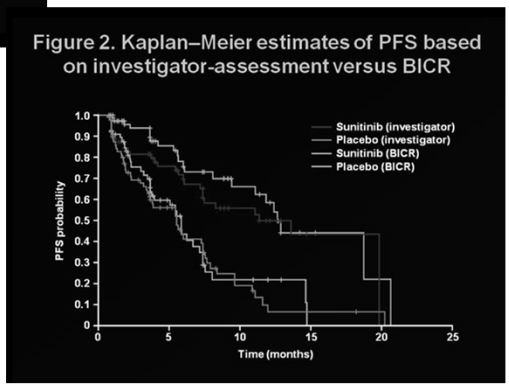
Better PFS with everolimus across all subgroups (age, sex, PS, tumor grade, primary site, prior somatostatin analog, prior chemotherapy).
B





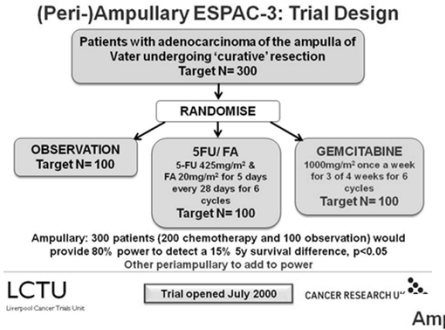
Sunitinib versus placebo for advanced unresectable pNET

Raymond et al., #4008



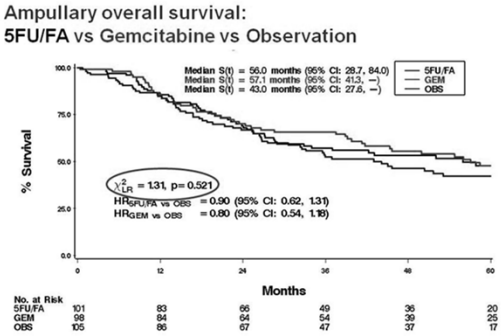
Better PFS for sunitinib
At study end, there were 9 and 21 deaths in SU and PBO arms, respectively;
By 6/2010, there were 34 and 39 deaths, respectively (median OS was 30.5 and 24.4 months, respectively.)

PANCREATIC AND AMPULLARY CANCER

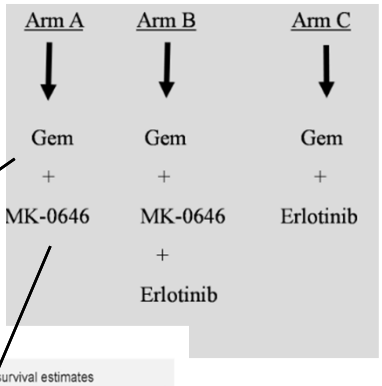


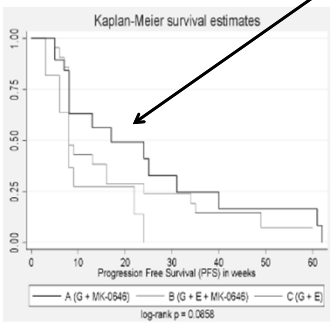
Ampullary cancer ESPAC-3 (v2) trial: A multicenter, international, open-label, randomized controlled phase III trial of adjuvant chemotherapy versus observation in patients with adenocarcinoma of the ampulla of vater
Neoptolemos et al, LBA4006

Overall, not statistically posittive but……
Survival benefit for chemotherapy in R0 resections



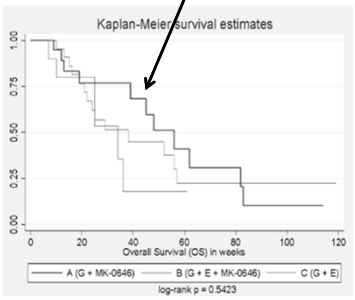
Randomized phase II study of gemcitabine (G) plus anti-IGF-1R antibody MK-0646, G plus erlotinib (E) plus MK-0646 and G plus E for advanced pancreatic cancer.
Javle et al, #4026





Median PFS: arm A=17 wks, arm B=8 wks, arm C=8 wks

Overall Survival:

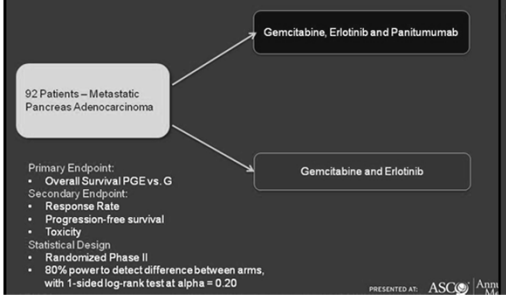


Median OS: arm A=56 wks, arm B=38 wks, arm C=34

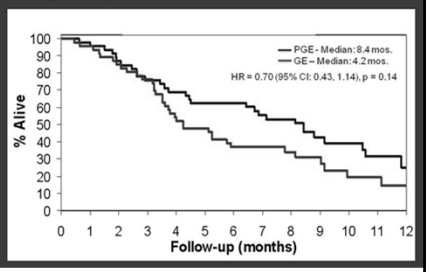
Randomized Phase II – Panitumumab, Gemcitabine and Erlotinib (PGE) versus Gemcitabine - Erlotinib (GE)

Kim et al.

Abstr 4030



Overall Survival



Single vs Dual EGFR Targeted Therapy

Median OS	Gem	Gem + Erlotinib	Gem + Cetuximab	PGE	HR, p-value
Ph III – Gem vs. Gem + Erlotinib	5.91 mos.	6.24 mos.			0.82, p=0.038
Ph III – Gem vs. Gem + Cetuximab	5.9 mos.		6.3 mos.		1.06, p=0.23 one-sided
Ph II – GE vs. PGE		4.2 mos.		8.4 mos.	0.70, p=0.14 one-sided

Study Conclusions

- The study did not meet its primary endpoint of OS; however, serves as a platform for further investigation of dual EGFR targeted therapy.
- Kras mutation status does not appear to be a determinant of outcome. However Kras analysis of stool DNA is feasible.