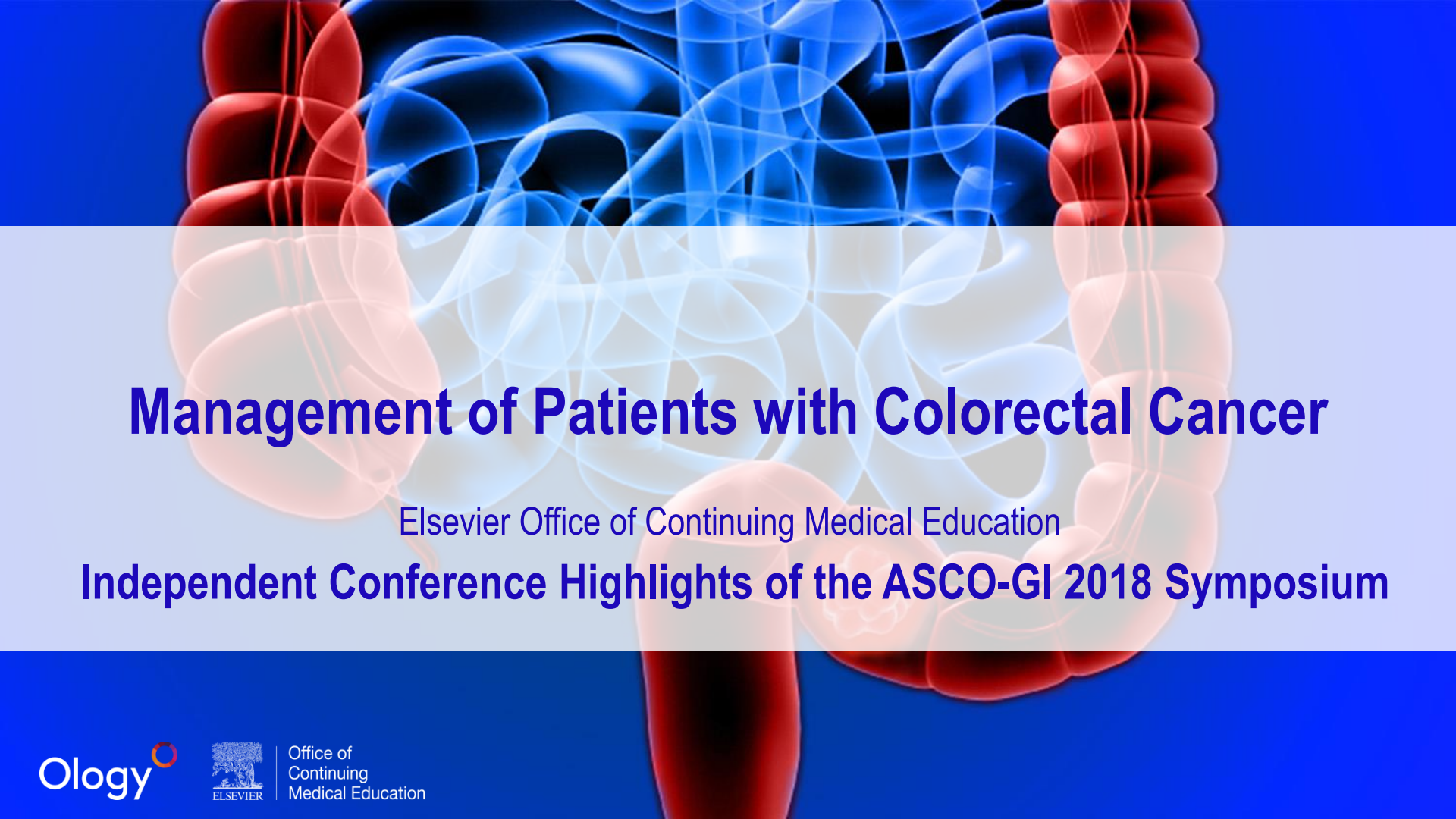

Management of Patients with Colorectal Cancer

Elsevier Office of Continuing Medical Education

Independent Conference Highlights of the ASCO-GI 2018 Symposium

Ology

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Faculty

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Prevalence/Management of Colorectal Cancer (CRC)

- Fourth most commonly diagnosed cancer in the USA
- 1.4 million new cases and 694,000 deaths worldwide in 2012
- 140,250 estimated new cases and 50,630 estimated deaths in 2018 in the USA
- Incidence decreasing overall, but increasing in people <50 years old

Management is evolving:

- Earlier diagnosis, prognostic and predictive molecular markers

Van Cutsem et al. Ann Oncol. 2016; 27:1386-1422.
Bailey CE, et al. JAMA Surg. 2015;150(1):17-22.
NCCN Colon v2.2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 2018.
SEER Cancer Statistics. Available from: https://seer.cancer.gov/statfacts/html/colorect.html. Accessed May 2018.

Current Treatment Options in CRC

- **Surgical resection: first assessment is always for possibility of cure through surgical resection**
- **First line, metastatic disease: chemotherapy +/− targeted therapy**
  - Chemotherapy: 5-FU- (oral capecitabine or infusion 5-FU + leucovorin) based chemotherapy (options include oxaliplatin, irinotecan, FOLFOX)
  - Targeted biologic: bevacizumab, panitumumab, or cetuximab (*KRAS*/*NRAS* WT and left-sided tumors only), nivolumab or pembrolizumab (dMMR/MSI-H only)
- **Maintenance therapy:** reduce toxicity while maintaining benefit
- **Second line: chemotherapy +/− targeted therapy**
  - Bevacizumab, ziv-aflibercept, ramucirumab, cetuximab, or panitumumab (*KRAS*/*NRAS* WT only), vemurafenib *BRAF* V600E- positive), nivolumab or pembrolizumab (dMMR/MSI-H only)
  - Dependent upon choices and success with first-line therapy, patient symptoms and goals
- **Third line:**
  - Cetuximab or panitumumab (*KRAS*/*NRAS* WT only), regorafenib, nivolumab, or pembrolizumab (dMMR/MSI-H only)
  - Re-challenge with chemotherapy
  - Investigational options

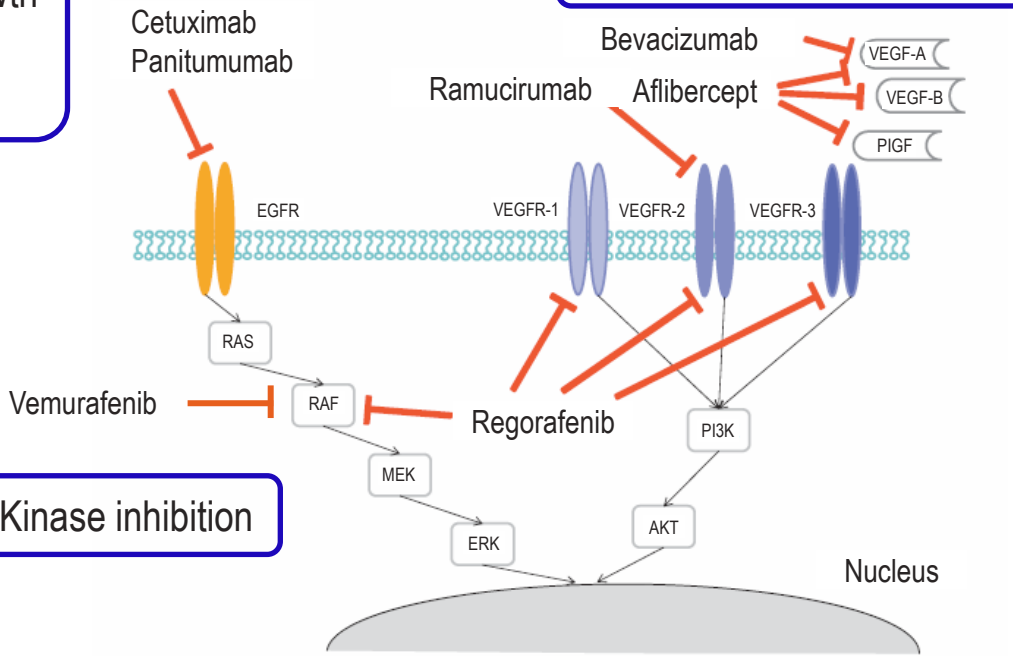
NCCN Colon v2.2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 2018.
NCCN Rectal v1.2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed May 2018.
Van Cutsem et al. Ann Oncol. 2016;27:1386-1422.
Personal Communication: JL Marshall.

5-FU, 5-fluorouracil; dMMR, DNA mismatch repair-deficient;
FOLFOX, folinic acid, fluorouracil and oxaliplatin;
MSI-H, microsatellite instability – high; WT, wild-type.

Targeted Therapies in CRC: Mechanism of Action

Anti-epidermal growth factor receptor (anti-EGFR)

Angiogenesis inhibition



Kinase inhibition

PlGF, placental growth factor; PI3K, phosphatidylinositide-3-kinase; VEGF, vascular endothelial growth factor.

Seeber A, Gastl G. Oncol Res Treat. 2016;39:796-802.
Le DT, et al. N Engl J Med. 2015;372:2509-20.

Discussion Outline

Anti-EGFR therapy
John L. Marshall:

745 – panitumumab vs cetuximab in mCRC

624 – panitumumab + irinotecan vs cetuximab + irinotecan in mCRC

729 – panitumumab + mFOLFOX6 vs panitumumab + 5-FU/LV in CRC

Regorafenib
Tanios S. Bekaii-Saab:

611 – regorafenib dosing

557 – regorafenib sequence

Tumor characteristics
Tanios S. Bekaii-Saab:

569 – genomic profiling

Johanna C Bendell:

558 – tumor sidedness

742 – tumor sidedness

830 – tumor sidedness

Final discussion

LV, leucovorin; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

Anti-EGFR Therapy

Abstracts:

- 745 – panitumumab vs cetuximab in mCRC
- 624 – panitumumab + irinotecan vs cetuximab + irinotecan in mCRC
- 729 – panitumumab + mFOLFOX6 vs panitumumab + 5-FU/LV in CRC

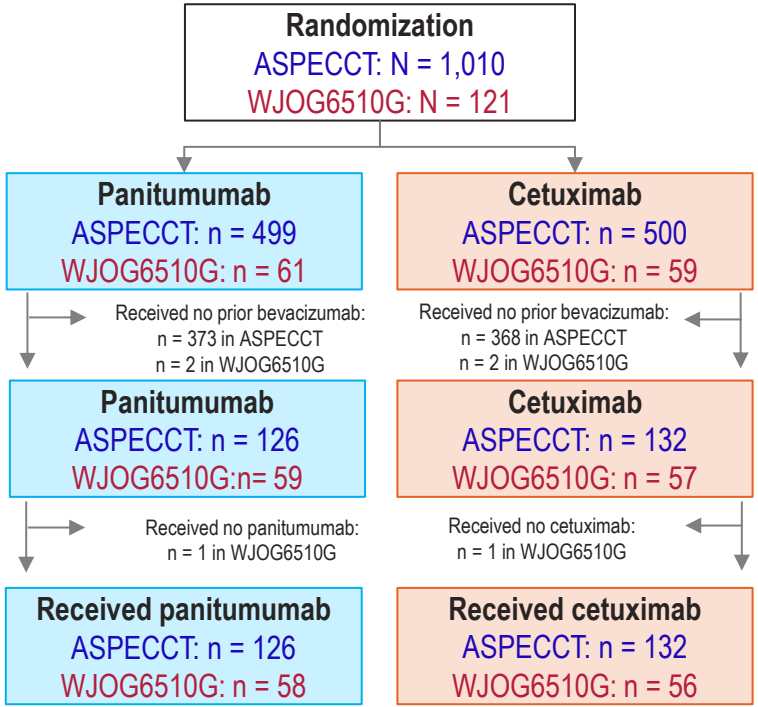
Abstract 745: Panitumumab versus cetuximab in patients with wild-type *KRAS* exon 2 metastatic colorectal cancer who received prior bevacizumab therapy: a combined analysis of individual patient data from ASPECCT and WJOG6510G

Objective:

- Combined analysis of ASPECCT and WJOG6510G trial data to assess differences in efficacy and toxicity between panitumumab and cetuximab in patients with chemotherapy-refractory wild-type *KRAS* exon 2 mCRC

Taniguchi H, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 745.
Abstract presented at ASCO-GI 2018.

Study Design



Patient enrollment:
Feb 2010–Jul 2012 in ASPECCT
Dec 2011–Sep 2014 in WJOG6510G

Full analysis set from each study

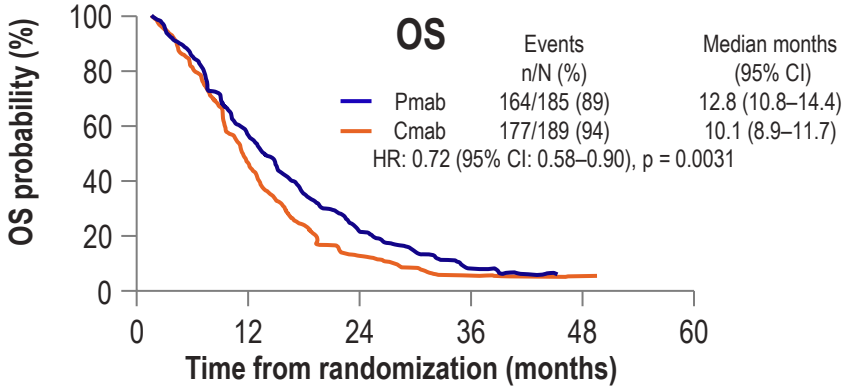
Efficacy analysis (n = 374)

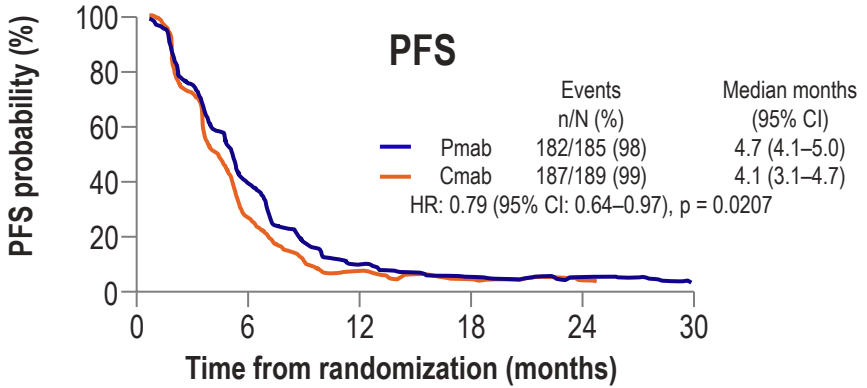
Safety analysis (n = 372)

Cut-off date: September 15, 2014 in ASPECCT, and March 31, 2017 in WJOG6510G.

Taniguchi H, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 745.
Abstract presented at ASCO-GI 2018.

Combined Analysis of OS and PFS





Adverse events

- The incidence of anti-EGFR-related skin toxicity was similar between the 2 treatments
- Infusion reactions were higher with cetuximab
- Hypomagnesemia was higher in the panitumumab group

*Log-rank test stratified by trial. HR stratified by trial. CI, confidence interval; Cmab, cetuximab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; Pmab, panitumumab.

Taniguchi H, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 745. Abstract presented at ASCO-GI 2018.

Author Conclusions

- In this combined analysis, panitumumab significantly prolonged OS and PFS compared with cetuximab, suggesting that panitumumab may be the more reliable anti-EGFR treatment option for patients with wild-type *KRAS* exon 2 mCRC who received prior bevacizumab

Taniguchi H, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 745.
Abstract presented at ASCO-GI 2018.

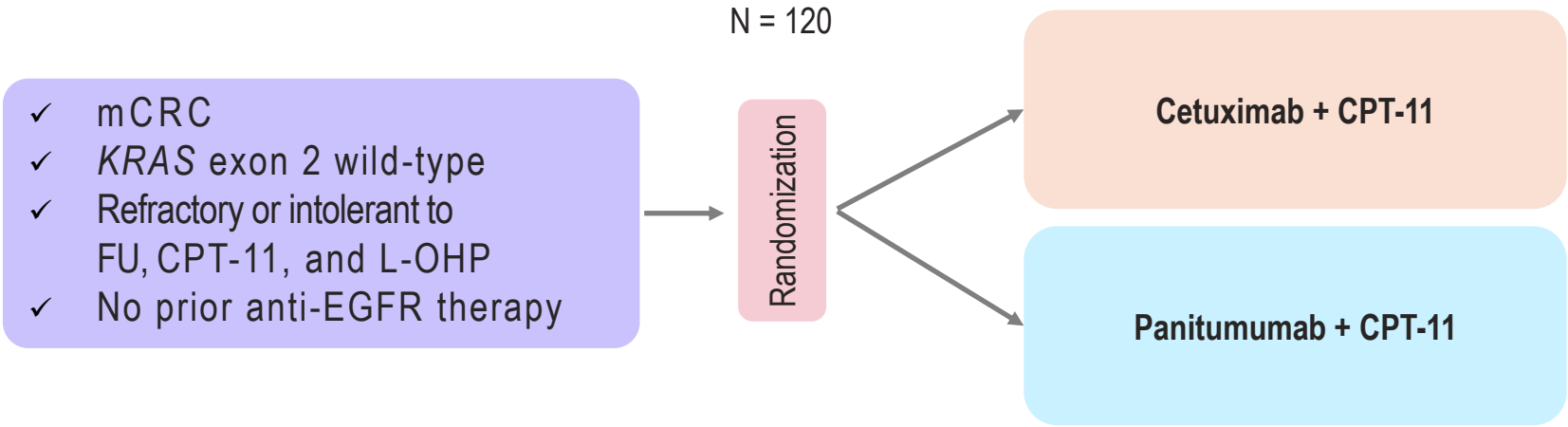
Abstract 624: Analysis of *RAS*/*BRAF* mutations in a randomized phase II WJOG6510G study of panitumumab plus irinotecan versus cetuximab plus irinotecan on chemorefractory metastatic colorectal cancer

Objective:

- Exploratory analysis of updated survival data from WJOG6510G according to *KRAS* exon 2 and *RAS/BRAF* status

Nishina T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 624.
Abstract presented at ASCO-GI 2018.

Study Design



- **Primary endpoint:** PFS

CPT-11, irinotecan; L-OHP, oxaliplatin.

Nishina T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 624.
Abstract presented at ASCO-GI 2018.

Results

Overall population	Panitumumab + CTP-11	Cetuximab + CPT-11	HR	p value
OS, months (n = 113)	14.85	11.53	0.675	0.037
Median PFS, months (n = 117)	5.42	4.27	0.674	0.035

Subset of patients with mutational analysis (n = 83)

***RAS/BRAF* mutations:**

- *RAS* mutations and *BRAF* mutations were identified in 23% and 5% of the analyzed patients, respectively
- Patients with *RAS* and *BRAF* mutations showed no significant response to the treatments

***RAS* WT:**

- Panitumumab PFS 6.06 months vs cetuximab 5.26 months (HR: 0.629; p = 0.08)
- Panitumumab OS 14.85 months vs cetuximab 11.26 months (HR: 0.818; p = 0.449)

Nishina T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 624.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- In mCRC patients with wild-type *KRAS* exon 2 and *RAS/BRAF* status, panitumumab + irinotecan was associated with a modest survival benefit compared with cetuximab + irinotecan
- It is still unclear whether *BRAF* mutations, including non-V600E mutations, have prognostic and predictive value for anti-EGFR therapy in chemorefractory mCRC. More studies are needed in this setting.

Nishina T, et al. J Clin Oncol. 2018;36:suppl 4S abstract 624.
Abstract presented at ASCO-GI 2018.

Abstract 729: SAPPHIRE: a randomized phase II study of mFOLFOX6 + panitumumab versus 5-FU/LV + panitumumab after 6 cycles of frontline mFOLFOX6 + panitumumab in patients with colorectal cancer

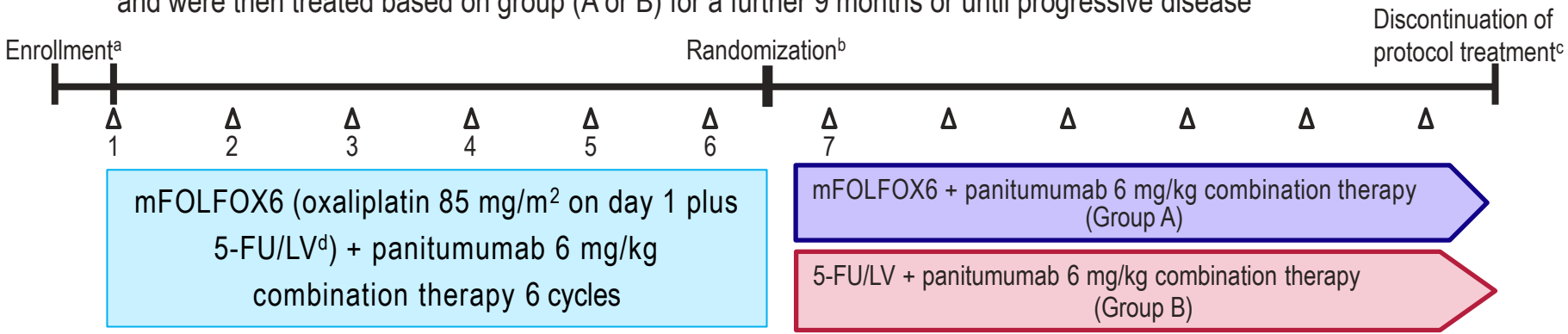
Objective:

- SAPPHIRE was a exploratory, randomized phase II trial that evaluated the efficacy and safety of mFOLFOX6 plus panitumumab and 5-FU/LV plus panitumumab after 6 cycles of first-line mFOLFOX6 plus panitumumab in CRC patients with chemotherapy-naive unresectable, advanced, or recurrent *RAS* wild-type disease

Nakamura M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 729.
Abstract presented at ASCO-GI 2018.

Study Design

- The study was a multicenter, randomized, open-label, non-comparative, parallel-group, phase II trial
- Patients received 6 treatment cycles (1 cycle every 2 weeks) prior to randomization, and were then treated based on group (A or B) for a further 9 months or until progressive disease



- **Primary endpoint:** PFS rate 9 months after randomization
- **Secondary endpoints:** PFS and response rates after randomization, safety

[a] The first cycle was administered within 14 days of enrollment.
[b] Conducted immediately before administration of the 7th cycle.
[c] 9 months after randomization or at progressive disease.
[d] LV 200 mg/m^2 on day 1, plus 5-FU bolus 400 mg/m^2 on day 1, then 5-FU infusion 2,400 mg/m^2 on days 1–3.

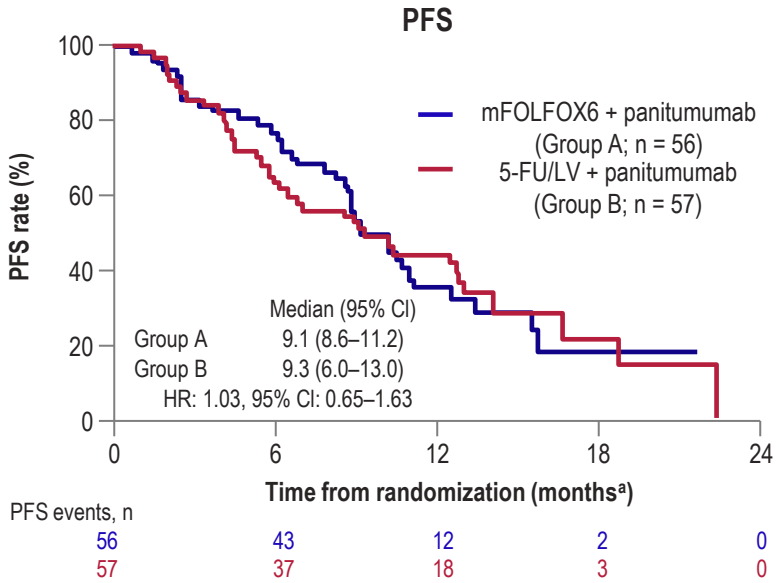
Nakamura M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 729.
Abstract presented at ASCO-GI 2018.

Results

- **Primary endpoint:**

PFS rate at 9 months after randomization		
	Group A (n = 56)	**Group B (n = 57)**
PFS rate (80% CI), %	46.4 (38.1–54.9)	47.4 (39.1–55.8)
H_0: PFS rate ≤ 30%	p = 0.0037	p = 0.0021

- Group A and Group B both met the primary endpoint with a PFS rate at 9 months significantly above the 30% threshold.



[a] 1 month = 28 days.

Nakamura M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 729.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- Combination therapy with 5-FU/LV plus panitumumab demonstrated continued efficacy after 6 cycles of mFOLFOX6 plus panitumumab without increasing the incidence of peripheral neuropathy compared to continued mFOLFOX6 plus panitumumab
- These data suggest that mFOLFOX6 plus panitumumab combination therapy followed by 5-FU/LV plus panitumumab can be a useful treatment option for patients with unresectable, advanced/recurrent CRC

OXA, oxaliplatin.

Nakamura M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 729.
Abstract presented at ASCO-GI 2018.

Discussion: Clinical Practice Implications

How do these results affect your practice?

- These studies confirm current practice and clinical belief that cetuximab and panitumumab have similar efficacy with slightly different toxicity profiles
- In some regions, you might prefer panitumumab because of the infusion reactions
- In terms of single-agent vs combination treatment, it is already current practice to add irinotecan or even irinotecan plus 5-FU (FOLFIRI) to anti-EGFR treatment, and these studies confirm that practice

Personal communication: JL Marshall and TS Bekaii-Saab.

Discussion: Choice of Anti-EGFR Therapy

Does your choice of anti-EGFR therapy vary in the Southern USA based on the infusion-site reaction differences between cetuximab and panitumumab?

- There is a kind of allergy belt in the Southern USA where higher rates of infusion reactions are observed with cetuximab, so panitumumab is used more often here
- Cetuximab is used when required in a clinical trial and specific precautions are taken to ensure patient safety at these times

Personal communication: JC Bendell.

Discussion: Pretreatment Testing

What mutations should be tested before initiation of anti-EGFR treatment?

- It is essential to test for the *RAS* mutational profile (*KRAS*, *NRAS*, *HRAS)*, *BRAF*, and *HER2*
- If a *BRAF* mutation is identified, anti-EGFR therapy is not preferable
- If there is *HER2* amplification, *HER2*-targeted therapy on a clinical trial should be considered first

Personal communication: JL Marshall and TS Bekaii-Saab.

Discussion: Anti-EGFR Therapy

What type of patient should receive anti-EGFR treatment as front-line therapy and in which other lines of therapy would you recommend anti-EGFR treatment?

- There are data from Europe on the use of anti-EGFR agents plus chemotherapy in the first-line setting; however, it is still unclear which patients will benefit from this
- mCRC patients receive first-line therapy for a long duration, and anti-EGFR therapy-related skin toxicity is an issue for patients for that length of time
- Anti-EGFR treatment can be used later on with or without irinotecan in *RAS* WT patients and/or *HER2*-negative patients or in the *BRAF* population in combination with a *BRAF* inhibitor and irinotecan in second line

Personal communication: JC Bendell.

Regorafenib

Abstracts:

- 611 – regorafenib dose optimization
- 557 – regorafenib sequence

Abstract 611: Regorafenib dose optimization study (ReDOS): randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC) – an ACCRU Network study

Objective:

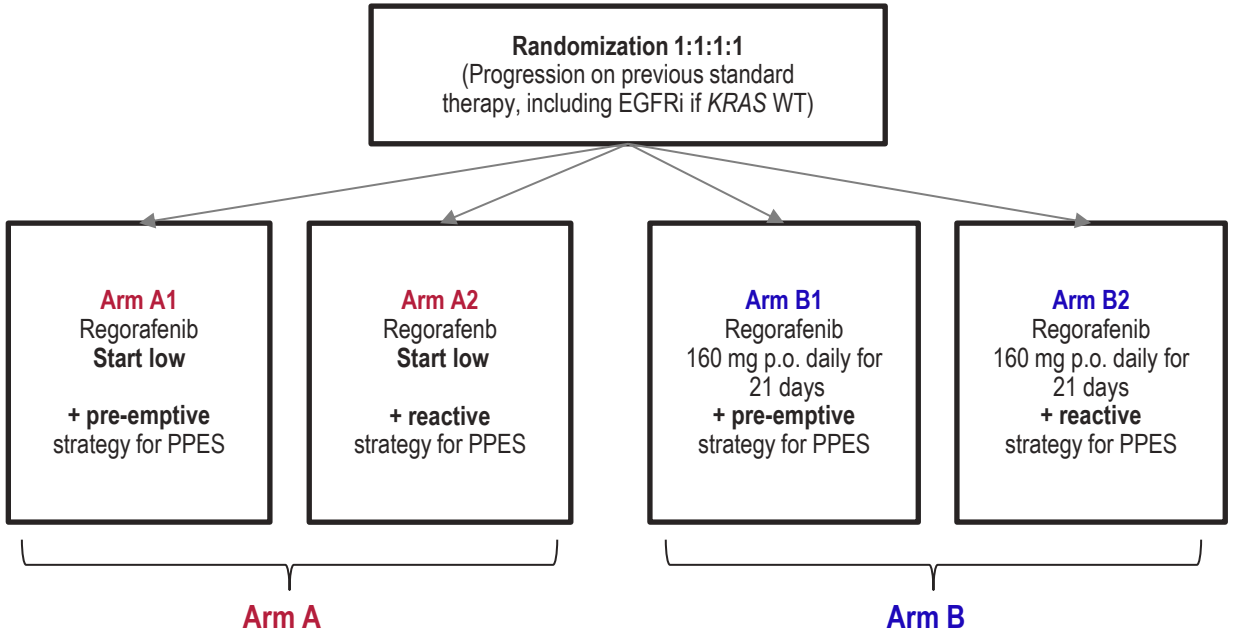
- To optimize the dosing of regorafenib in patients with refractory mCRC to maintain efficacy and improve the tolerability profile

Bekaii-Saab T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 611.
Abstract presented at ASCO-GI 2018.

Study Design

Week of C1		Dose
1	Starting dose C1	80 mg
2	↓	120 mg
3	End dose C1	160 mg
4		off

Week of C2+		Dose
1		Dose from C1



- **Primary endpoint:** proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A and arm B
- **Secondary endpoints:** OS, PFS, TTP

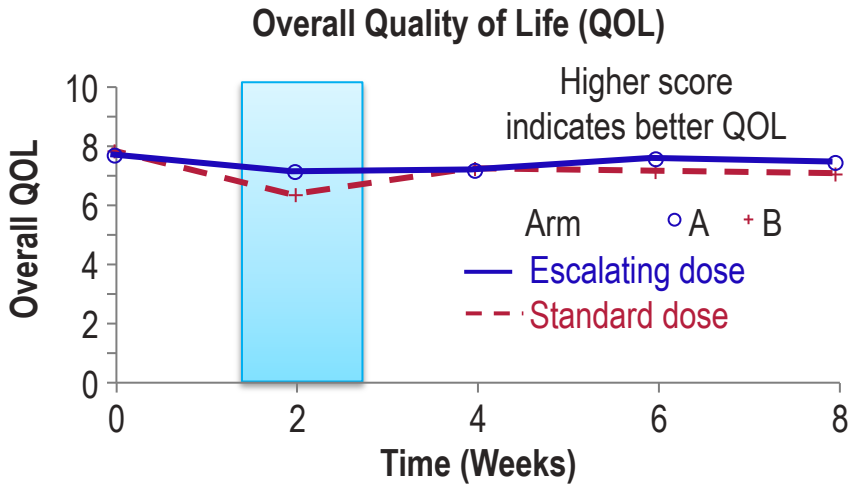
C1, cycle 1; C2, cycle 2; EGFRi, epidermal growth factor receptor inhibitor; PPES, palmar–plantar erythrodysesthesia syndrome; p.o., per os; TTP, time to progression.

Bekaii-Saab T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 611.
Abstract presented at ASCO-GI 2018.

Results

- **Primary endpoint:** Proportion of patients starting Cycle 3

	Arm A n = 54	Arm B n = 62	p value
Primary endpoint, patients initiating 3rd cycle	43%	24%	0.028
mOS, months	9	5.9	0.094
mPFS, months	2.5	2.0	0.553
HFSR	15%	16%	n/a
Hypertension	7%	15%	n/a
Fatigue	13%	18%	n/a



HFSR, hand–foot skin reaction; mOS, mean overall survival; mPFS, mean progression-free survival.

Bekaii-Saab T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 611. Abstract presented at ASCO-GI 2018.

Author Conclusions

- Weekly dose escalation of regorafenib from 80 mg to 160 mg/day was demonstrated to be superior to a starting dose of 160 mg/day with a trend toward improved OS in the dose-escalation arm
- Unlike the standard dose administration, patients who underwent the dose-escalation strategy did not have compromised quality of life at 2-weeks after initiation of therapy
- These results suggest that a dose escalation strategy could provide a new standard for optimizing regorafenib dosing in this setting

Bekaii-Saab T, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 611.
Abstract presented at ASCO-GI 2018.

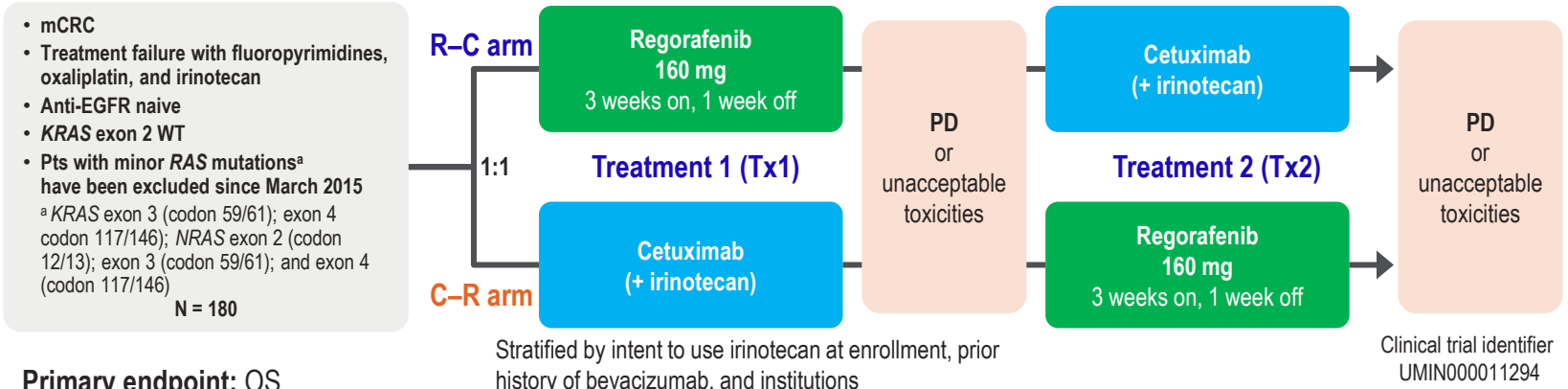
Abstract 557: REVERCE: randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan

Objective:

- To compare safety and efficacy of treatment with regorafenib followed by cetuximab to the reverse sequence of cetuximab followed by regorafenib in previously treated mCRC patients

Shitara K, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 557.
Abstract presented at ASCO-GI 2018.

REVERCE: Study Design and Endpoints

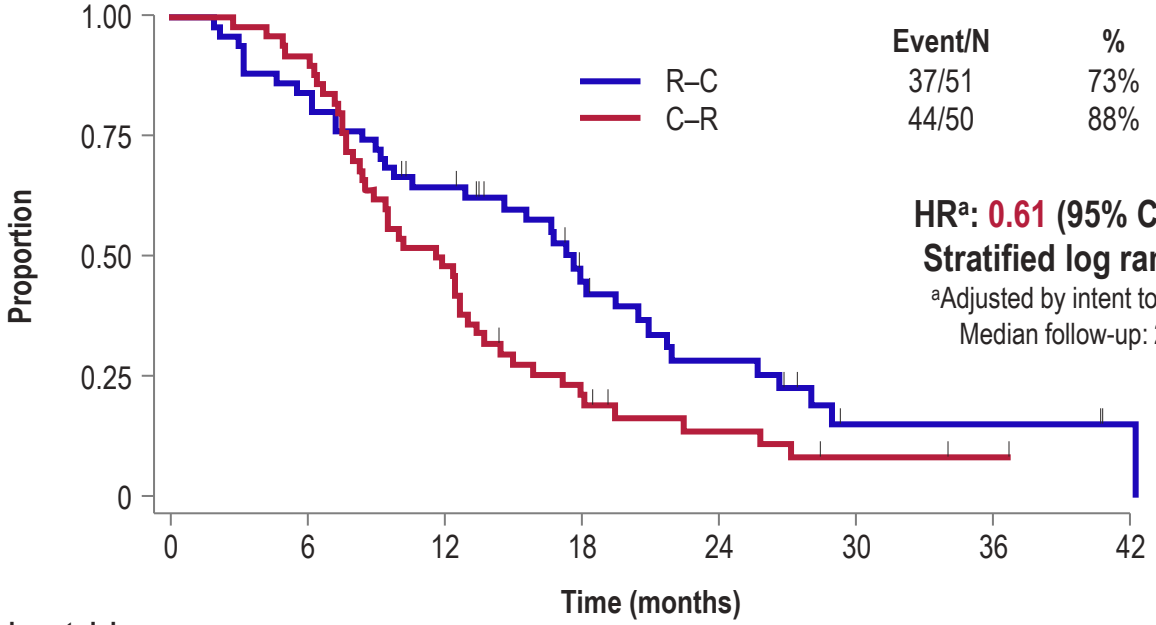


- **Primary endpoint:** OS
  - **To show similarity (HR: 0.8–1.25, expected median OS of 12 months)** with probability of more than 80%
  - **Target 180 subjects** to observe 132 events
- **Secondary endpoint:** TTF, PFS, ORR, DCR, toxicities, and QOL (pre treatment, at week 4, and 8 in Tx1 and Tx2)
- Exploratory liquid biomarker analysis (pre and post Tx1)
- Discontinued enrollment in September 2016 because of slow accrual
  - **A total of 101 patients** were randomized from 29 centers between November 2013 and September 2016
  - **Data cut-off for final analysis with 81 events in August 2017**

C–R, cetuximab–regorafenib; ORR, overall response rate; Pts, patients; R–C, regorafenib–cetuximab.

Shitara K, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 557.
Abstract presented at ASCO-GI 2018.

Overall Survival



	Event/N	%	Median (months)
R–C	37/51	73%	17.4 (10.5–20.7)
C–R	44/50	88%	11.6 (8.4–12.9)

HR[a]: 0.61 (95% CI: 0.39–0.96)

Stratified log rank p = 0.029

[a]Adjusted by intent to use irinotecan

Median follow-up: 29.0 months

Number at risk

R–C	51	43	31	18	10	3	3	1
C–R	50	46	24	11	5	2	1	0

Shitara K, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 557.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- OS was longer for regorafenib followed by cetuximab compared to the reverse sequence (OS 17.4 vs 11.6 months (HR: 0.61; p = 0.029))
- This finding was consistent across all subgroups
- PFS was comparable for regorafenib vs cetuximab during the first treatment in the sequence (HR: 0.97)
- PFS was longer for cetuximab for the second treatment in the sequence (HR: 0.29)
- The two arms had comparable safety and QOL
  - QOL scores were lower for regorafenib in both arms

PFS1, PFS of Tx1; PFS2, PFS of Tx2

Shitara K, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 557.
Abstract presented at ASCO-GI 2018.

Discussion: Clinical Practice Implications

How does this data affect your daily clinical practice?

- It has become clear that regorafenib can improve outcomes for patients with good performance status
- ReDOS shows that regorafenib toxicity can be managed with a dose-escalation strategy and allows regorafenib to be “moved up” to be used earlier in the treatment line before re-cycling chemotherapy

Personal communication: JL Marshall.

Discussion: Clinical Practice Implications (cont.)

How does this data affect your practice?

- This study confirms clinical observations that the regorafenib dose of 160 mg is challenging for patients and confirms that the practice of starting at a lower dose of 80 mg or 120 mg and escalating is effective

Personal communication: JC Bendell.

Discussion: Regorafenib Before Anti-EGFR?

Would you consider using regorafenib before an anti-EGFR therapy based on this phase II randomized trial?

- In *RAS/BRAF* wild-type left-sided tumors, anti-EGFR therapy is the best choice in the first or second line
- In right-sided tumors, anti-EGFR therapy seems not to be as effective; considering regorafenib before anti-EGFR therapy might be an option for these cases

Personal communication: TS Bekaii-Saab.

Discussion: Regorafenib Before Anti-EGFR? (cont.)

Do you have comments on the sequence of regorafenib and anti-EGFR treatment?

- This small study may not change practice, but it does suggest that regorafenib prior to anti-EGFR treatment should be considered in good performance status patients

Personal communication: JC Bendell.

Discussion: Prescribing a Dose Escalation

ReDOS brings up a question regarding how to prescribe the appropriate dose when a dose escalation is planned. How do we handle this in terms of insurance, shelf-life, and patient follow-up?

- More appointments and testing may be required in the first cycle of therapy
  - Weekly basis is desired
- Prescription can be ordered for 160 mg and then administered according to dose-escalation plan
- Close follow-up of the patient, clear instructions, and good communication are key

Personal communication: JL Marshall, TS Bekaii-Saab, and JC Bendell.

Tumor Characteristics

Abstracts:

- 569 – genomic profiling

Abstract 569: Comprehensive genomic profiling of ctDNA in patients with colon cancer and its fidelity to the genomics of the tumor biopsy

Objective:

- To compare the genome profiles from ctDNA solid tumor samples from the same patient to assess whether ctDNA accurately reflects the profile of the solid tumor

ctDNA, circulating tumor DNA.

Gregg JP, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 569.
Abstract presented at ASCO-GI 2018.

Study Design

- Hybrid-capture-based genomic profiling of 62 genes on ctDNA from 91 patients was performed[a]
- Fraction of ctDNA in the blood was estimated using the maximum somatic allele frequency (MSAF)
- Frequencies of alterations were compared with those from tumor samples tested with comprehensive genomic profiling[b]

[a] FoundationACT™; [b] FoundationOne®

Gregg JP, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 569.
Abstract presented at ASCO-GI 2018.

Concordance Between ctDNA and Tumor Profiling

Concordance between ctDNA and tumor profiling per alteration for insertions/deletions and substitutions

	Insertions/Deletions and Substitutions	Insertions/Deletions and Substitutions, Only NCCN Alterations	Insertions/Deletions and Substitutions < 60 Days Between F1 and F-ACT	NCCN Alterations, < 60 Days Between F1 and F-ACT, Only
Colon CUS, MSAF > 0	81% n = 118	83% n = 52	86% n = 36	92% n = 15
Colon CUS, MSAF > 0.25%	85% n = 112	85% n = 49	86% n = 34	92% n = 14
Colon CUS, MSAF > 0.5%	88% n = 102	90% n = 44	85% n = 33	92% n = 14

CUS, clinical utility study; F1, FoundationOne; F-ACT, Foundation-ACT; NCCN, National Comprehensive Cancer Network.

Gregg JP, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 569.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- Concordance between matched tissue and blood sample genomic profiles was high: ~ 90% in NCCN-recommended genes (*NRAS*, *KRAS*, and *BRAF*)
- Stage IV patients had more ctDNA than earlier stage patients
- These results provide compelling evidence that, in cases where tumor profiling is not possible, comprehensive molecular profiling of ctDNA in colon cancer can be used to identify most clinically relevant aberrations and accurately reflects the genomics of the tumor

Gregg JP, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 569.
Abstract presented at ASCO-GI 2018.

Discussion: Clinical Practice Implications

Are you using ctDNA testing in daily practice to screen patients for inclusion in clinical trials or for monitoring?

- ctDNA is sometimes used in clinical trials, but tissue testing is still mainly used in the clinic. There is hope that ctDNA testing will be more reliable in the future

Personal communication: JC Bendell.

Discussion: ctDNA Profiling

How do you feel about the 90% concordance rate in this trial in terms of tumor heterogeneity and current practice?

- Tumor DNA is still the gold standard
- Important to get tissue within 1 year of initiation of treatment, even though *RAS*/*BRAF* mutations are quite stable

Personal communication: JL Marshall and TS Bekaii-Saab.

Tumor Characteristics

Abstracts:

- 558 – tumor sidedness
- 742 – tumor sidedness
- 830 – tumor sidedness

Abstract 558: SCOT: tumor sidedness and the influence of chemotherapy duration on DFS

Objective:

- To evaluate data from the SCOT trial to determine whether patients with right-sided disease have different DFS than those with left-sided disease

Rationale:

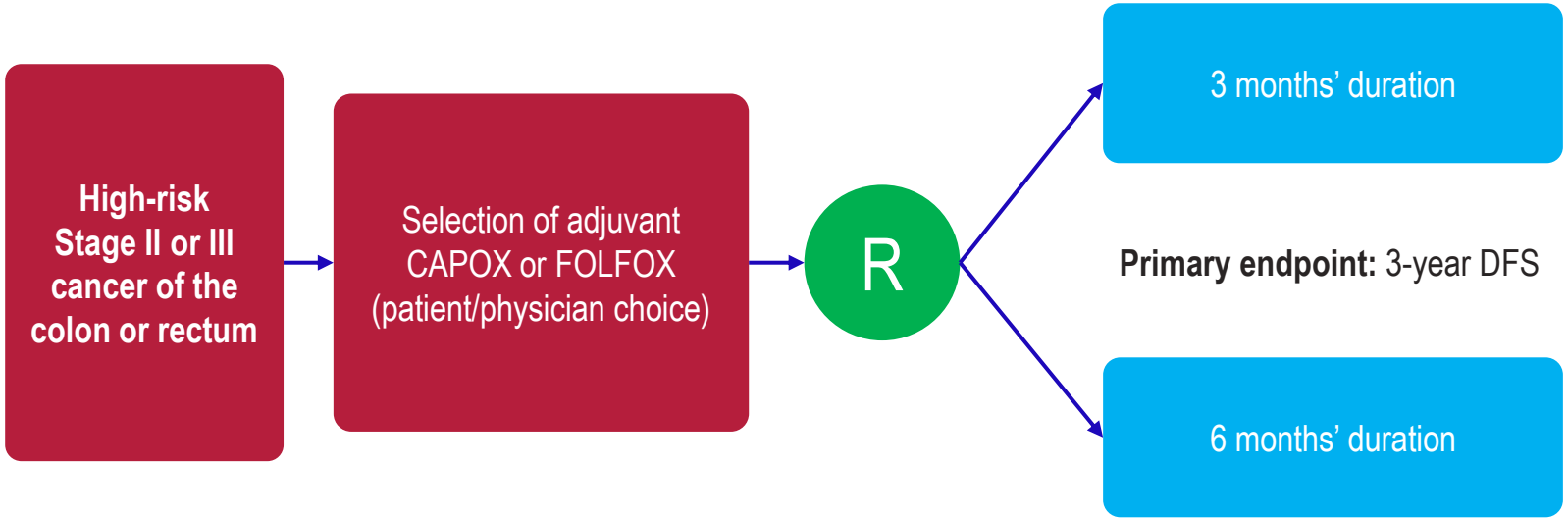
- Studies have suggested that patients with right-sided tumors have a worse prognosis

DFS, disease-free survival.

Saunders M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 558.
Abstract presented at ASCO-GI 2018.

SCOT Design

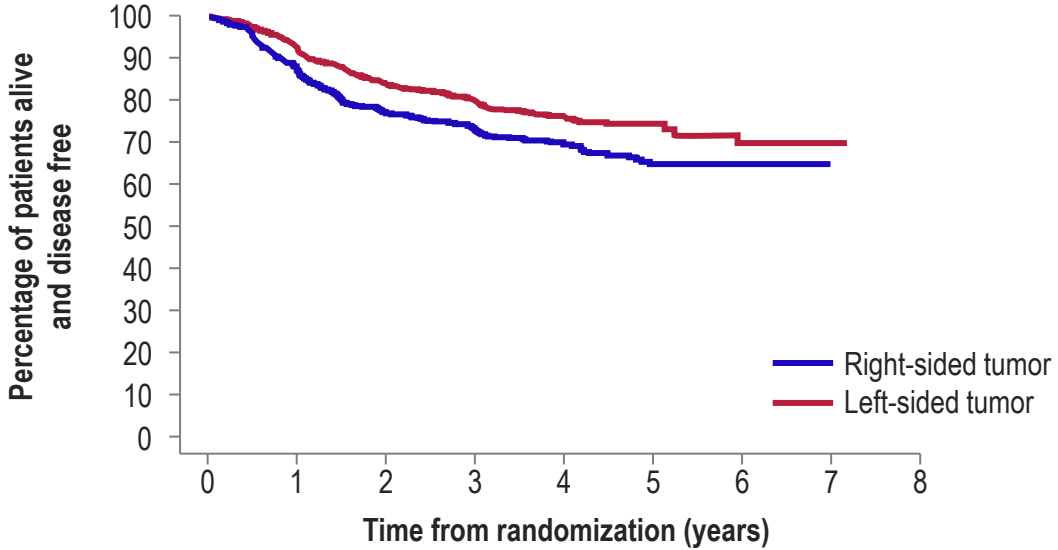
6,088 patients from 244 centers from 6 countries



CAPOX, capecitabine plus oxaliplatin; R, randomization.

Saunders M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 558.
Abstract presented at ASCO-GI 2018.

Kaplan–Meier plot of DFS by sidedness



Number at risk									
Left	2011	1822	1601	1051	419	124	33	4	0
Right	1207	1033	891	578	259	100	19	1	0

- Patients with right-sided tumors had a significantly worse DFS
  (3-year DFS right: 73%, left: 80%. HR: 1.401 (95% CI: 1.216–1.615; p < 0.0001)

Saunders M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 558.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- This study provides the first demonstration that unselected patients with right-sided tumors have worse DFS than those with left-sided tumors
- 3-month and 6-month chemotherapy duration comparisons in the SCOT trial were not affected by tumor sidedness

Saunders M, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 558.
Abstract presented at ASCO-GI 2018.

Abstract 742: sidedness, mutations, and survival in Stage IV colon cancer: a U.S. population-based study

Objective:

- To evaluate registry data for Stage IV colon cancer patients for interactions between tumor sidedness and molecular biomarkers

Lin AY, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 742.
Abstract presented at ASCO-GI 2018.

Study Design

- National Cancer Institute 2014 Patterns of Care Study data for 1,299 Stage IV colon cancer patients were evaluated
- Chi-square tests were used to compare demographic, tumor, molecular, and treatment data
- OS across demographic, tumor, molecular biomarker, and treatment subgroups were compared using Cox proportional hazards models

Lin AY, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 742.
Abstract presented at ASCO-GI 2018.

HRs for Stage IV colon cancer patients who were tested for *KRAS* and received any chemotherapy by sidedness (n = 587)

		Multivariate Model			
		Right (n = 277)		Left (n = 310)	
		HR	CI	HR	CI
Age, years	20–49	0.74	(0.21, 2.62)	1.95	(0.53, 7.23)
	50–69	0.70	(0.25, 1.99)	2.49	(0.77, 8.02)
	70+	1.00	REF	1.00	REF
Histology	Adenocarcinoma	1.00	REF	1.00	REF
	Other	0.28	(0.04, 2.29)	0.42	(0.09, 1.95)
Grade	Well differentiated	1.00	REF	1.00	REF
	Moderately differentiated	1924242	(0.00, .)	1.24	(0.16, 9.59)
	Poorly/undifferentiated/unknown	3374619	(0.00, .)	1.42	(0.17, 11.65)
KRAS results	Wild-type	1.00	REF	1.00	REF
	Mutated	0.59	(0.24, 1.49)	0.96	(0.42, 2.22)
BRAF results	Wild-type	1.00	REF	1.00	REF
	Mutated	2.61	(0.72, 9.45)	1.15	(0.46, 2.90)
	Not done/unknown	3.24	(0.57, 18.41)	0.00	(0.00, .)
MSI results	Microsatellite stable (MSS)	1.00	REF	1.00	REF
	Microsatellite unstable (MSI high)	0.76	(0.08, 7.55)	0.00	(0.00, .)
	Not done/unknown	0.66	(0.26, 1.69)	1.44	(0.59, 3.55)
Surgery	Yes	1.00	REF	1.00	REF
	No/unknown	**6.07**	**(2.41, 15.26)**	2.22	(0.98, 5.02)
Radiation	Yes	1.00	REF	1.00	REF
	No/unknown	**0.12**	**(0.03, 0.53)**	0.76	(0.17, 3.42)
Cetuximab/ panitumumab	Yes	1.00	REF	1.00	REF
	No	2.10	(0.61, 7.18)	3.71	(1.00, 13.71)
Bevacizumab	Yes	1.00	REF	1.00	REF
	No	1.61	(0.64, 4.02)	**4.34**	**(1.95, 9.68)**

Distribution of molecular biomarkers by sidedness

		Right (n = 699)		Left (n = 600)		p value
		n	%	n	%	
KRAS status[1]	Wild-type	163	48.4	227	64.5	< 0.0001
	Mutated	174	51.6	125	35.5	
BRAF status[2]	Wild-type	66	71.0	113	89.0	0.0007
	Mutated	27	29.0	14	11.0	
MSI[3]	Microsatellite stable (MSS)	189	85.9	187	93.0	0.0181
	Microsatellite unstable (MSI high)	31	14.1	14	7.0	

Lin AY, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 742.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- Among patients tested for *KRAS* (n = 587) in this population-based analysis, bevacizumab treatment was associated with lower odds of death in the left-sided colon cancer model
- Nearly significant associations with lower odds of death were observed for cetuximab and panitumumab in left-sided colon cancer (p = 0.05), but not right-sided (p = 0.24)
- The distribution of mutated *KRAS* or *BRAF* and microsatellite instability-high markers vary significantly by primary tumor location

Lin AY, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 742.
Abstract presented at ASCO-GI 2018.

Abstract 830: Predictive value of primary tumor location (TL) in patients (pts) with *PAN-RAS* wild-type (WT) metastatic colorectal cancer (mCRC) receiving chemotherapy (CTX) with or without cetuximab or panitumumab (C/P): an updated meta-analysis

Objective:

- To compare the efficacy of chemotherapy plus panitumumab or cetuximab with that of chemotherapy alone in right-sided versus left-sided *RAS* wild-type mCRC

Wang ZX, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 830.
Abstract presented at ASCO-GI 2018.

Study Design

- Systematic literature review
- Included trials:
  - 3 first-line RCTs (CRYSTAL, PRIME, and TAILOR)
  - 1 second-line RCT (20050181)
- Collected data for tumor location, treatment, and outcomes
- Evaluated OS, PFS, ORR
- If significant heterogeneity was present, a random-effects meta-analysis model was used
- Fixed-effects models were otherwise used

RCT, randomized controlled trial.

Wang ZX, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 830.
Abstract presented at ASCO-GI 2018.

Author Conclusions

- In patients with *RAS* WT left-sided mCRC, adding cetuximab or panitumumab to chemotherapy provided a clear benefit in terms of OS, PFS, and ORR
- Improvements in OS were attenuated in patients with right-sided mCRC
- However, in patients with *RAS* WT right-sided mCRC, the addition of cetuximab or panitumumab improved PFS and ORR, and the treatment effects did not significantly differ by tumor location

Wang ZX, et al. J Clin Oncol. 2018;36:suppl 4S:abstract 830.
Abstract presented at ASCO-GI 2018.

Discussion: Tumor Sidedness

What is the impact of this information on the sidedness of tumors in the context of molecular testing?

- These studies confirm our clinical practice and continue to confirm that anti-EGFR therapies have a prime role in the treatment of left-sided tumors
- In earlier-stage disease, sidedness also seems to be able to predict prognosis
- Some benefit can still be obtained from using anti-EGFR therapies in right-sided tumors, but should perhaps be used at a later stage in treatment
- The adjuvant analysis shows that adding more chemotherapy in poor prognosis patients may not be of benefit

Personal communication: JL Marshall and TS Bekaii-Saab.

Discussion: Toxicity

Do you make treatment decisions not going for the therapy with best proven survival/ response rate (FOLFIRINOX/bevacizumab or anti-EGFR-based therapy in left-sided, *RAS* WT patients) based on concerns about toxicity?

- Concerns about toxicity play a role in treatment decisions
- We are trying to shift to consider anti-EGFR-based therapy earlier on in patients where a greater benefit is expected
- These therapies can be very effective, but benefit should be balanced by patient QOL and impact of toxicity; some patients are not comfortable with skin toxicity that may last a year while on treatment

Personal communication: TS Bekaii-Saab and JC Bendell.

Final Discussion: Key Insights in mCRC

How are we moving forward in the management of mCRC today?

- There is a lot of research in this area now. Research into immunotherapies and bi-specific antibodies show some promise in CRC as do vaccines and solid tumor CAR-T therapies
- In the future, we will be doing more profiling of patients and we will be developing new individualized treatments

CAR-T, chimeric antigen receptor T-cell.

Personal communication: JC Bendell.

Final Discussion: Personalized Medicine

How is personalized medicine being applied to CRC?

- A current effort is to take the molecular heterogeneity of CRC and break it down into relevant subsets
- In the COLOMATE trial, patients who progress on a couple of therapies are screened by liquid and tissue profiling and assigned to different specific therapeutic arms that are individually powered

- There seems to be evidence of the involvement of the microbiome in the etiology of colon cancer and response to therapy

Personal communication: TS Bekaii-Saab and JL Marshall.

ASCO-GI 2018 Key Messages

- Patients with wild-type *RAS*/*BRAF* mCRC may have a survival advantage associated with panitumumab-based treatment versus cetuximab-based treatment, but these 2 treatments are essentially equivalent in this setting with slightly different toxicity profiles
- Escalated dosing of regorafenib improves its tolerability profile. Sequenced dosing seems to favor regorafenib before cetuximab rather than the reverse sequence
- Patients with right-sided tumors have worse DFS than those with left-sided tumors. Patients with left-sided disease benefit from therapies that include bevacizumab, panitumumab, or cetuximab
- ctDNA could be used in the future to identify most clinically relevant genetic aberrations. However, tumor DNA is still the gold standard in mCRCs

Personal communication: JL Marshall.