Thank you for joining us.
The program will commence momentarily.

Recent Advances in Medical Oncology: Colorectal and Gastric Cancer

Monday, July 27, 2020

5:00 PM – 6:30 PM ET

Faculty

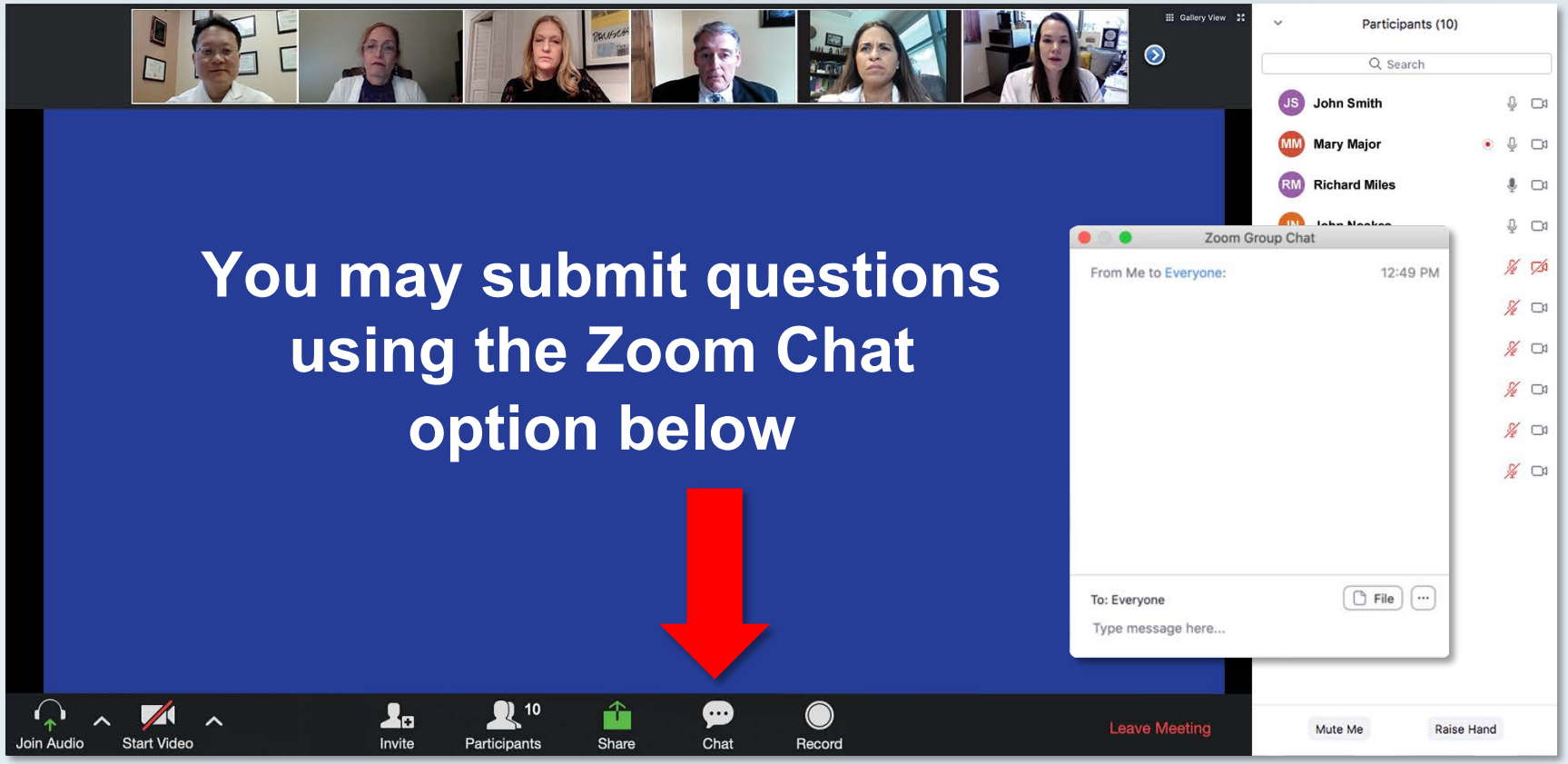
Johanna Bendell, MD
Crystal Denlinger, MD
Axel Grothey, MD

Moderator

Neil Love, MD

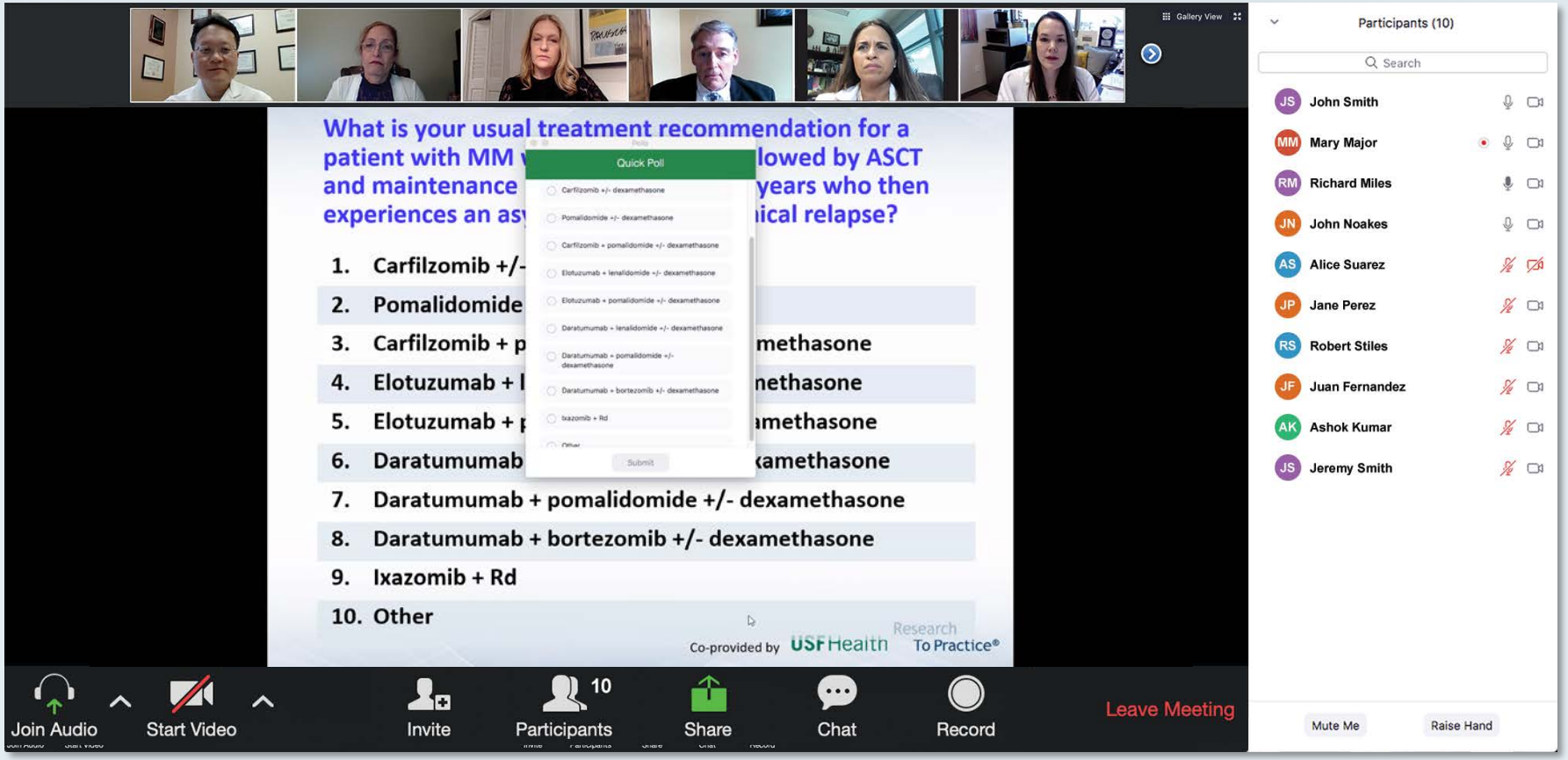
RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



Feel free to submit questions **now before** the program commences and **throughout the program.**

Familiarizing yourself with the Zoom interface
How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seattle Genetics, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc, Tolero Pharmaceuticals and Verastem Inc.

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Dr Bendell — Disclosures

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Dr Denlinger — Disclosures

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Dr Grothey — Disclosures

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Consulting Agreements	Array BioPharma Inc, a subsidiary of Pfizer Inc, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Genentech, a member of the Roche Group
Contracted Research	Array BioPharma Inc, a subsidiary of Pfizer Inc, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Merck
Data and Safety Monitoring Board/Committee	Regeneron Pharmaceuticals Inc

Upcoming Live Webinars

Wednesday, July 29, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: Ovarian Cancer

Faculty
Mansoor Raza Mirza, MD
Kathleen Moore, MD
Shannon N Westin, MD, MPH

Moderator
Neil Love, MD

Thursday, July 30, 2020
12:00 PM – 1:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Rafael Fonseca, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Friday, July 31, 2020
9:00 AM – 10:00 AM ET

Virtual Molecular Tumor Board: Role of Genomic Profiling for Patients with Solid Tumors and the Optimal Application of Available Testing Platforms

Faculty
Andrew McKenzie, PhD
Bryan P Schneider, MD
Milan Radovich, PhD

Moderator
Neil Love, MD

Monday, August 3, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: Urothelial Bladder Carcinoma

Faculty
Arjun Balar, MD
Thomas Powles, MBBS, MRCP, MD
Arlene Siefker-Radtke, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Tuesday, August 4, 2020
12:00 PM – 1:00 PM CT

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Shaji K Kumar, MD

Moderator
Neil Love, MD

Wednesday, August 5, 2020
5:00 PM – 6:30 PM ET

Recent Advances in Medical Oncology: Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Faculty
Edward B Garon, MD, MS
Stephen V Liu, MD
David R Spigel, MD

Moderator
Neil Love, MD

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Neil Love, MD

RTP RESEARCH TO PRACTICE

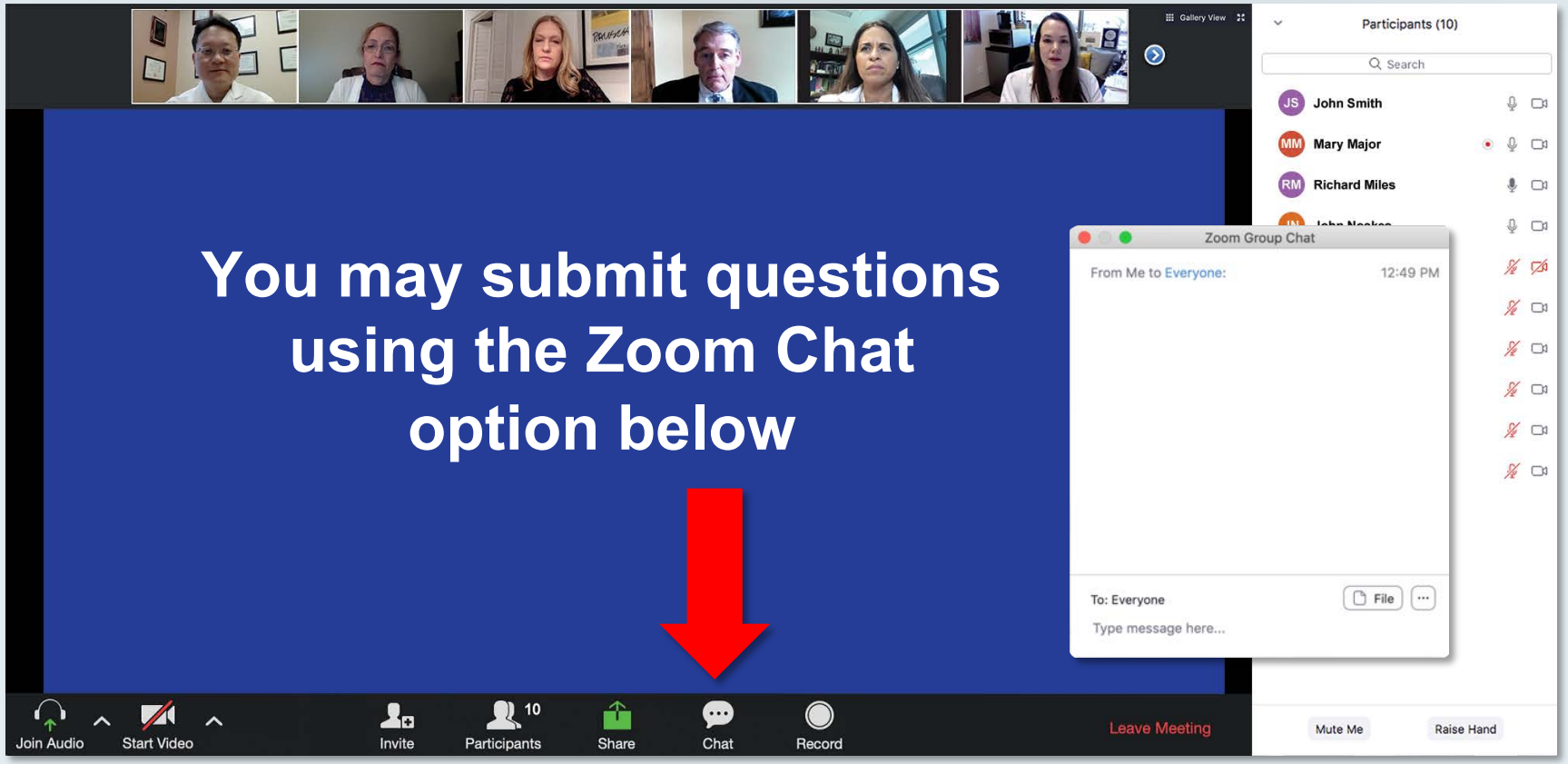
Faculty

Johanna Bendell, MD
Chief Development Officer
Director, Drug Development Unit Nashville
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Axel Grothey, MD
Director, GI Cancer Research
West Cancer Center and Research Institute
Chair, OneOncology Research Network
OneOncology
Germantown, Tennessee

Crystal Denlinger, MD
Chief, GI Medical Oncology
Director, Survivorship Program
Deputy Director, Phase 1 Program
Associate Professor, Department of Hematology/Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Dr Love and Faculty Encourage You to Ask Questions



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Co-provided by USF Health

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WITH DR NEIL LOVE

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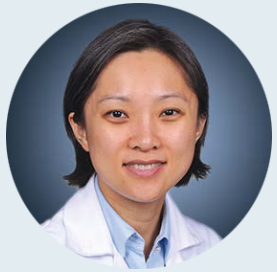
Community Oncologists

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Maen Hussein, MD
Advent Health Waterman
Central Florida Health Alliance
(Leesburg and The Villages)
Tavares, Florida

Atif Hussein, MD, MMM
Memorial Healthcare System
Clinical Associate Professor
Florida International University
Herbert Wertheim College of Medicine
Hollywood, Florida



YanJun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Agenda

Module 1: BRAF-Mutated Colorectal Cancer

Module 2: Checkpoint Inhibitors in Colorectal and Gastroesophageal Cancer

Module 3: HER2-Positive Colorectal and Gastroesophageal Cancer

Module 4: Other Treatment Strategies for Advanced Colorectal and Gastroesophageal Cancer

Biomarker testing for metastatic CRC in 2020

Aberration	Percentage	Therapy Option
KRAS/NRAS/BRAF Wild-Type (*KRAS* and *NRAS* exon 2, 3, 4)	40%	**Cetuximab-based therapy *** **Panitumumab-based therapy ***
BRAF V600E Mutation	8%	**Encorafenib + Cetuximab** **Encorafenib + Panitumumab**
HER2 Positive (IHC 3+ or 2+ with ISH+; or NGS panel) IF *KRAS/NRAS* Wild-Type	3%	Trastuzumab + Pertuzumab Trastuzumab + Lapatinib Trastuzumab + Tucatinib? **T-DXd?**
MSI-High (PCR or NGS panel) / Deficient Mismatch Repair	8%	Pembrolizumab Nivolumab Nivolumab + Ipilimumab
NTRK Gene Fusion	<0.5%	Larotrectinib Entrectinib

We must ensure appropriate testing is done as standard of care.

* For 1st line therapy must be left-sided

Presented By Michael Lee at TBD

Courtesy of Johanna Bendell

A patient presents with partial bowel obstruction and extensive hepatic metastases from a pan-RAS wild-type, MS-stable cecal adenocarcinoma. Are you more likely to use up-front systemic therapy for this patient now during the COVID-19 pandemic than you were in 2019?

a. Yes
b. No

Case Presentation — Dr Atif Hussein: A 42-year-old woman with de novo mCRC with partial bowel obstruction

- Presented recently with abdominal pain and nausea
- Nearly obstructive cecal primary mass and hepatic lesions

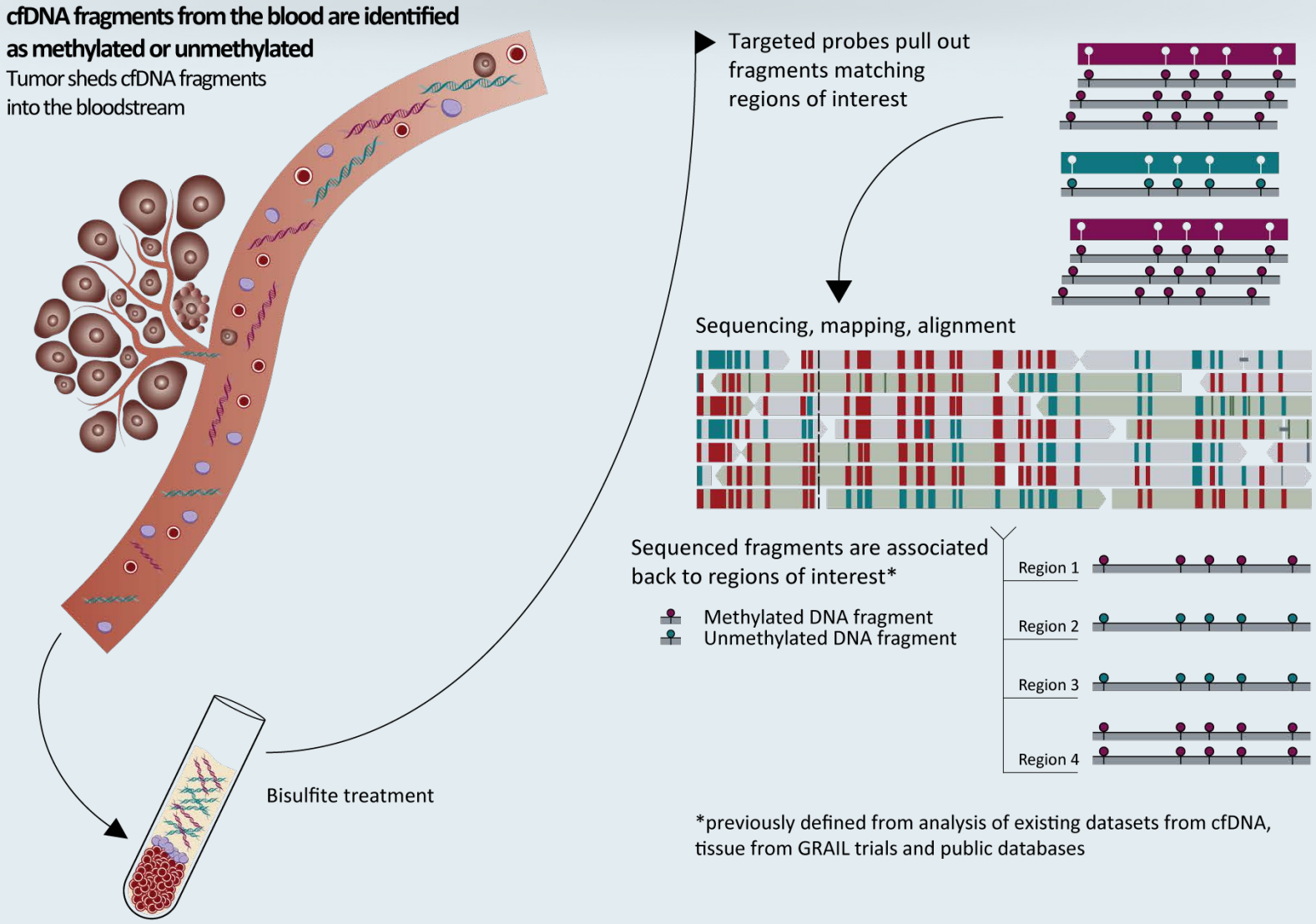
Atif Hussein, MD, MMM

Case Presentation — Dr Favaro: A 39-year-old man with mCRC and a BRAF V600E tumor mutation

- Metastatic CRC, with a BRAF V600E tumor mutation
  - MSS, very low tumor mutational burden
- FOLFOXIRI x 6 months → maintenance therapy → PD
- Cetuximab + BRAF inhibitor + MEK inhibitor x 9 months → PD, with bone mets
- Radiation therapy
- FOLFIRI x 3-4 months → brain mets → WBRT
- Enrolled on CRICKET trial of cetuximab/irinotecan rechallenge
  - Guardant360: KRAS wildtype

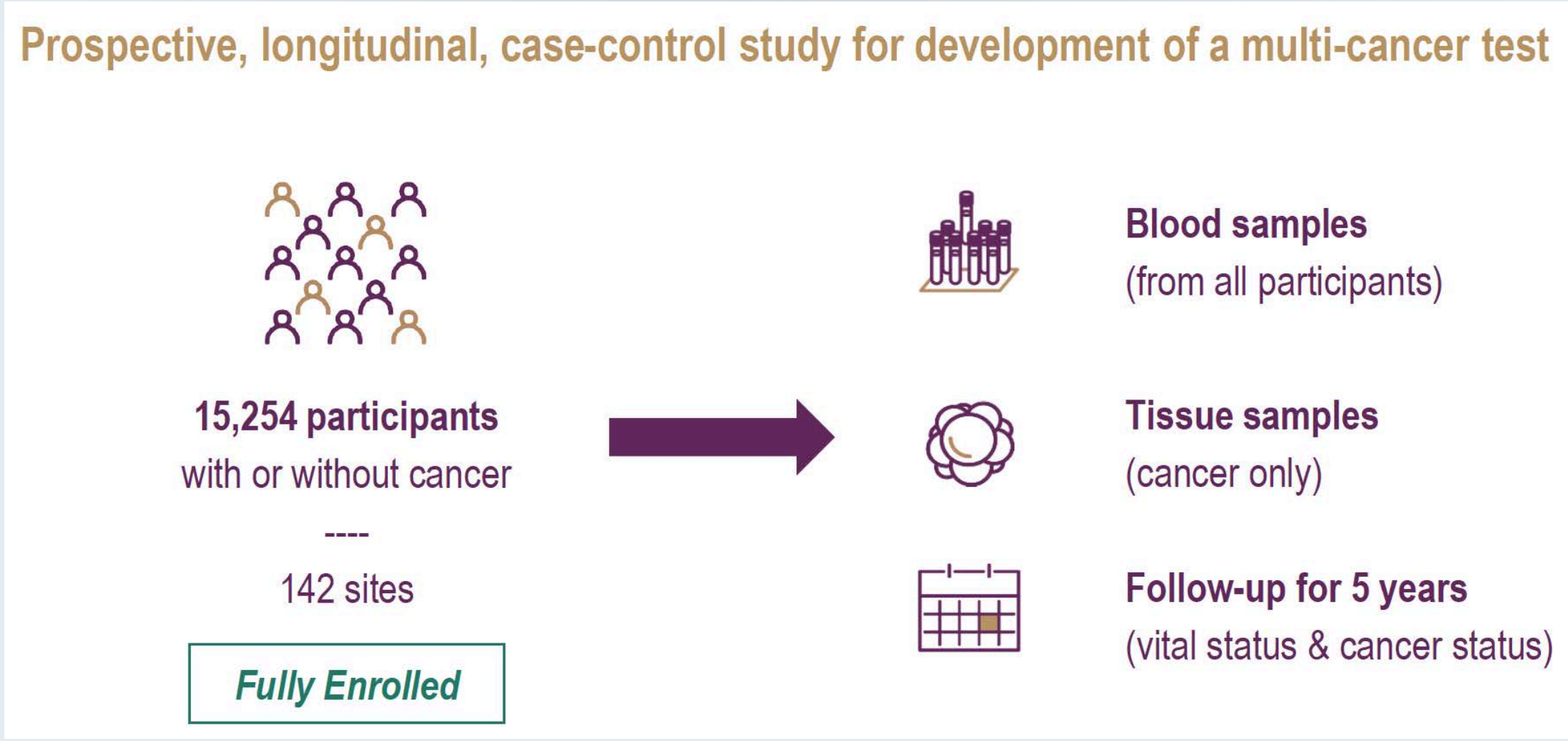
Justin Peter Favaro, MD, PhD

CCGA Study: Development and Validation of a cfDNA-based Assay for Multi-Cancer Detection



Liu MC et al. *Annal Oncol* 2020;31(6):745-59.

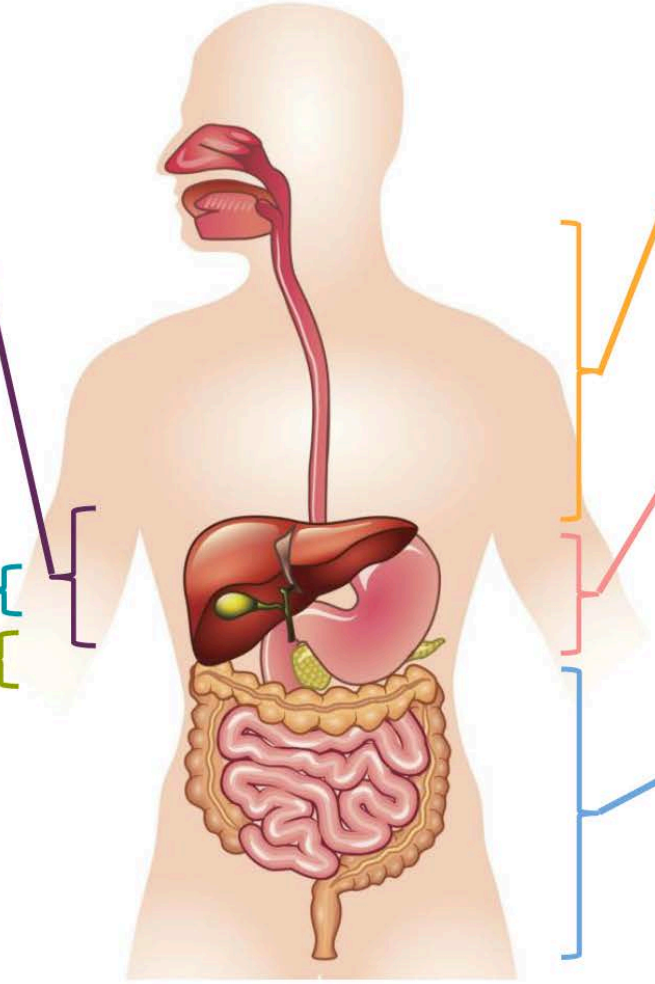
The Circulating Cell-Free Genome Atlas (CCGA) Study



Wolpin BM et al. *Gastrointestinal Cancers Symposium* 2020;Abstract 283.

Gastrointestinal Cancers (N = 447) in CCGA Substudy 2

A subset of the total 2,185 cancer participants across >20 cancer types in CCGA substudy 2



Liver / Bile Duct

Stage	I-III	IV	All
Training	19	10	29
Validation	7	4	11
All	**26**	**14**	**40**

Gallbladder

Stage	I-III	IV	All
Training	7	4	11
Validation	3	0	3
All	**10**	**4**	**14**

Pancreas

Stage	I-III	IV	All
Training	42	42	84
Validation	22	17	39
All	**64**	**59**	**123**

Esophagus

Stage	I-III	IV	All
Training	31	19	50
Validation	13	8	21
All	**44**	**27**	**71**

Stomach

Stage	I-III	IV	All
Training	9	8	17
Validation	5	3	8
All	**14**	**11**	**25**

Colon / Rectum

Stage	I-III	IV	All
Training	76	45	121
Validation	32	21	53
All	**108**	**66**	**174**

Wolpin BM et al. *Gastrointestinal Cancers Symposium* 2020;Abstract 283.

Case Presentation — Dr Atif Hussein: A 42-year-old woman with de novo mCRC with partial bowel obstruction

- Presented recently with abdominal pain and nausea
- Nearly obstructive cecal primary mass and hepatic lesions
- FOLFOX + bevacizumab

Atif Hussein, MD, MMM

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a 65-year-old patient with asymptomatic pan-RAS wild-type, MS-stable metastatic colorectal cancer (mCRC) and a BRAF V600E mutation with minimal disease burden?

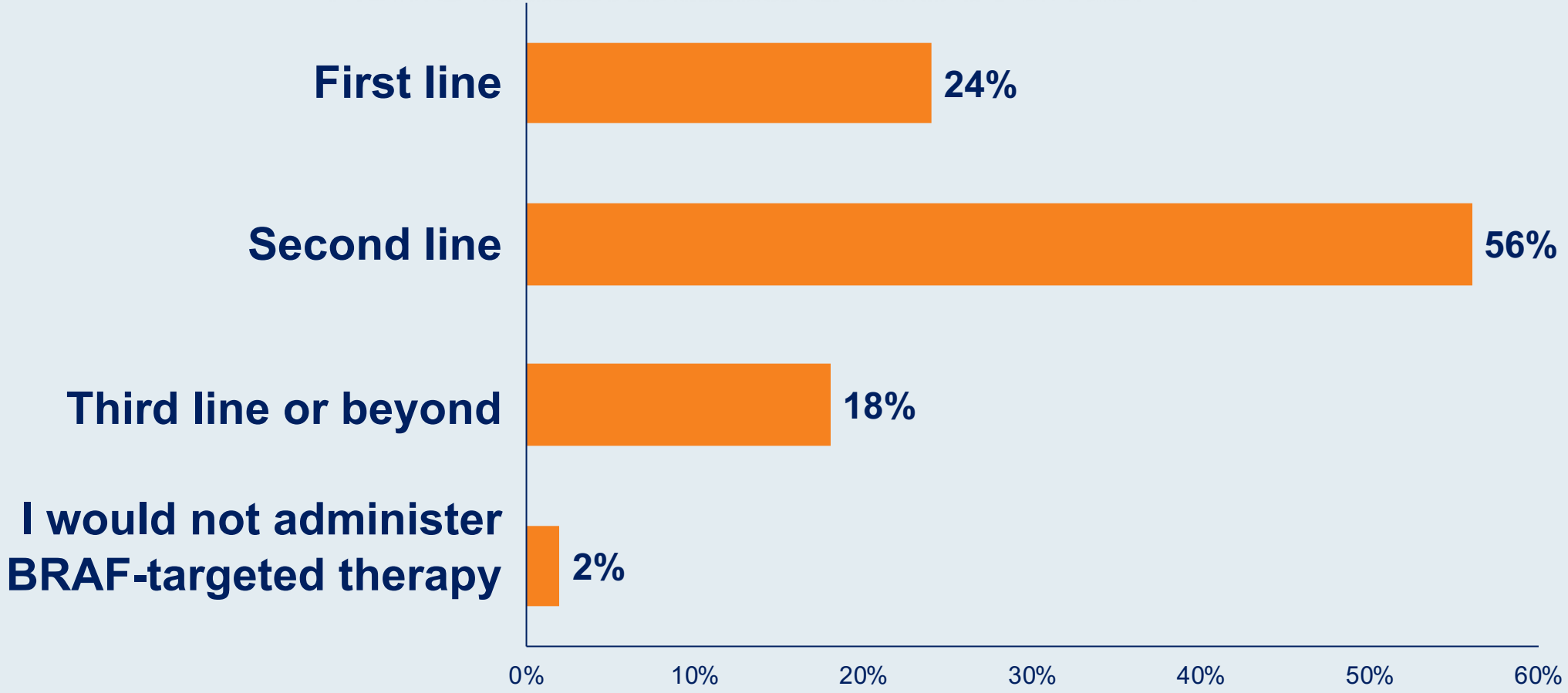
a. Chemotherapy
b. Chemotherapy/bevacizumab
c. Irinotecan + vemurafenib + EGFR antibody
d. Dabrafenib + trametinib + EGFR antibody
e. Encorafenib + binimetinib + EGFR antibody
f. Encorafenib + EGFR antibody
g. Other

Case Presentation — Dr Maen Hussein: A 65-year-old woman with mCRC and a BRAF tumor mutation

- Adjuvant FOLFOX x 6-8 months → Recurred with metastatic disease
- FOLFOX + bevacizumab, with response
  - Significant neuropathy
  - Hospitalized for dehydration secondary to diarrhea
- Molecular profiling: BRAF mutation
- Cetuximab + encorafenib x 2 months and ongoing
  - No side effects to date

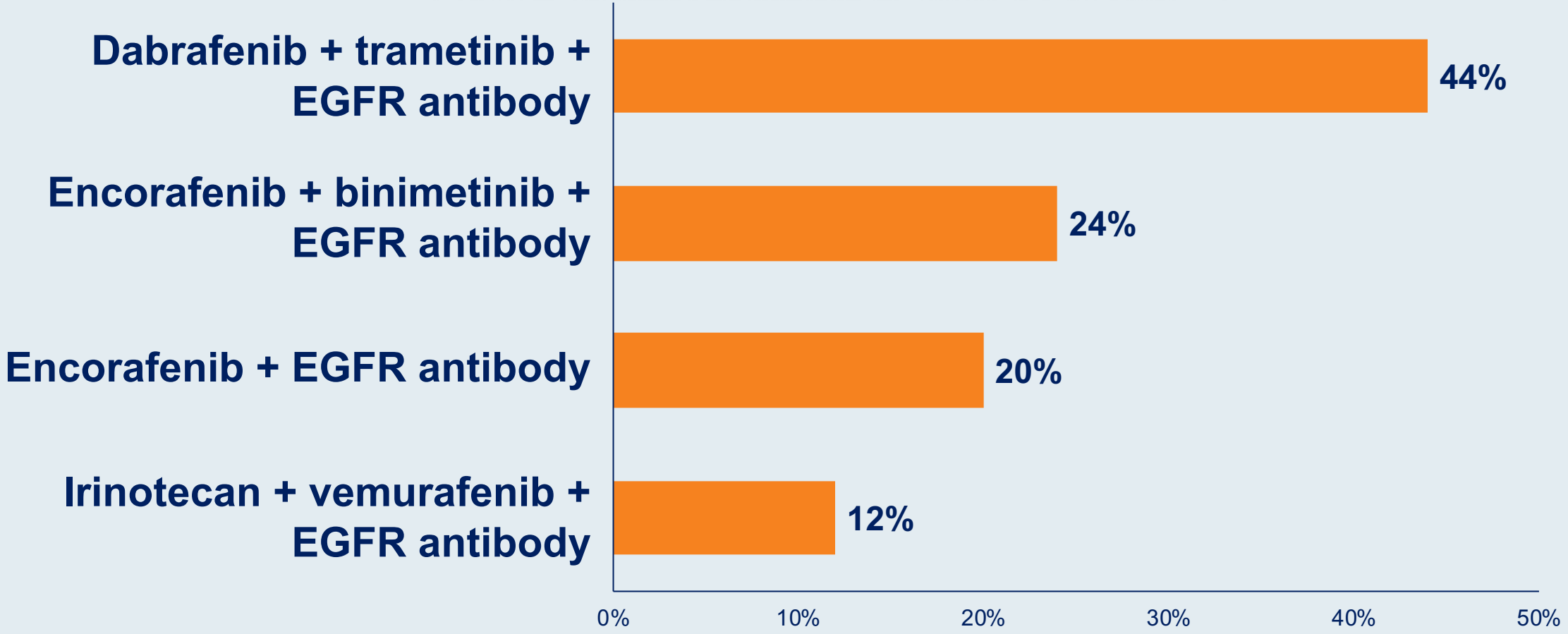
Maen A Hussein, MD

Regulatory and reimbursement issues aside, for a patient with pan-RAS wild-type mCRC and a BRAF V600E mutation, in what line of therapy would you generally administer BRAF-targeted therapy?



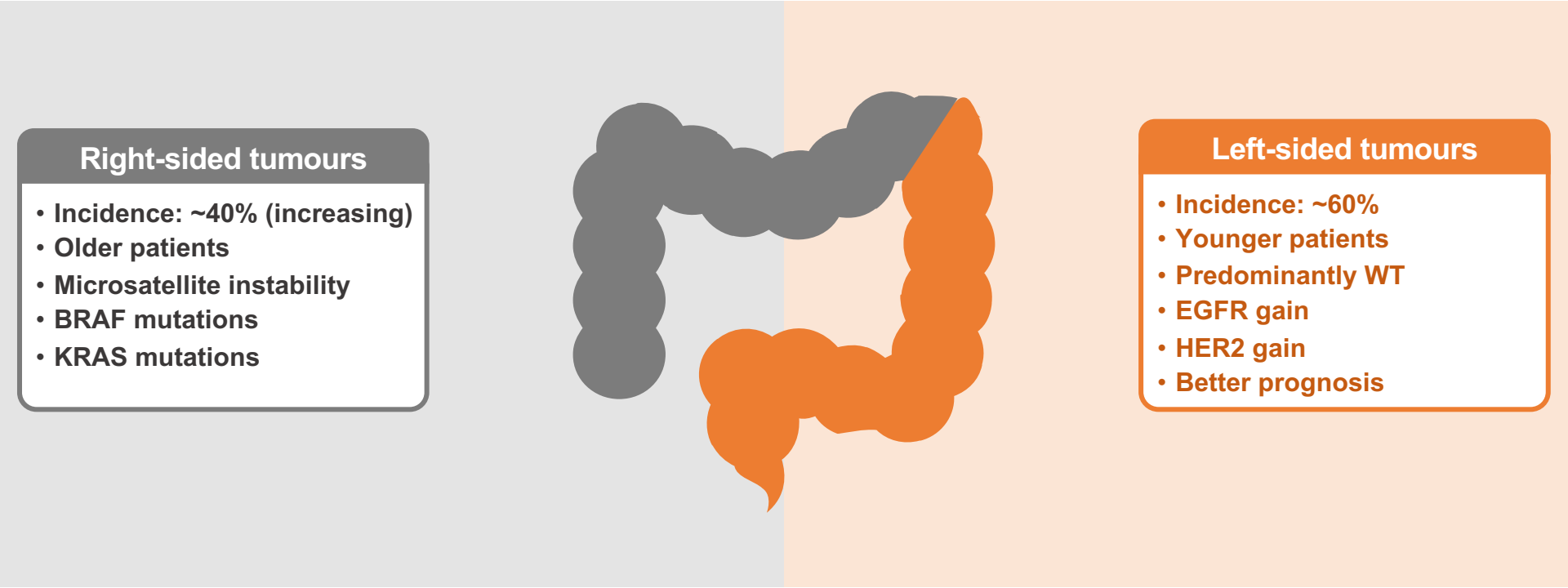
Survey of 50 US-based medical oncologists

For a patient with mCRC and a BRAF V600E mutation to whom you would administer BRAF-targeted therapy, what would be your preferred treatment?



Survey of 50 US-based medical oncologists

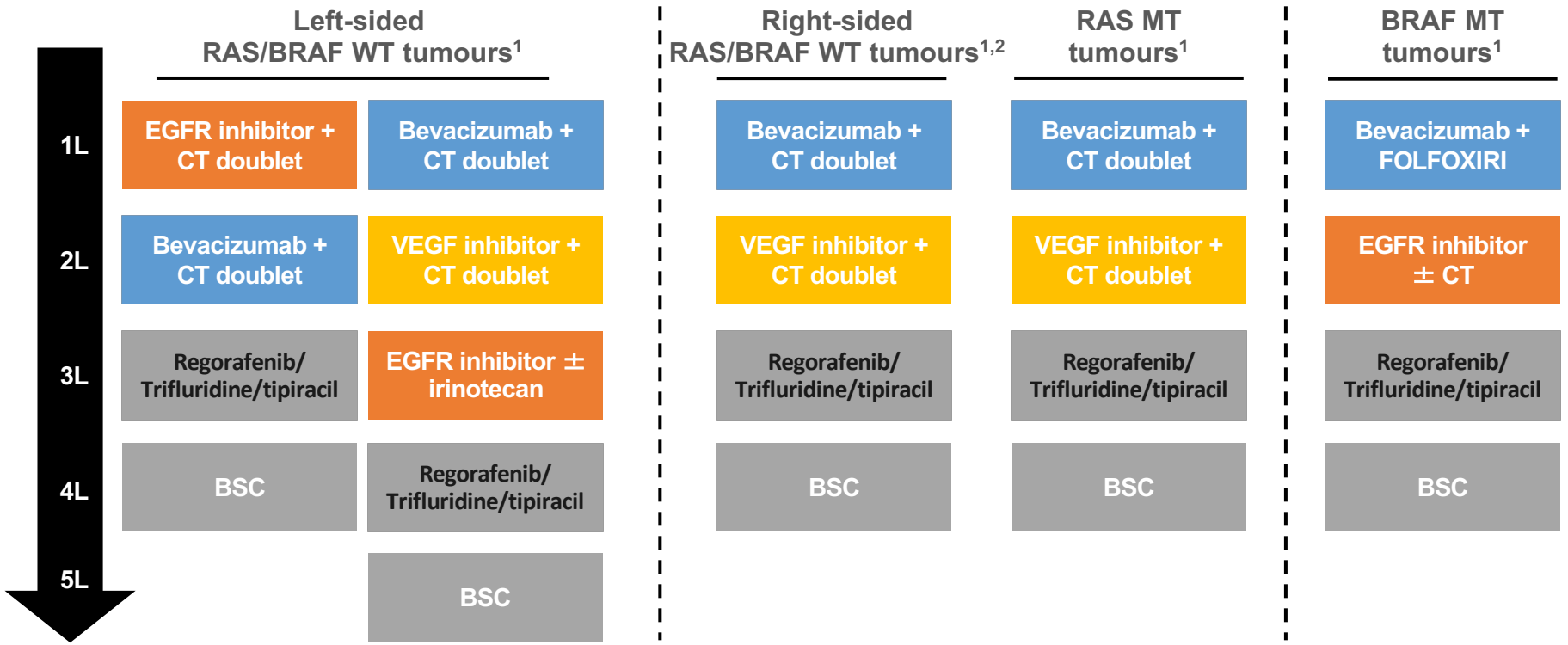
Enrichment of Molecular Characteristics by Side



Bufill JA. *Ann Intern Med* 1990; Missiaglia E, et al. *Ann Oncol* 2014; Brule SY, et al. *J Clin Oncol* 2013; The Cancer Genome Atlas Network. Nature 2012; Bendardaf R, et al. *Anticancer Res* 2008

Courtesy of Johanna Bendell

Treatment Algorithm by Tumour Side and Molecular Subgroup



1. Modified from Sridharan et al. *Oncology* (Williston Park) 2014
2. NCCN Clinical Practice Guidelines in Oncology: *Colon Cancer v2*.2018

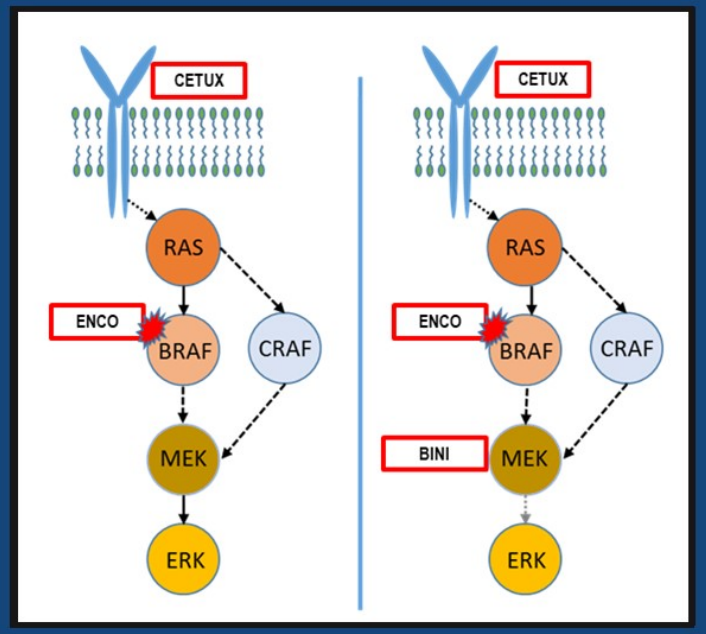
1L anti-EGFRs are recommended in RAS WT left-sided tumours only
BSC, best supportive care; CT, chemotherapy

Courtesy of Johanna Bendell

MAPK Pathway Inhibition in *BRAF V600E*-mutant CRC

- *BRAF* V600E mutation occurs in 10%–15% of patients and confers a poor prognosis[1-3]
- BRAF inhibitors alone are ineffective due to the feedback activation of EGFR, leading to continued cell proliferation[4-6]
  - Feedback may be overcome by targeting multiple pathway nodes, ie BRAF/MEK/EGFR
  - Preclinically, addition of MEK inhibitor improved outcomes
- In the primary analysis of the BEACON CRC study, the regimens of Encorafenib (ENCO) + Cetuximab (CETUX) ± Binimetinib (BINI) had manageable safety profile and encouraging activity in patients with *BRAF* V600E mCRC[7]

MAPK Signaling in Colorectal Cancer[8]

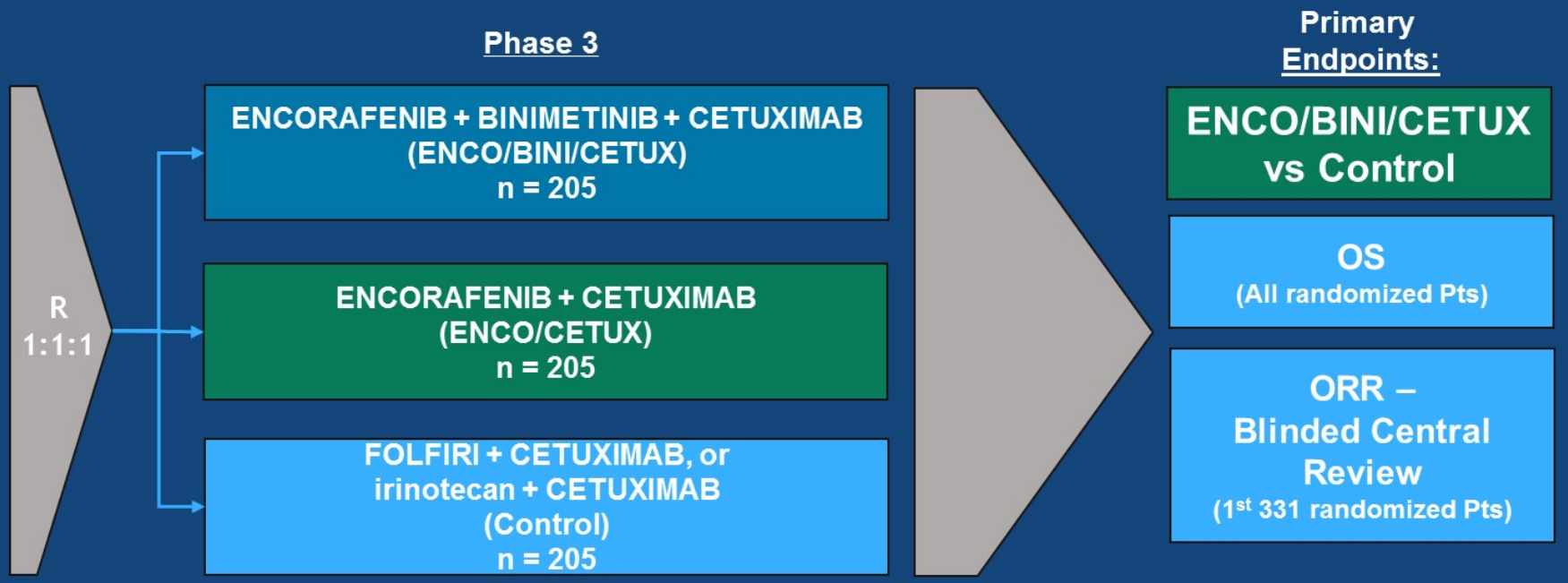


CETUX=cetuximab; EGFR=epidermal growth factor receptor; ENCO=encorafenib; MAPK=mitogen-activated protein kinase; mCRC=metastatic colorectal cancer; PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

1. De Roock W, et al. *Lancet Oncol*. 2010;11(8):753. 2. Sorbye H, et al. PLoS One. 2015;10:e0131046. 3. Loupakis F, et al. *Br J Cancer*. 2009;101:715. 4. Kopetz S, et al. *J Clin Oncol*. 2017;35(15):3505. 5. Corcoran RB, et al. *Cancer Disc*. 2012;2(3):227. 6. Prahallad A, et al. *Nature* 2012;100:100. 7. Kopetz et al. N Engl J Med 2019; 381:1632-1643. 8. Adapted From: Strickler JH. *Cancer Treat Rev*. 2017; 60:109.

BEACON CRC Study Design

Patients with *BRAF* V600E-mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor



Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

Secondary Endpoints: ENCO/CETUX vs Control and ENCO/BINI/CETUX vs ENCO/CETUX - OS & ORR, PFS, Safety, QOL

Post hoc Updated Analysis: includes 6 months of additional follow-up since cut off for primary analysis

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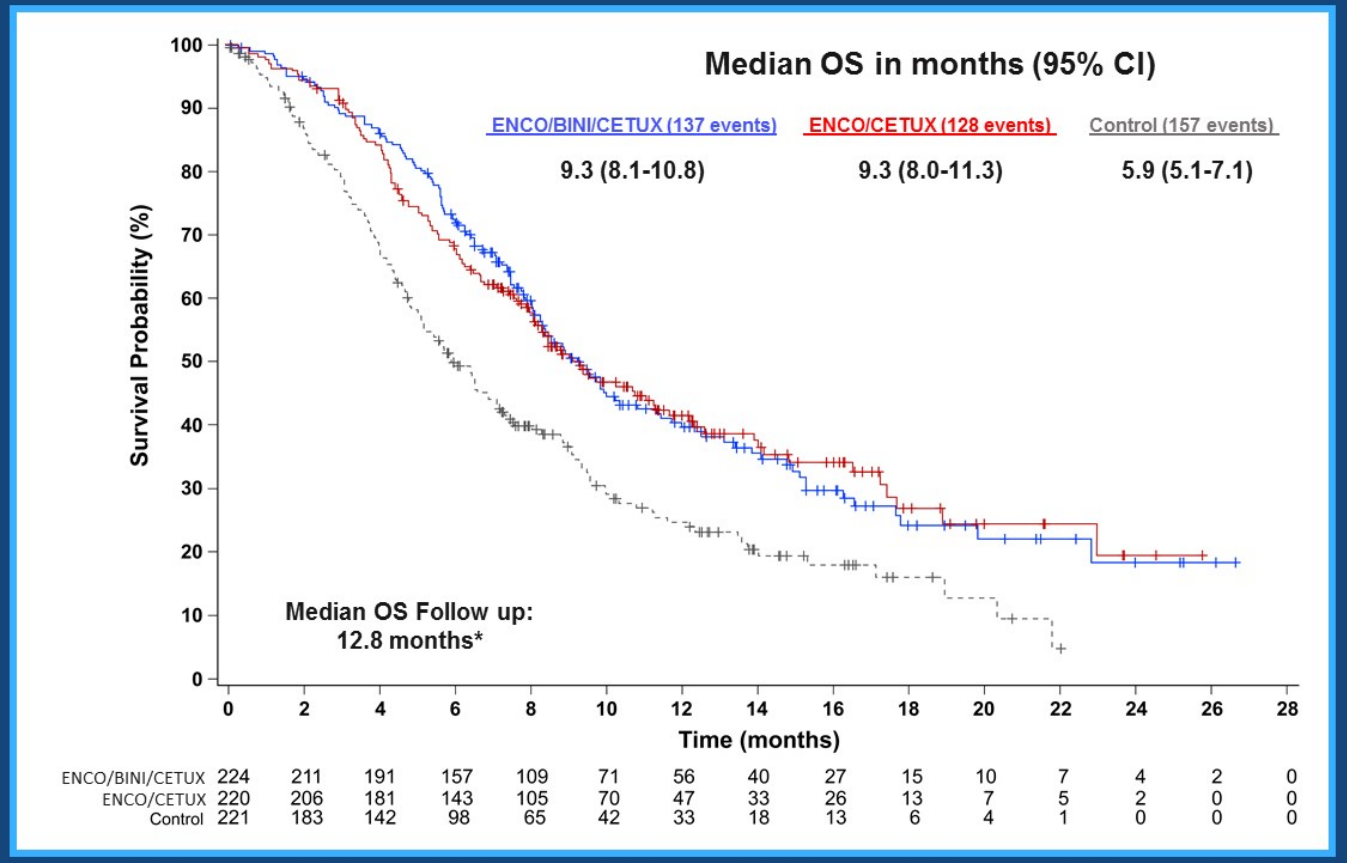
PRESENTED BY: Scott Kopetz, MD, PhD

Updated Overall Survival: ENCO/BINI/CETUX vs ENCO/CETUX vs Control



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PRESENTED BY: Scott Kopetz, MD, PhD

Presented By Scott Kopetz at ASCO 2020

Courtesy of Johanna Bendell

Updated Objective Response Rates

Confirmed Response by BICR	ENCO/BINI/CETUX N=224	ENCO/CETUX N=220	Control N=221
Objective Response Rate[a]	**27%**	**20%**	**2%**
95% (CI)	(21, 33)	(15, 25)	(<1, 5)
Best Overall Response[b]			
Complete Response (CR)	4%	3%	0%
Partial Response (PR)	23%	16%	2%
Stable Disease[c]	48%	56%	29%
Progressive Disease	11%	10%	34%
Non Evaluable by RECIST[d]	14%	15%	32%

BICR=blinded independent central review.

a. Confirmed responses per RECIST 1.1; Objective Response Rate equals the percentage of patients with a complete response or a partial response.

b. Best overall response percentage may not add up to 100% due to rounding.

c. Stable disease includes measurable disease patients who were either stable disease or non-measurable disease patients who were non-complete response/non-progressive disease per RECIST 1. Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

d. This category refers to patients who discontinued the trial regimen because of adverse events or whose disease could not be assessed centrally but who had clinical or radiologic disease progression according to local assessment.

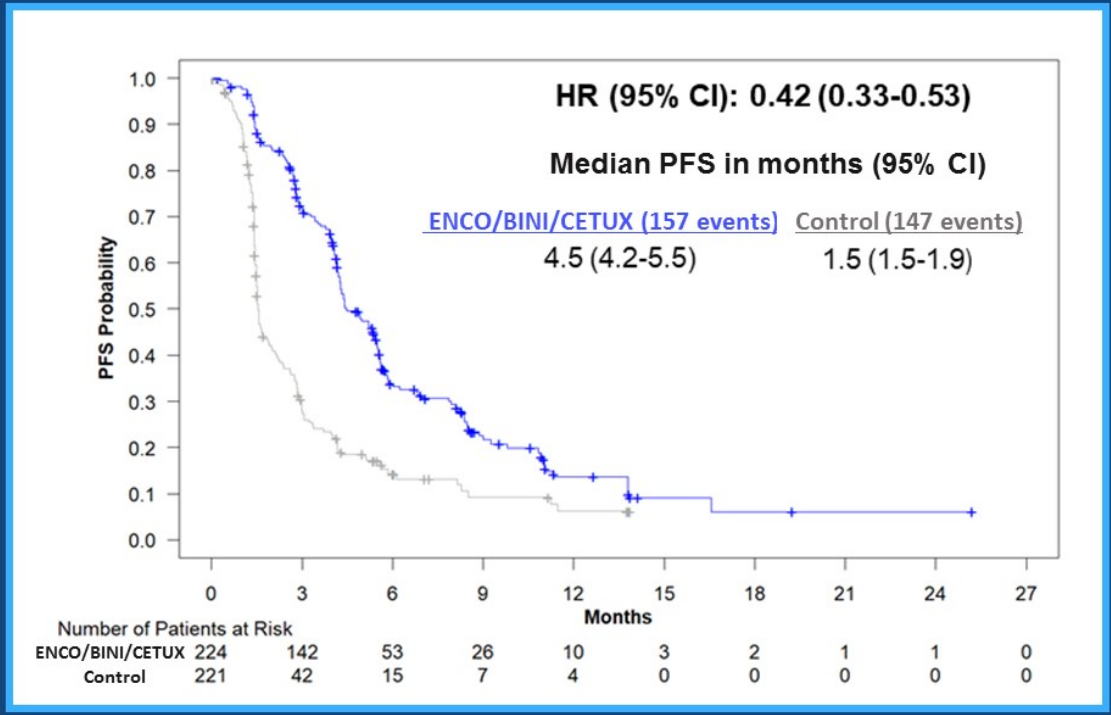
PRESENTED BY: Scott Kopetz, MD, PhD

Presented By Scott Kopetz at ASCO 2020

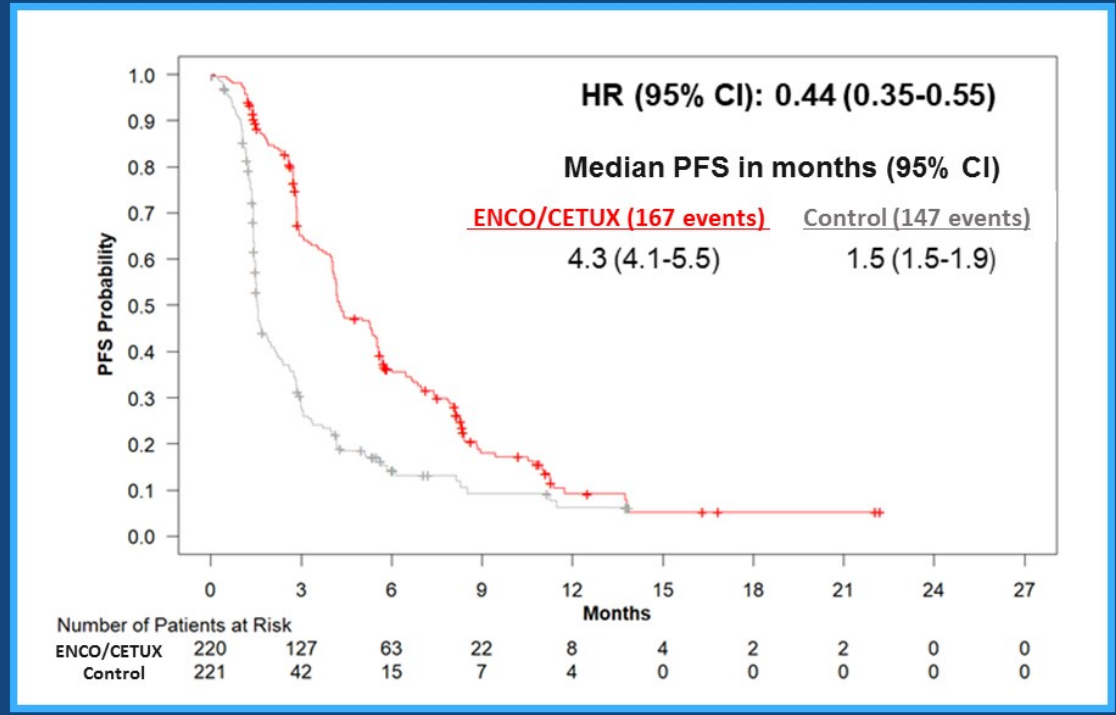
Courtesy of Johanna Bendell

Updated Progression Free Survival*

ENCO/BINI/CETUX vs Control



ENCO/CETUX vs Control



*PFS by BICR (blinded independent central review).

Updated Grade ≥3 Adverse Events and Laboratory Abnormalities*

Consistent with previously reported safety profile†

Adverse Event (Preferred term)	ENCO/BINI/CETUX N=222 Grade ≥3	ENCO/CETUX N=216 Grade ≥3	Control N=193 Grade ≥3
Diarrhea	11%	3%	10%
Abdominal pain	6%	3%	5%
Nausea	5%	<1%	2%
Vomiting	5%	1%	3%
Intestinal obstruction	5%	5%	3%
Pulmonary embolism	4%	1%	5%
Asthenia	4%	4%	5%
Acute kidney injury	3%	2%	<1%
Dermatitis acneiform	3%	<1%	3%
Fatigue	2%	4%	5%
Ileus	2%	2%	2%
Urinary tract infection	1%	2%	1%
Cancer pain	<1%	2%	<1%
Laboratory Abnormality**			
Hemoglobin (g/L), hypo	23%	6%	5%
Creatinine (μmol/L), hyper	5%	3%	1%
Creatine Kinase (IU/L), hyper	4%	0%	<1%
Bilirubin (μmol/L), hyper	3%	3%	3%

*Occurring in at least 2% of patients in either ENCO/BINI/CETUX or ENCO/CETUX arms.

† Kopetz et al. N Engl J Med 2019; 381:1632-1643

**Selected laboratory abnormalities associated with adverse events.

Presented By Scott Kopetz at ASCO 2020

Courtesy of Johanna Bendell

- On April 8, 2020, the Food and Drug Administration **approved** **encorafenib** in **combination** with **cetuximab** for the treatment of adult patients with metastatic colorectal cancer (CRC) with a **BRAF** V600E mutation, detected by an **FDA-approved** test, after prior therapy.

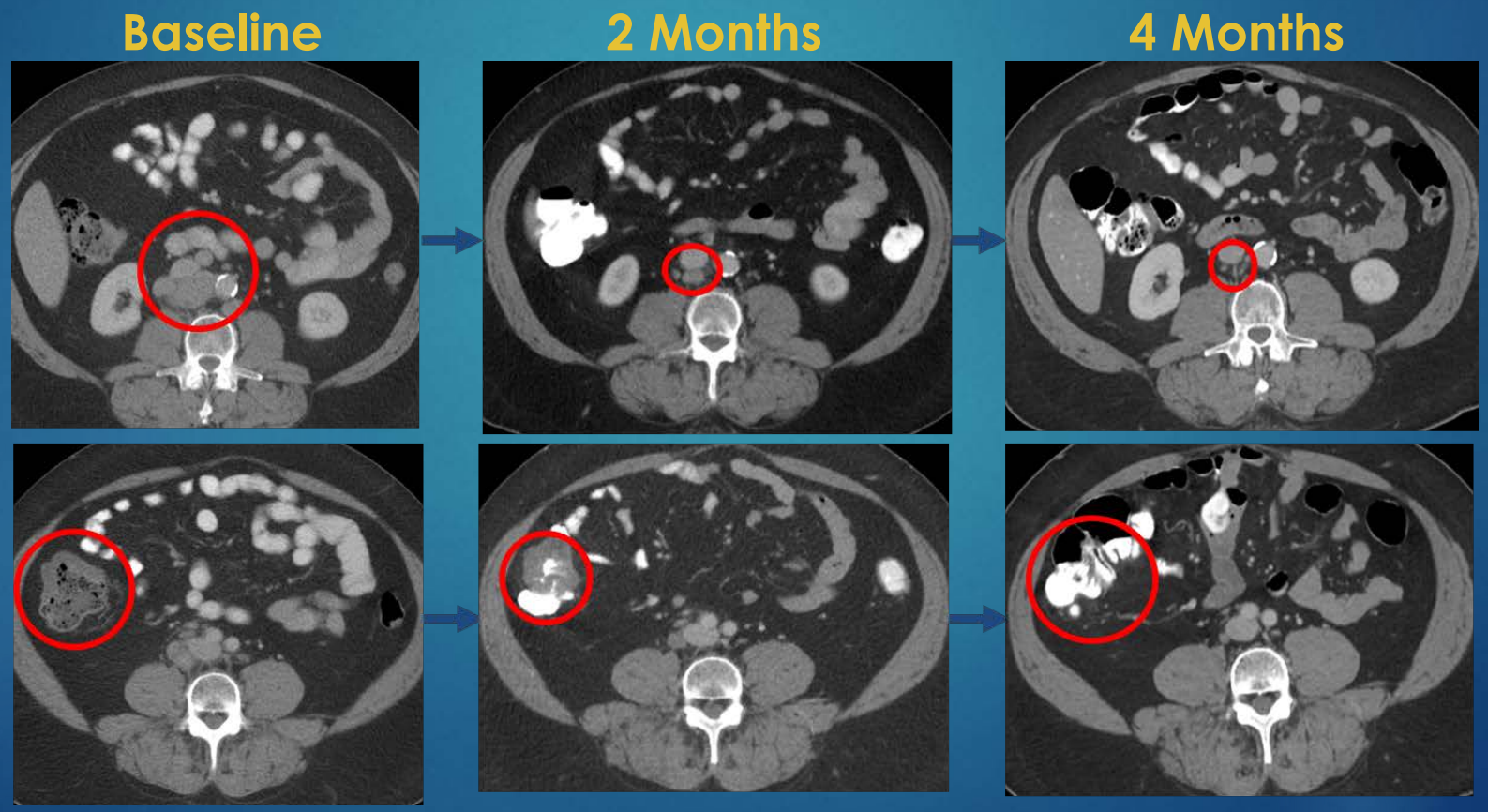
Courtesy of Johanna Bendell

Case Presentation – Dr Bendell: A 45-year-old woman with mCRC

- 45 year old woman who presented with anemia to her PCP
- Workup led to colonoscopy, which showed mass in the ascending colon. Biopsy showed a moderately differentiated adenocarcinoma, MSS, RAS WT, BRAF V600E mutated.
- Staging CT scans showed the right sided mass and aortocaval lymphadenopathy.
- She was started on FOLFOXIRI-bev. She had a response to this and transitioned to maintenance capecitabine-bev after 6 months of chemotherapy.
- She eventually had progression of disease 6 months later.

Case Presentation – Dr Bendell: A 45-year-old woman with mCRC (cont)

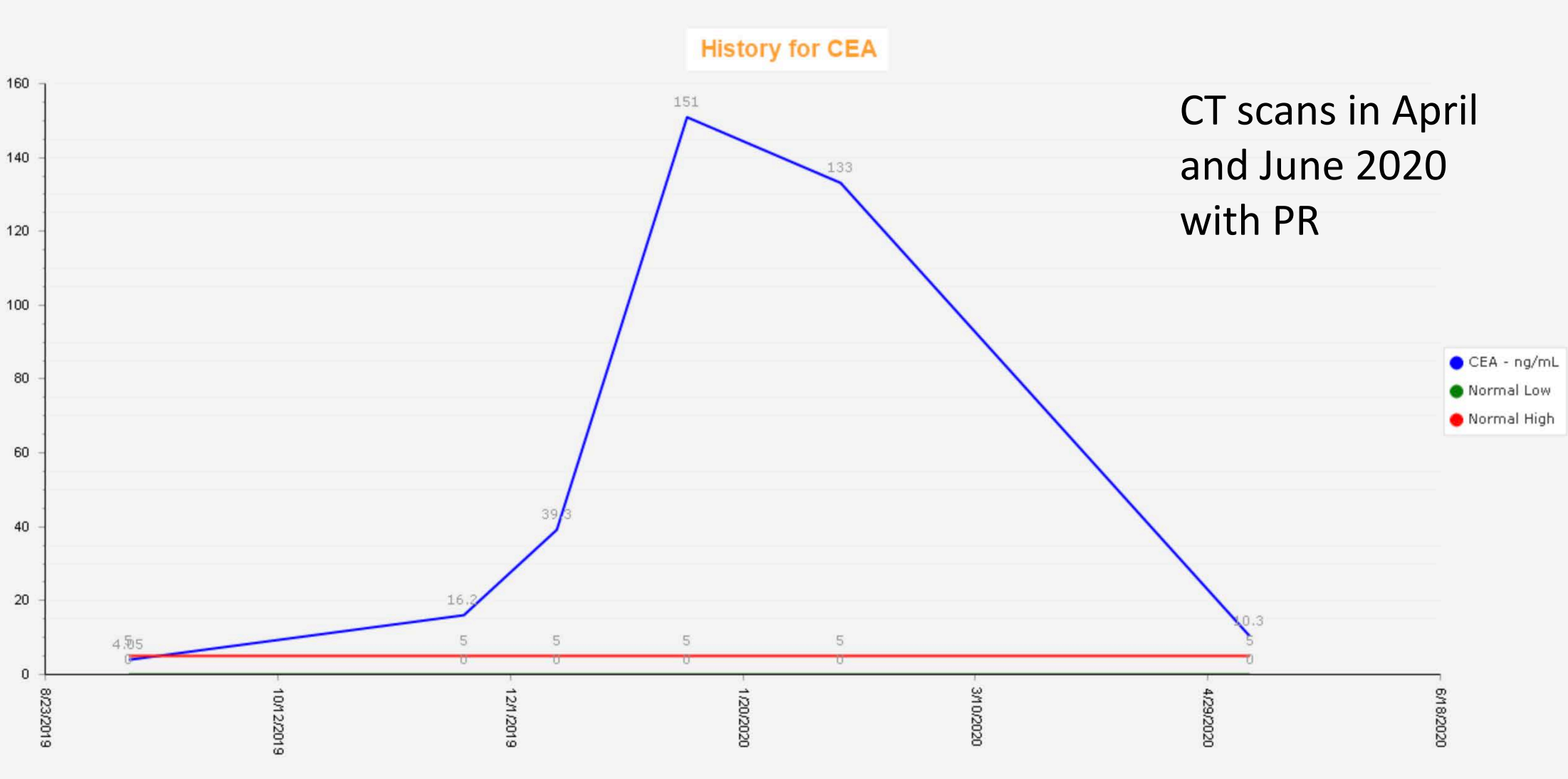
- She was then started on cetuximab plus encorafenib plus binimetinib with partial response
- Side effects included acneiform rash and mild diarrhea and nausea



Case Presentation – Dr Grothey: A 66-year-old patient with mCRC and a BRAF V600E tumor mutation

- 66 yo pt with PMH of HTN, GERD
- August 2019: Weight loss, anemia (Hb 7.9)
- September 15, 2019: CT abd/pelvis shows liver mass in segm 6, retroperitoneal adenopathy, peritoneal implants, mass in ascending colon with bowel obstruction
- September 16, 2019: Right hemicolectomy. pT3 pN2b (15/16), M1c cancer
- CARIS profile: BRAF V600E mutation, MSS, TMB 10
- October 31, 2019: CT scan before initiation of chemotherapy with progression of liver and peritoneal metastases, lymphadenopathy
- November 2019: Pt screen failure for ANCHOR study due to low EF (43%), start FOLFOXIRI + BEV → rising CEA on therapy. Pt developed more pain in RUQ
- January 2020: CT after 4 cycles of chemo shows PD
- February 2020: Start BEACON triplet. Clinical response within 2 (!) days!

Case Presentation – Dr Grothey: A 66-year-old patient with mCRC and a BRAF V600E tumor mutation -- CEA levels on therapy



CT scans in April and June 2020 with PR

FOLFOXIRI-BEV

BEACON

Agenda

Module 1: BRAF-Mutated Colorectal Cancer

Module 2: Checkpoint Inhibitors in Colorectal and Gastroesophageal Cancer

Module 3: HER2-Positive Colorectal and Gastroesophageal Cancer

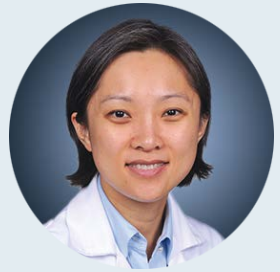
Module 4: Other Treatment Strategies for Advanced Colorectal and Gastroesophageal Cancer

Regulatory and reimbursement issues aside, what would you recommend for a young patient with MSI-high mCRC and liver-only metastases that are potentially resectable with tumor shrinkage?

a. Pembrolizumab
b. Ipilimumab/nivolumab
c. Chemotherapy/pembrolizumab
d. Chemotherapy/ipilimumab/nivolumab
e. Chemotherapy/biologic
f. Other

Case Presentation — Dr Ma: A very frail woman in her 80s with de novo MSI-H mCRC

- Pembrolizumab
  - Currently, 1.5 years later still receiving treatment in complete remission
  - Tolerated treatment well, without side effects
- Family gratified that she did not receive chemotherapy



YanJun Ma, MD

A 63-year-old patient with locally advanced MS-stable gastric cancer has a complete response to carboplatin/paclitaxel and radiation therapy but then develops recurrent disease 3 months later. CPS = 10. What treatment would you recommend?

a. FOLFOX
b. Other chemotherapy
c. Pembrolizumab
d. Nivolumab
e. Other

FDA Limits the Use of Atezolizumab and Pembrolizumab for Some Patients with Urothelial Cancer

Press Release – July 5, 2018

"FDA has limited the use of atezolizumab and pembrolizumab for patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy. The Agency took this action on June 19, 2018, due to decreased survival associated with the use of pembrolizumab or atezolizumab as single therapy (monotherapy) compared to platinum-based chemotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1).

The labels of both drugs have been revised to reflect the limitation in the indication:

- **Pembrolizumab** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- **Atezolizumab** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - Are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or
  - Are not eligible for any platinum-containing therapy regardless of PD-L1 status."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-limits-use-tecentriq-and-keytruda-some-urothelial-cancer-patients

Case Presentation — Dr Favaro: A 63-year-old man with HER2-negative metastatic GEJ adenocarcinoma

- Presents with a GE junction adenocarcinoma
  - Mesenteric lymph nodes, small muscle and lung mets on PET scan
  - HER2 non-amplified, PD-L1 CPS: 10, MSS
- Carboplatin/paclitaxel and radiation therapy → CR
- Local recurrence
- FOLFOX

Justin Peter Favaro, MD, PhD

Case Presentation — Dr Favaro: A 90-year-old man with metastatic esophageal cancer and Parkinson's disease

- Locally-advanced esophageal cancer treated with radiation therapy and low-dose chemotherapy → remission x 10 years
- Currently, presents with dysphagia
  - Locally recurrent disease and liver metastases
  - PD-L1 CPS: 10
- Pembrolizumab x 6 months and ongoing
  - Reduction in liver mets, renewed ability to swallow
  - No side effects

Justin Peter Favaro, MD, PhD

In general, what dose of pembrolizumab are you currently administrating to patients with gastrointestinal cancers?

a. 400 mg every 6 weeks
b. 200 mg every 3 weeks
c. Using both doses depending on the situation

FDA approves new dosing regimen for pembrolizumab

Press Release – April 28, 2020

The Food and Drug Administration granted accelerated approval to a new dosing regimen of 400 mg every six weeks for pembrolizumab across all currently approved adult indications, in addition to the current 200 mg every three weeks dosing regimen.

The approval was based on pharmacokinetic modeling and exposure-response analyses that compared the predicted exposure of pembrolizumab 400 mg every six weeks to observed exposures of pembrolizumab in patients who received pembrolizumab at 2 mg/kg every three weeks, 200 mg every three weeks, and 10 mg/kg administered every two weeks. The pharmacokinetic modeling were supported by additional exposure-response analyses across the pembrolizumab development program and an interim analysis of pharmacokinetics and overall response rate (ORR) in a cohort of patients (Cohort B) enrolled in Study KEYNOTE-555 (NCT03665597). Cohort B of Study KEYNOTE-555 was an international, single-arm, multi-center study that enrolled 101 patients with advanced or metastatic melanoma who had not received prior PD-1, PD-L1, or CTLA-4 inhibitors (other than CTLA-4 inhibitors in the adjuvant setting). The ORR was 39% (95% CI: 24, 55) in the first 44 patients enrolled in KEYNOTE-555.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-new-dosing-regimen-pembrolizumab

Targeting the hypermutant genotype

The average number of somatic mutations in a representative group of human cancers	
Tumor	**# of mutations per case**
Tumors exposed to mutagenic therapies	>1000
Sun exposed melanomas	>1000
Mismatch repair deficient tumors	**>600**
Non-small cell lung cancers	540
Colorectal cancers	77
Pancreatic cancers	48
Glioblastomas	36
Medulloblastomas	8

Courtesy of Axel Grothey, MD

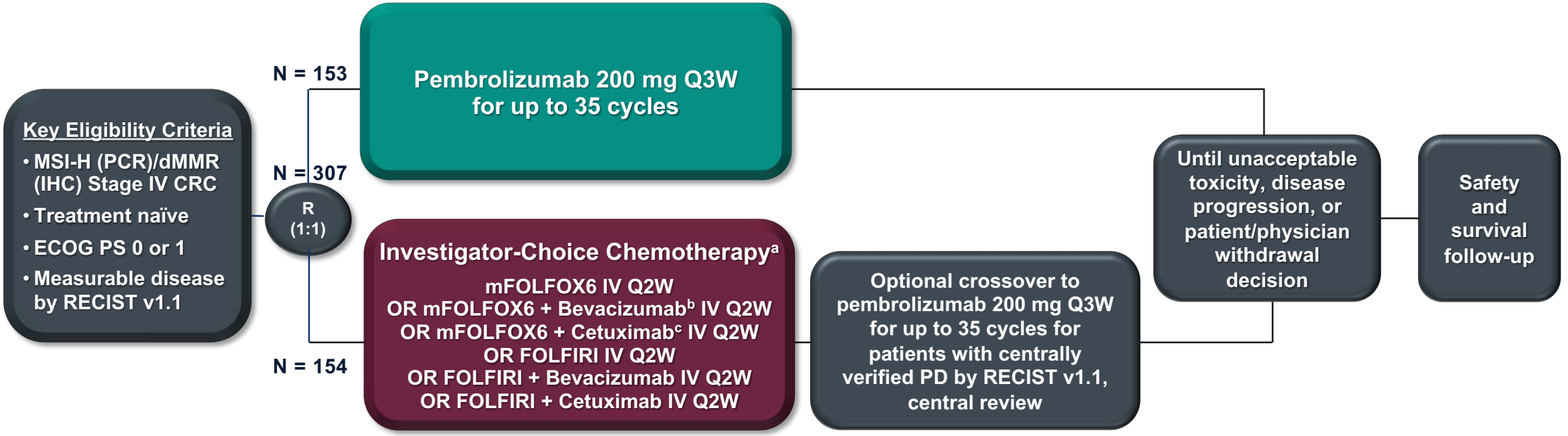
MSI-H in Colon Cancer: Prevalence and Prognosis

Stage	Prevalence	Prognosis compared to MSS
II	15-20%	excellent
III	8-10%	same
IV	4-5%	same or worse

- Hypermutated cancers too “deranged” to metastasize
- Immune system can prevent spread
- But once a metastatic clone has been selected, same or worse prognosis than MSS

Courtesy of Axel Grothey, MD

KEYNOTE-177 Study Design (NCT02563002)

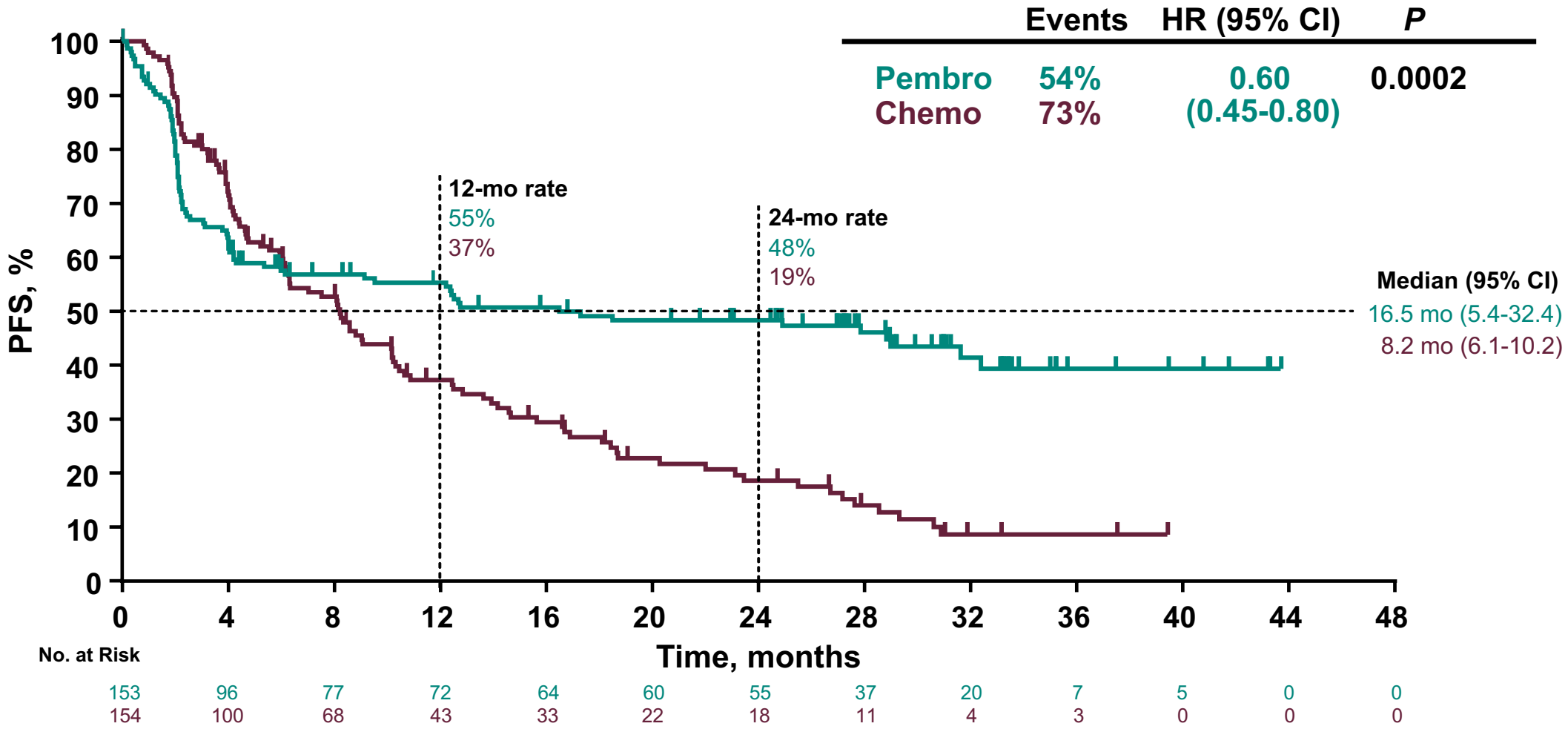


- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Courtesy of Axel Grothey, MD

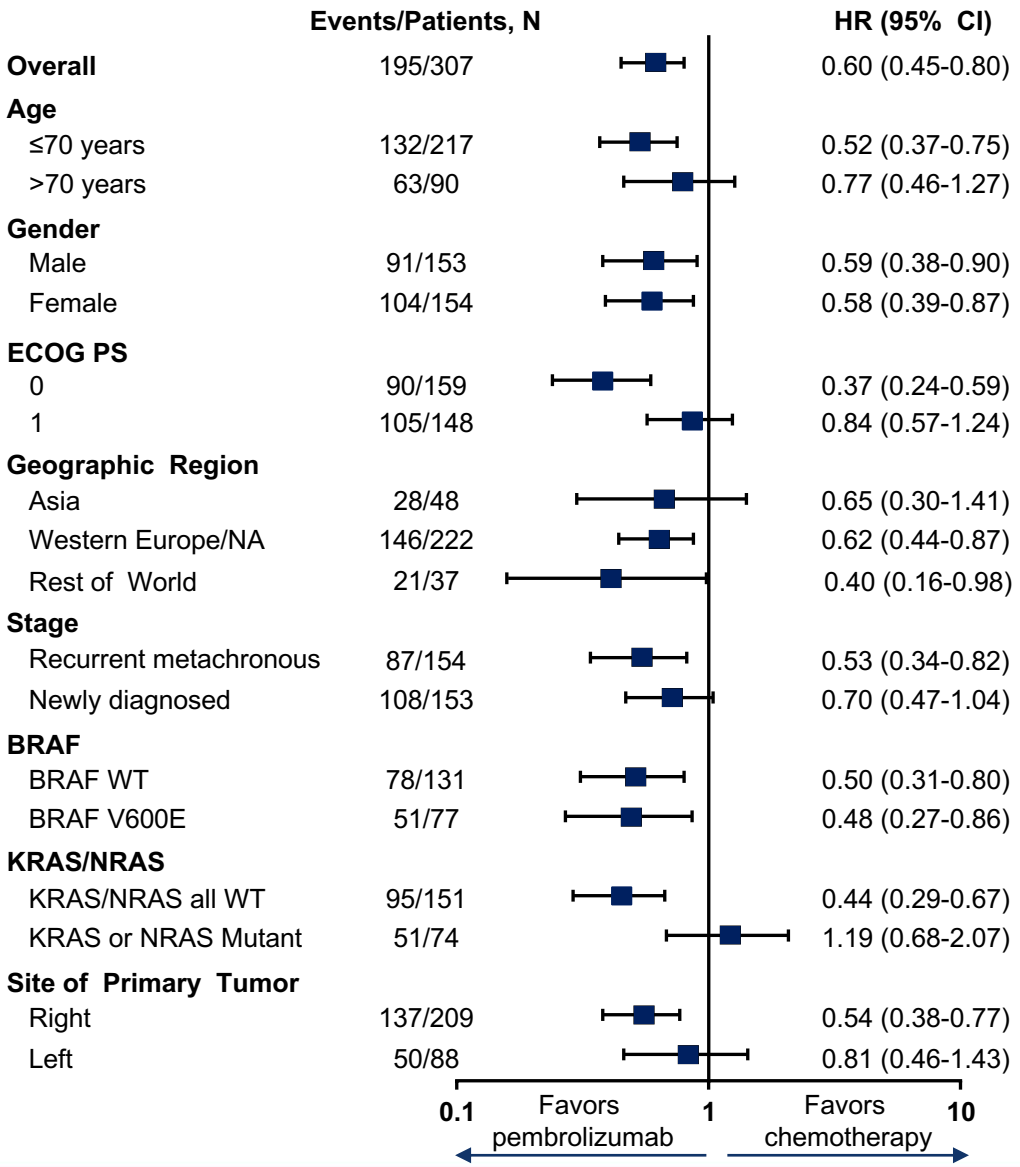
Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR; Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Courtesy of Axel Grothey, MD

Progression-Free Survival in Key Subgroups



NA, North America; Data cut-off: 19Feb2020.

Courtesy of Axel Grothey, MD

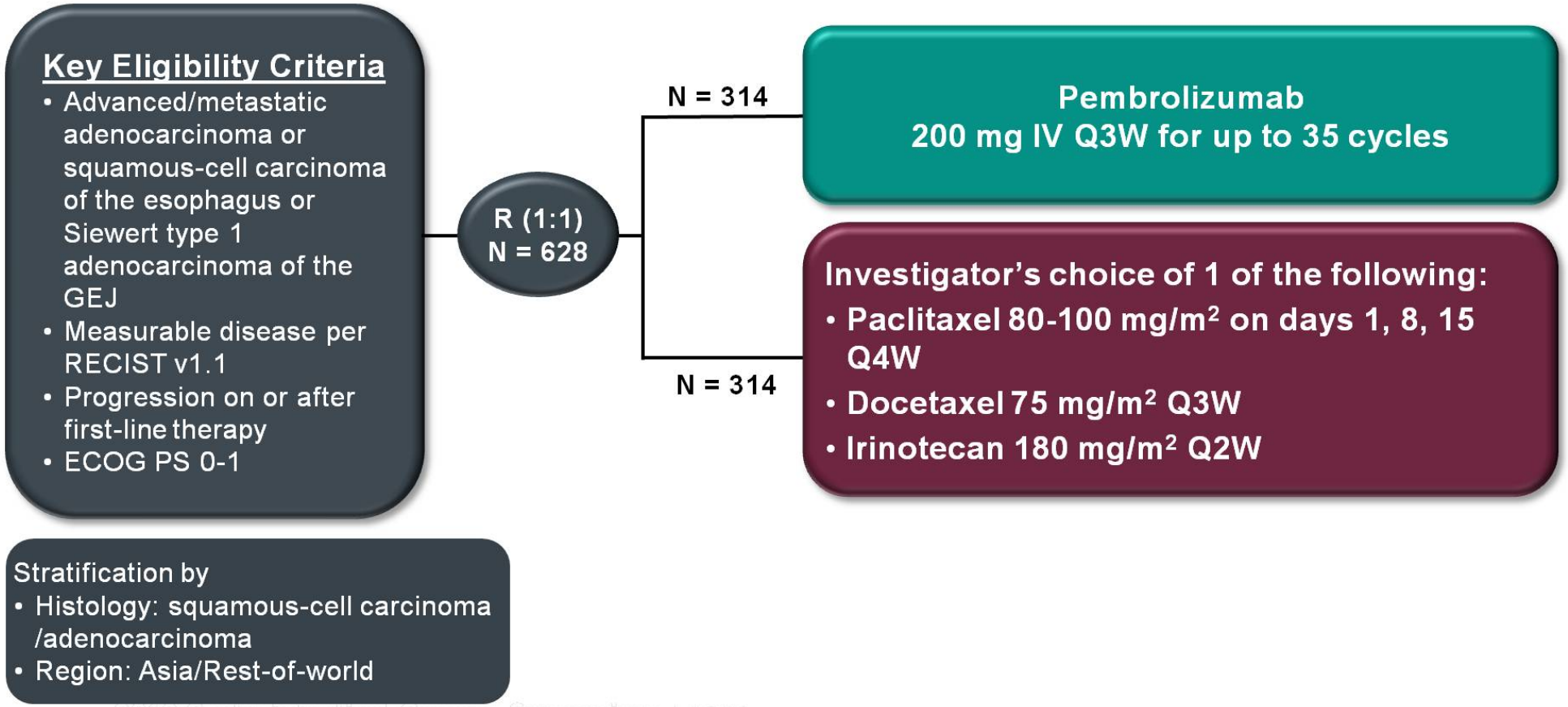
Antitumor Response

	Pembrolizumab N = 153		Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**		**51 (33.1)**
Difference, estimate (95% CI) *P*-value		10.7 (-0.2-21.3) 0.0275	
Best Overall Response, n (%)			
Complete response	17 (11.1)		6 (3.9)
Partial response	50 (32.7)		45 (29.2)
Stable disease	32 (20.9)		65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)		116 (75.3)
Progressive disease	45 (29.4)		19 (12.3)
Not evaluable	3 (2.0)		2 (1.3)
No assessment	6 (3.9)		17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)		2.1 (1.7-24.9)

Data cut-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.

Courtesy of Axel Grothey, MD

Phase 3 KEYNOTE-181 Study (NCT02564263)



Primary end points

OS in patients
- In the ITT group
- With SCC
- Whose tumor had a PD-L1 CPS ≥10

Secondary end points

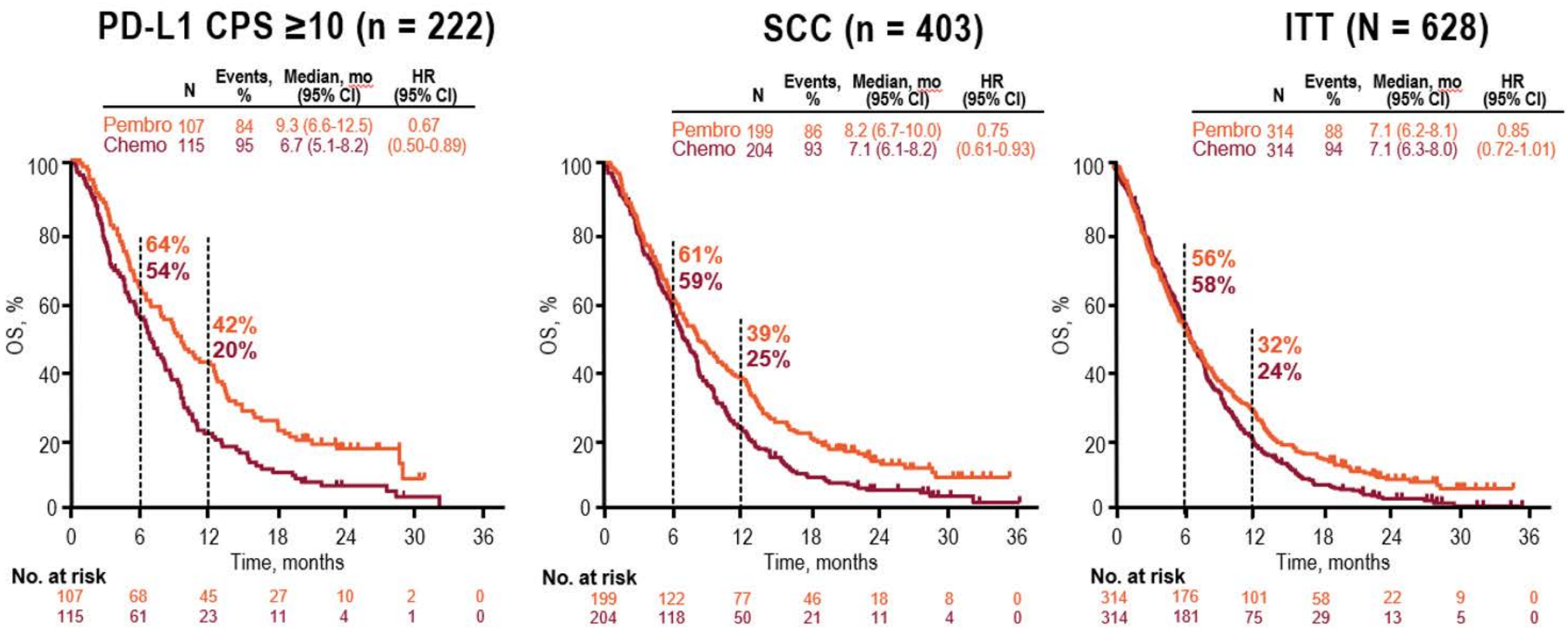
- PFS
- ORR
- Safety

Exploratory end points

- HRQoL in patients whose tumor had a PD-L1 CPS ≥10

Presented By Takashi Kojima at 2019 Gastrointestinal Cancer Symposium and Sung-Bae Kim at 2019 ESMO Asia Congress

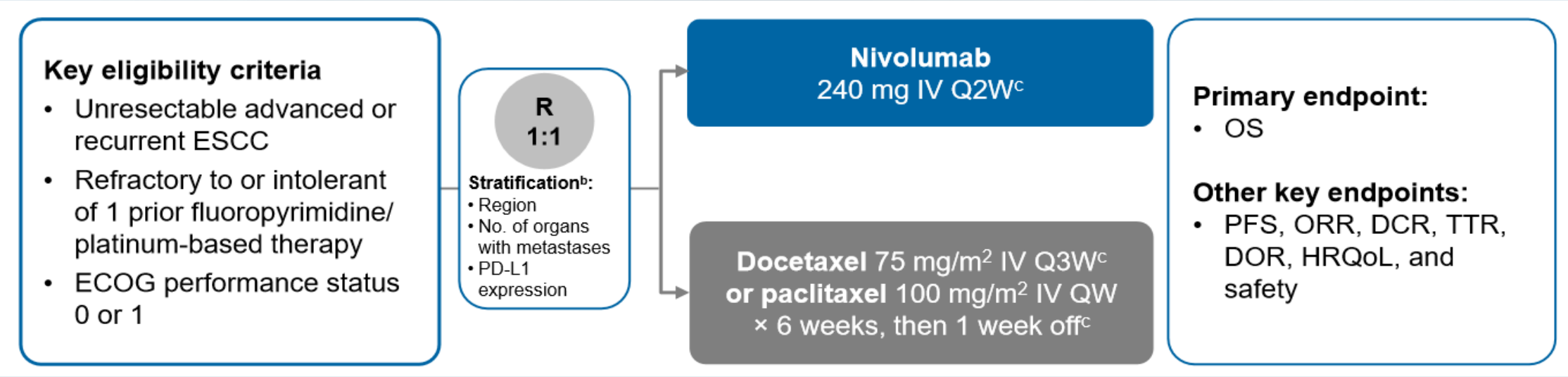
KEYNOTE-181: Overall Survival in the Global Population



Data cutoff: February 13, 2019; these data represent an additional 4 months of follow up data from the October 15, 2018 cutoff.

Bang et al, 2019 ESMO Asia

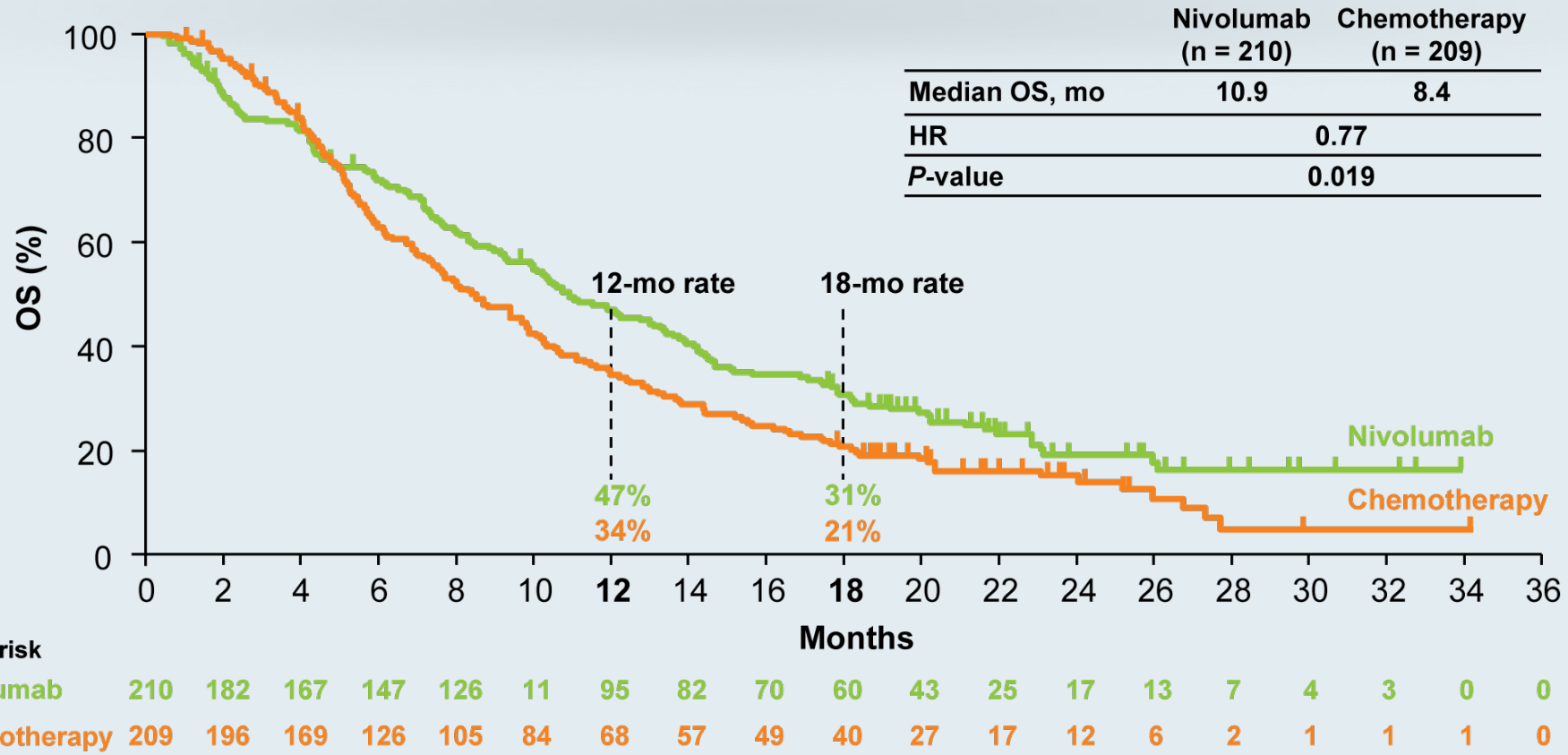
ATTRACTION-3: Nivolumab in Esophageal Squamous Cell Carcinoma (ESCC)



	Nivolumab	Chemotherapy	P value
Overall Response Rate	19%	22%	0.63
Disease Control Rate	37%	63%	
Median Time to Response	2.6 months	1.5 months	
Duration of Response	6.9 months	3.9 months	
Treatment-Related Adverse Events	66%	95%	
Dose delays due to Adverse Events	39%	50%	

Cho BC et al ESMO 2019 Annual Congress and Kato K et al Lancet Oncology 2019

ATTRACTION-3: Overall Survival



	Nivolumab (n = 210)	Chemotherapy (n = 209)
Median OS, mo	10.9	8.4
HR	0.77	
P-value	0.019	

No. at risk																			
Nivolumab	210	182	167	147	126	11	95	82	70	60	43	25	17	13	7	4	3	0	0
Chemotherapy	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

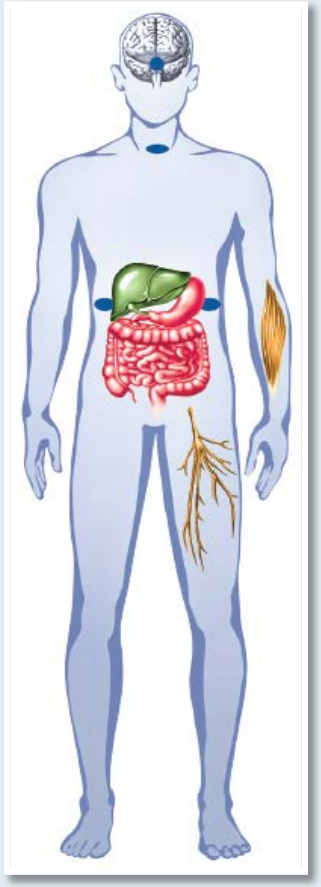
- Nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS versus chemotherapy:
  - 23% reduction in the risk of death and a 2.5-month improvement in median OS
- Nivolumab showed an improved safety profile compared with chemotherapy:
  - More than 3 times lower incidence (18% vs 63%) of Grade 3-4 TRAEs

Cho BC et al. *Proc ESMO* 2019;Abstract LBA11.

Immune-Related Adverse Events (irAEs)

Activation of the immune system against tumors
can result in a novel spectrum of irAEs

- May be due to cytokine release by activated T cells
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious
- Requires prompt recognition and treatment
- Requires patient and HCP education



Occasional (5%-20%) irAEs
Grade 3/4 Uncommon

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
  - Macropapular/pruritus
- Pneumonitis
- Hepatitis
- Pancreatitis
- Arthritis
- Neuropathies

Amos SM, et al. *Blood* 2011;118:499–509; YERVOY immune-related adverse reactions management guide. October 2012. Available at https://www.yervoy.co.uk/Images/6682_IrAR%20management%20guide%20731EMEA12PM014.pdf. Accessed September 2014; Chin K, et al. Poster presented at ESMO 2008 (abstr. 787P).

Case Presentation – Dr Grothey: A 73-year-old man with right-sided colon cancer, RAS/BRAF wt, MSI-H

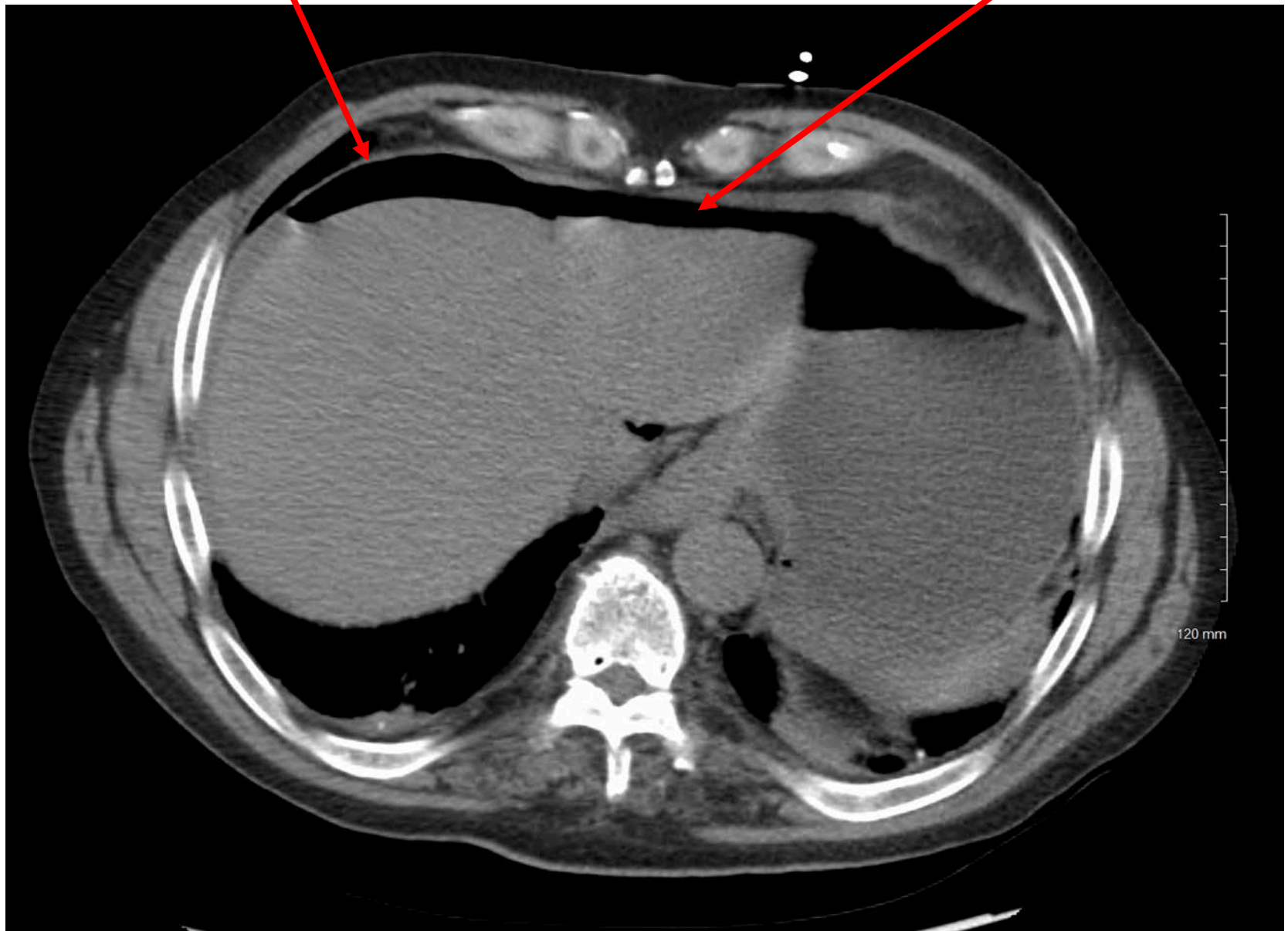
- July 24, 2019: Rapid onset of abdominal pain, nausea and vomiting
- July 26, 2019: Presentation to the ER. CT abdomen and pelvis without contrast reveals pneumoperitoneum, free fluid in abdomen and colon mass at hepatic flexure. Perforation site not visible. Same day exploratory laparotomy. Extended right hemicolectomy and biopsy of what appeared to be extensive liver metastases. Pathology confirms poorly differentiated adenocarcinoma, pT4a pN1b (2/25), M1a (liver). Cecal perforation present.
- July 31, 2019: CT chest without evidence of metastases. MRI abdomen with multiple, bilobar intrahepatic metastases.
- September 4, 2019: cycle 1 day 1 modified FOLFOX 7 given. CT chest abdomen pelvis shows metastatic colon cancer with mets to the liver peritoneum as well as a portacaval lymph node
- September 20, 2019: profile reveals MSI-H, PD-L1 40%, KRAS/NRAS/BRAF wild type, TMB 22
- October 30, 2019: CT chest abdomen pelvis showed 25-40% response to therapy. Bevacizumab added to patient's treatment plan
- December 30, 2019: CT chest abdomen pelvis identifies continued response to therapy. Switch treatment after 8 cycles of FOLFOX, the last 4 with bevacizumab, to maintenance therapy with capecitabine plus bevacizumab

Case Presentation – Dr Grothey: A 73-year-old man with right-sided colon cancer, RAS/BRAF wt, MSI-H (cont)

- February 18, 2020: Patient presents with significant side effects on capecitabine plus bevacizumab, in particular hand-foot syndrome and fatigue.
- February 25, 2020: CT scan of chest abdomen pelvis identifies new ascites as well as mesenteric nodularity consistent with peritoneal disease. In view of poor tolerability of therapy and apparent progression of disease on maintenance therapy switched to pembrolizumab single agent treatment for MSI high colorectal cancer
- March 5, 2020: Start systemic therapy with pembrolizumab
- May 27, 2020: CT CAP with 1. Near resolution of the moderate size left pleural effusion and resolution of the right effusion. 2. Near resolution of the ascites within the abdomen since 2/25/2020. 3. A few punctate nodular foci seen within the peritoneum, although improved since 2/25/2020. 4. Stable left hydronephrosis, hepatic cysts, and gallstones.
- July 22, 2020: CT chest, abdomen and pelvis with unchanged findings, excellent tolerability of pembrolizumab single agent therapy. Continuation of treatment

Diaphragm

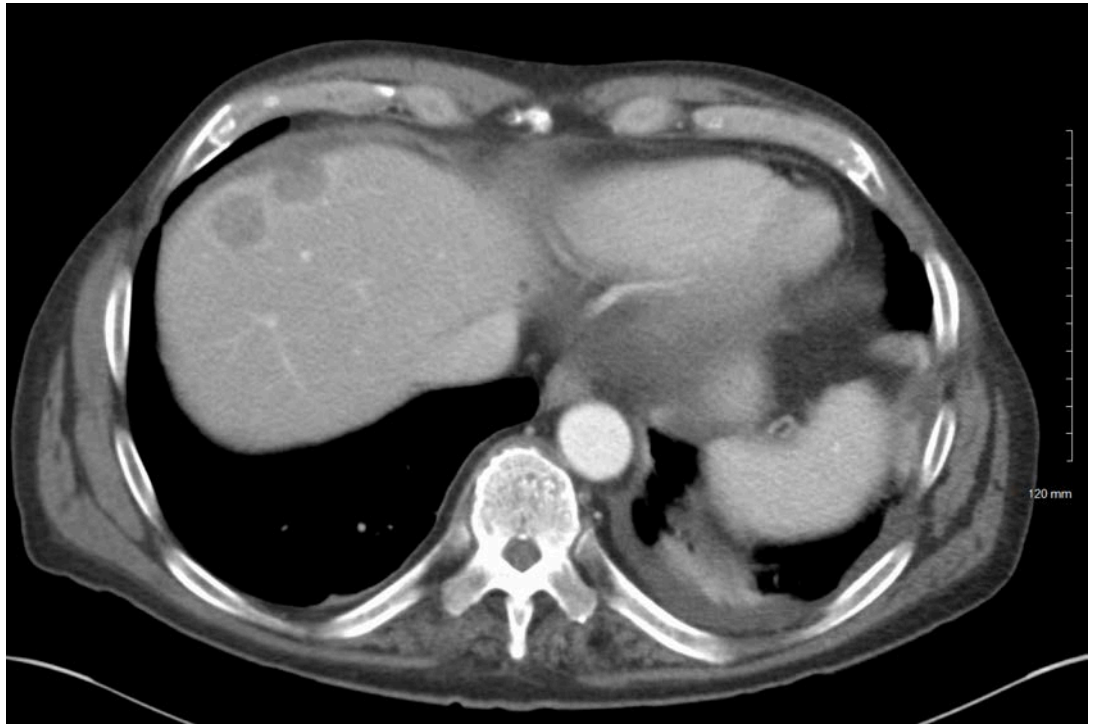
Pneumoperitoneum after perforation of cecal mass

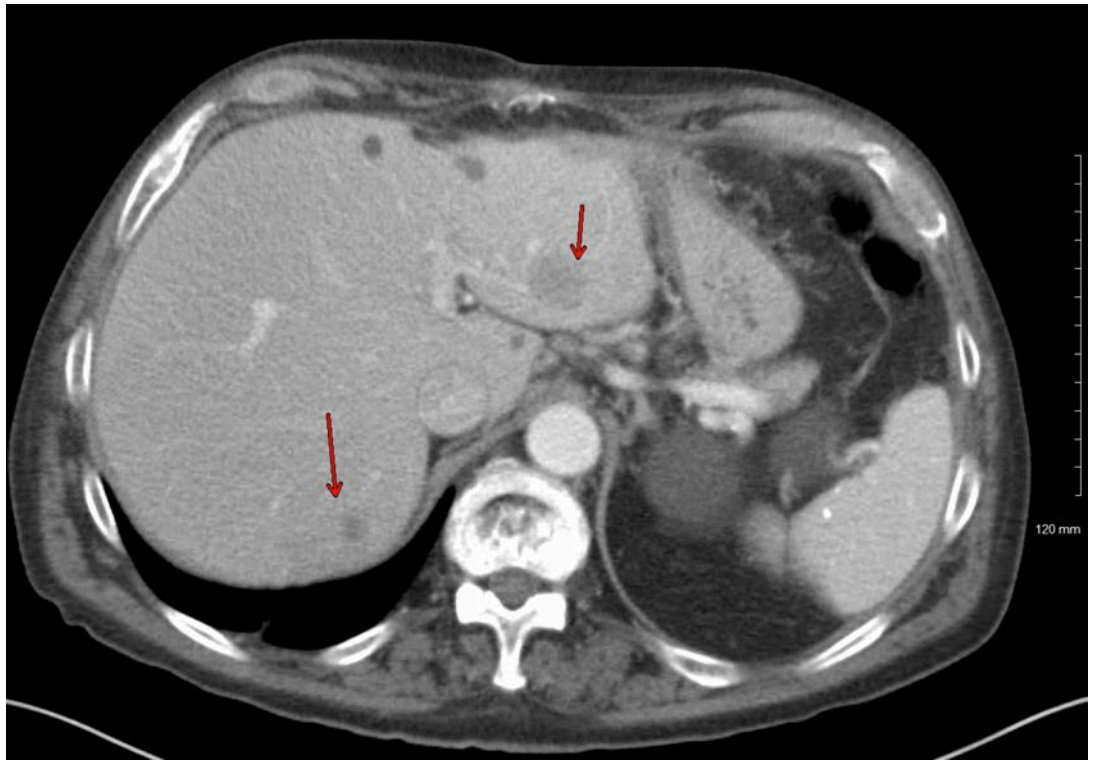


July 25, 2019

Case Presentation – Dr Grothey: A 73-year-old man with right-sided colon cancer, RAS/BRAF wt, MSI-H (cont)

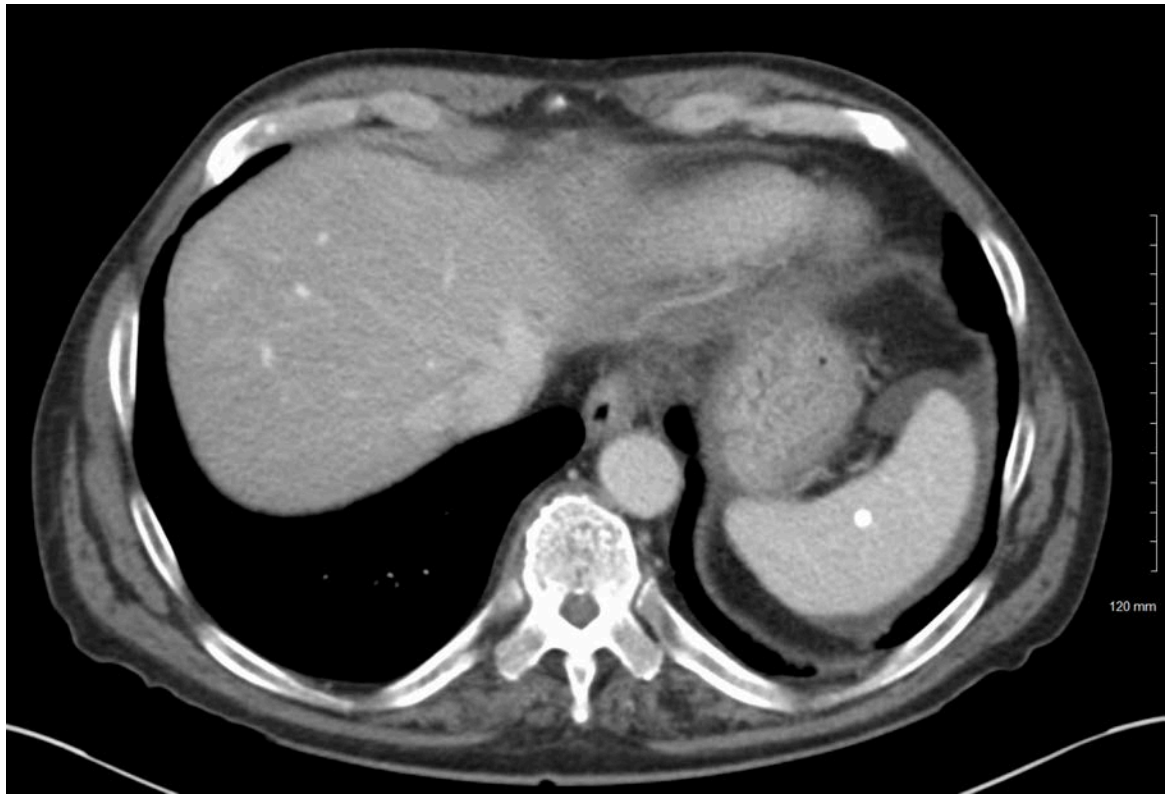
Sep 4, 2019: Before initiation of systemic therapy with mFOLFOX7

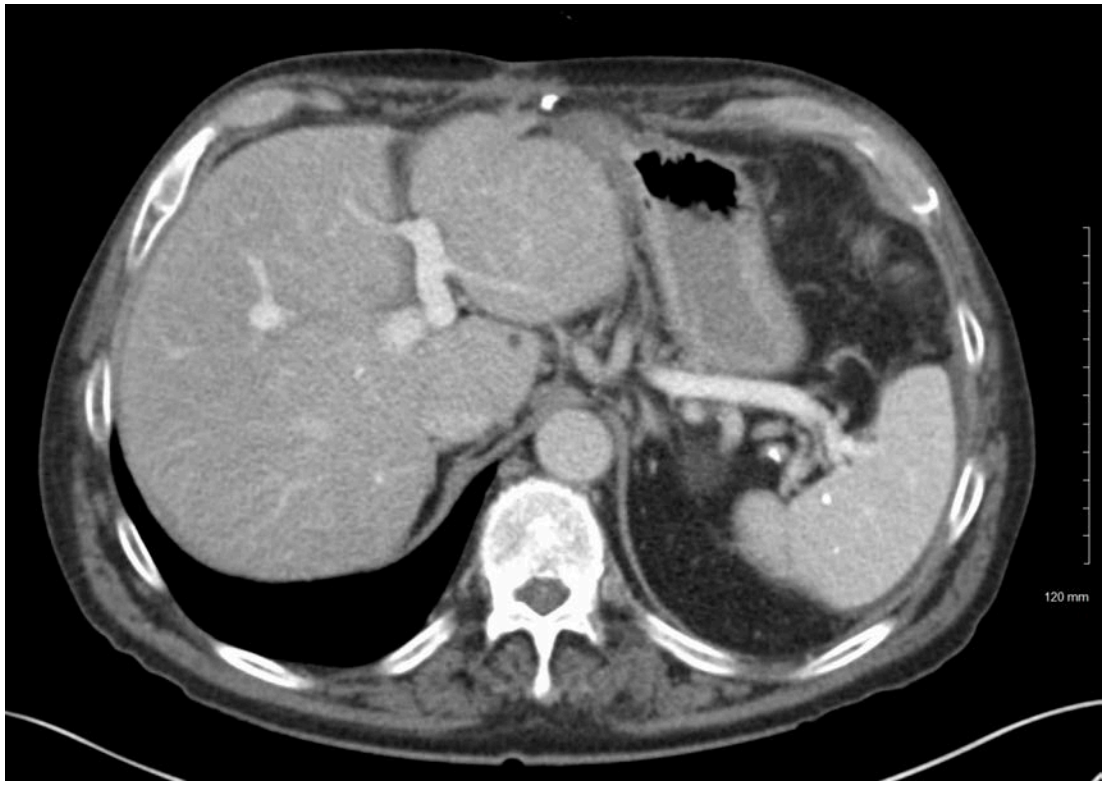




Case Presentation – Dr Grothey: A 73-year-old man with right-sided colon cancer, RAS/BRAF wt, MSI-H (cont)

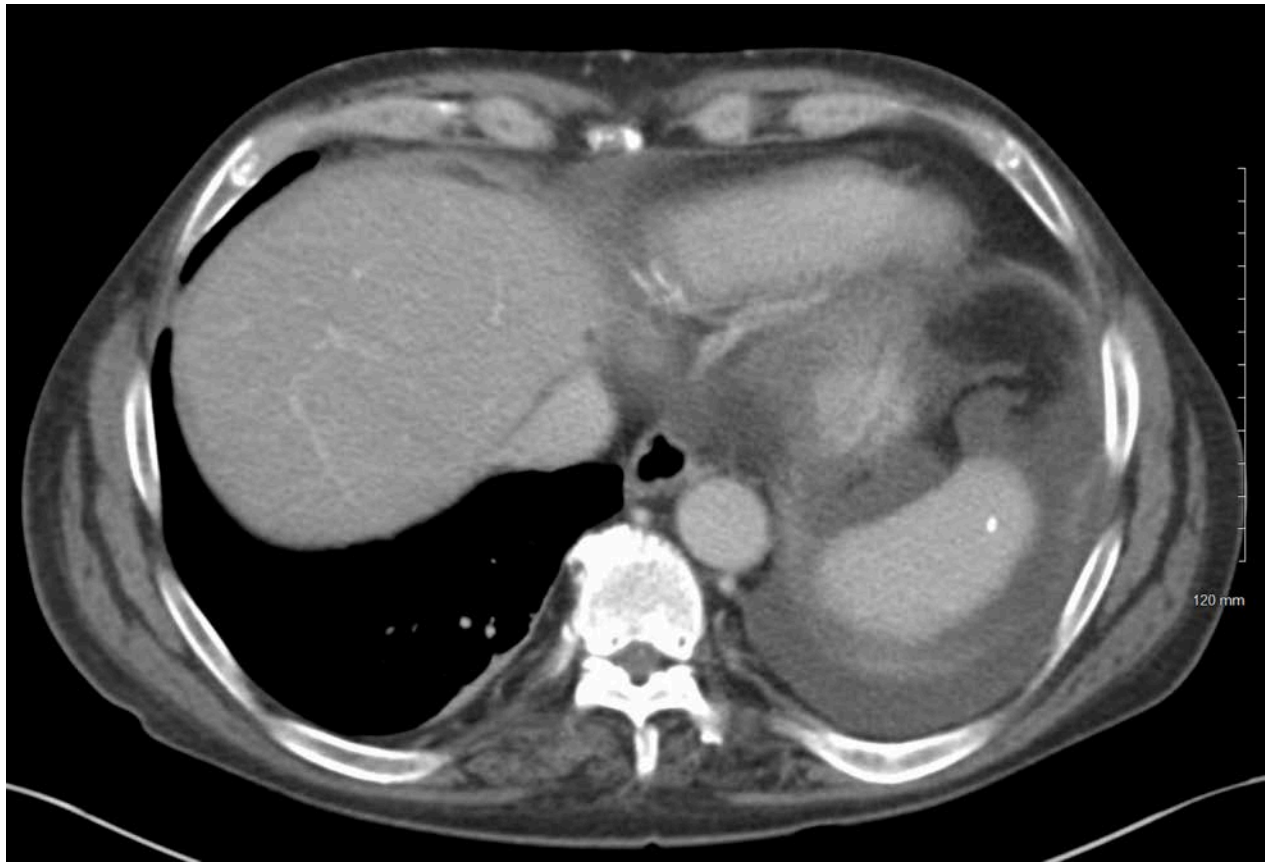
Dec 30, 2019: Response of liver mets after 8 cycles of mFOLFOX7 (4 with BEV)

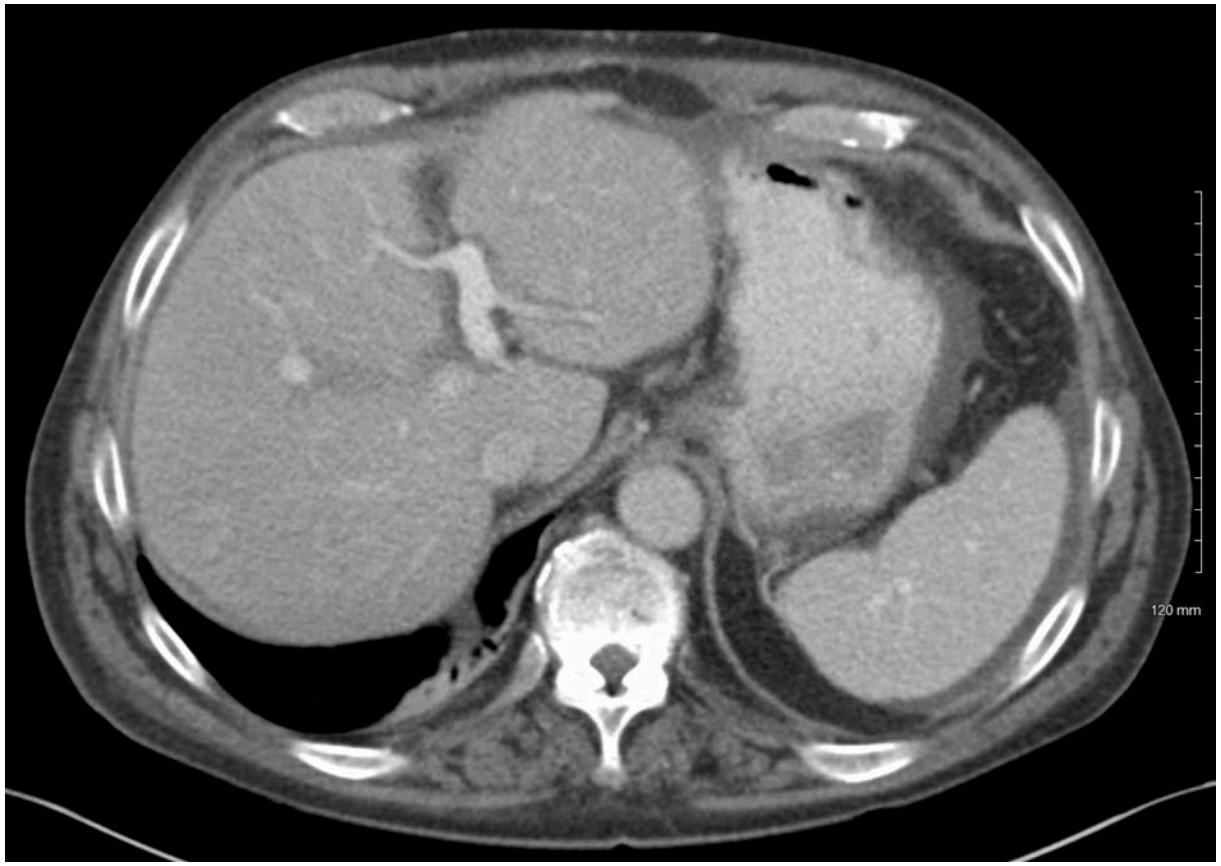




Case Presentation – Dr Grothey: A 73-year-old man with right-sided colon cancer, RAS/BRAF wt, MSI-H (cont)

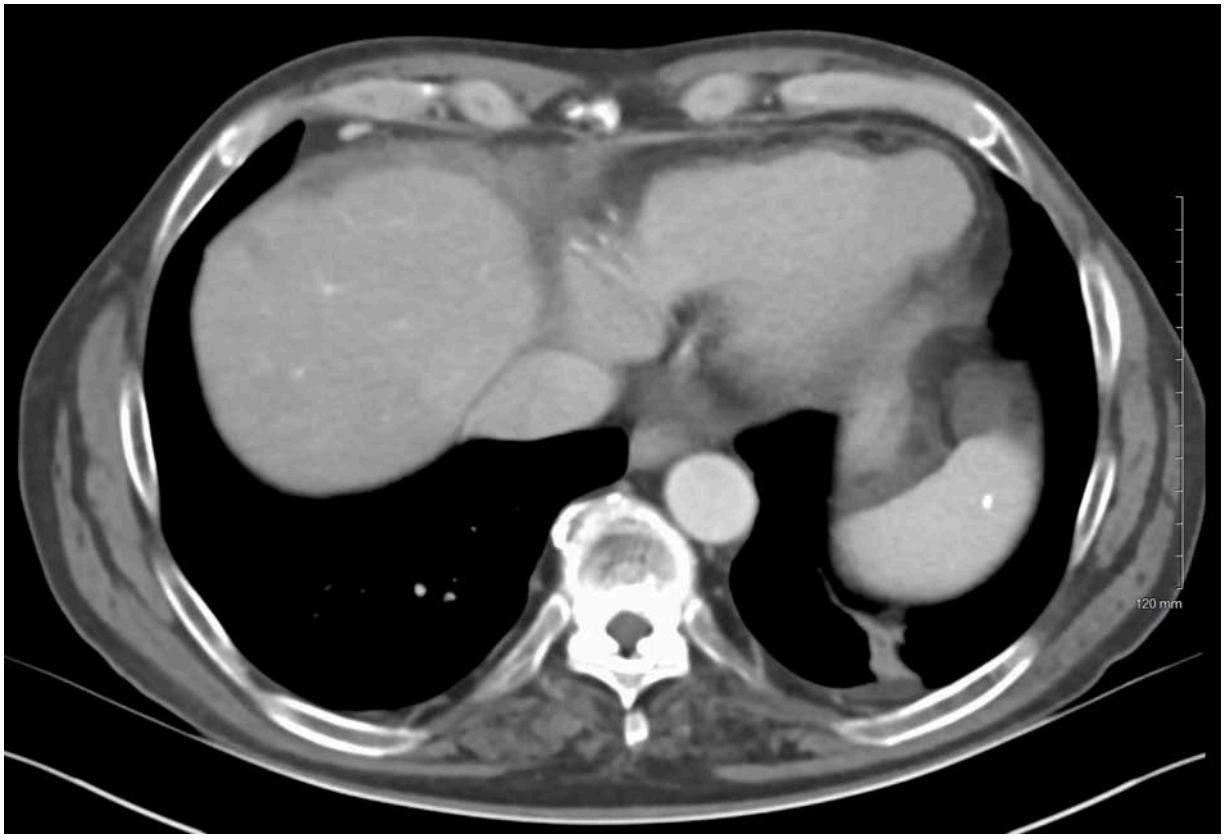
Feb 25, 2020: PD with pleural effusion, ascites, peritoneal carcinomatosis on capecitabine/bevacizumab

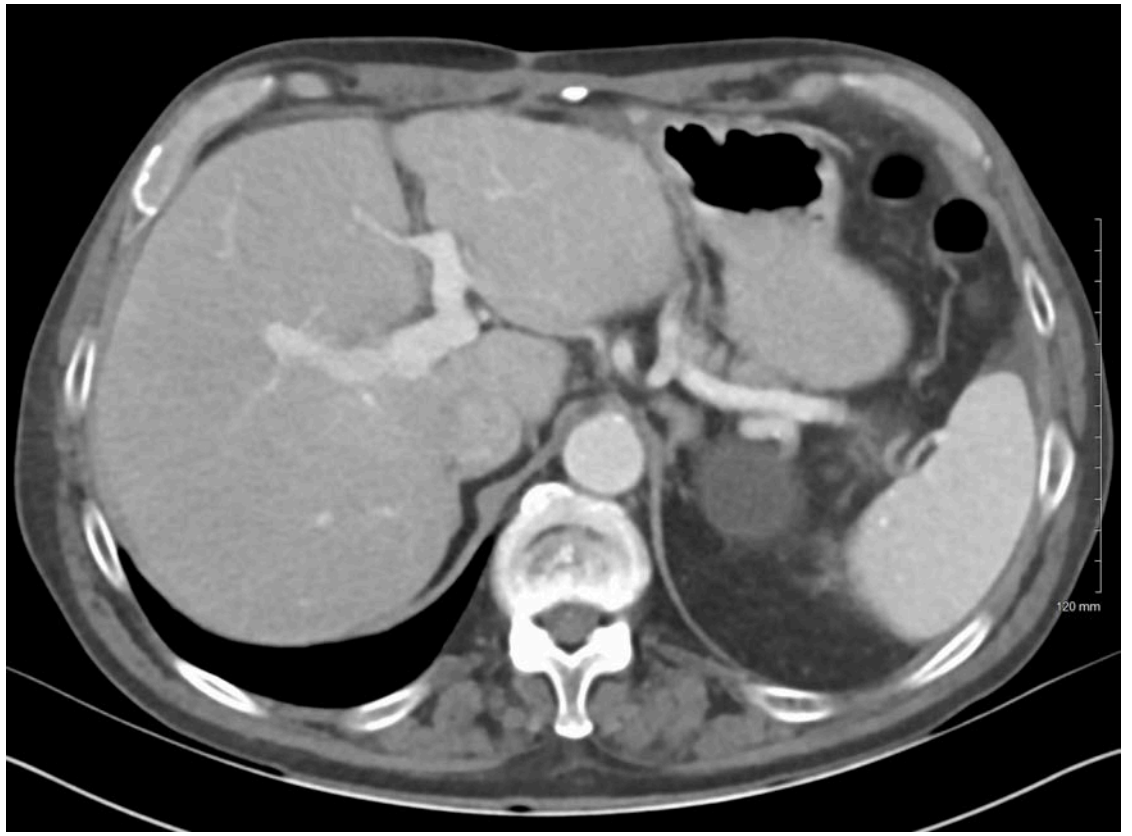




Case Presentation – Dr Grothey: A 73-year-old man with right-sided colon cancer, RAS/BRAF wt, MSI-H (cont)

May 27, 2020: Almost complete resolution of pleural effusion, ascites, reduced peritoneal implants after 2 months of pembrolizumab single agent





Agenda

Module 1: BRAF-Mutated Colorectal Cancer

Module 2: Checkpoint Inhibitors in Colorectal and Gastroesophageal Cancer

Module 3: HER2-Positive Colorectal and Gastroesophageal Cancer

Module 4: Other Treatment Strategies for Advanced Colorectal and Gastroesophageal Cancer

Case Presentation — Dr Atif Hussein: A 66-year-old man with HER2-negative metastatic gastric adenocarcinoma

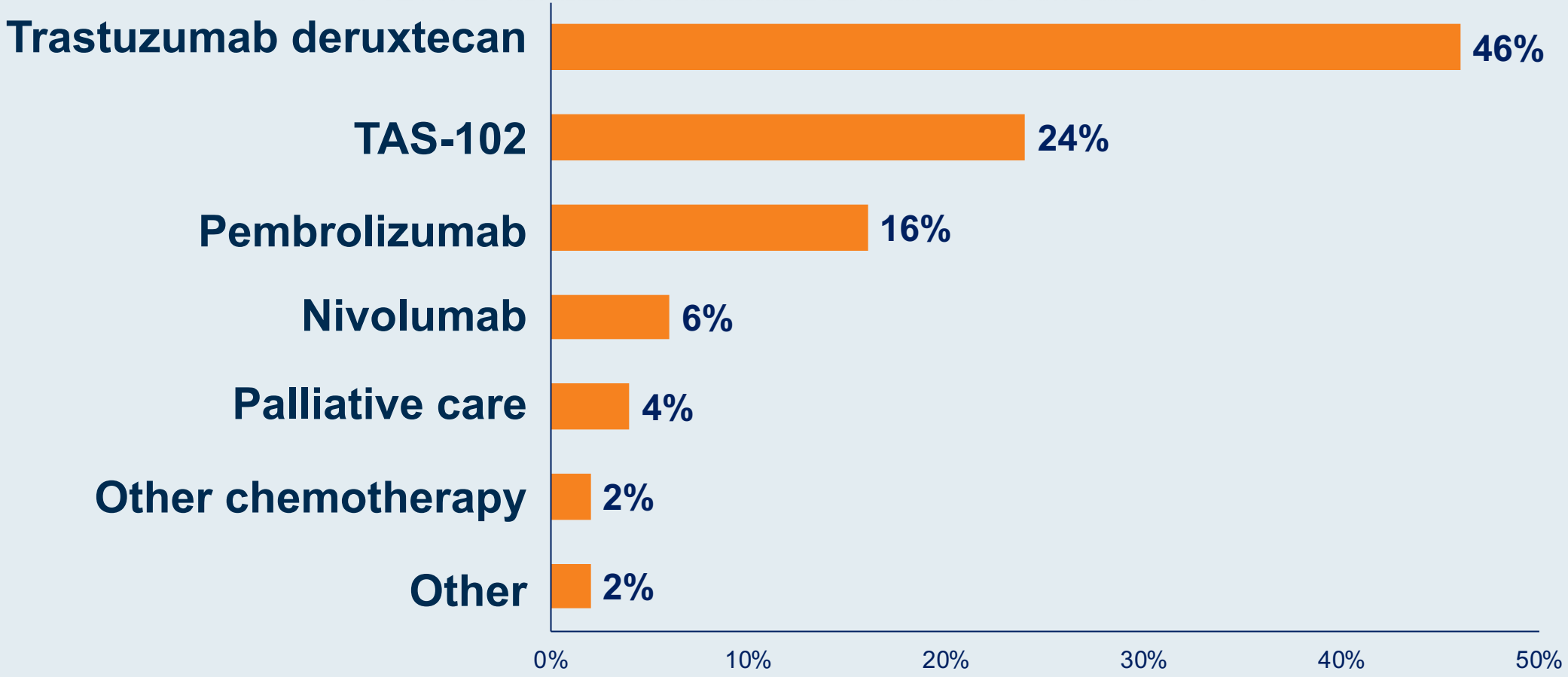
- Presented with epigastric pain and weight loss
- Multiple hepatic masses
  - CT-guided biopsy: Adenocarcinoma, likely gastric in origin
- Upper gastrointestinal endoscopy: Large gastric mass
- Biopsy: HER2-negative gastric adenocarcinoma
- Next generation sequencing (NGS)
  - PD-L1 combined positive score (CPS): 28
  - Tumor mutational load: 18 mutations/megabase
  - Microsatellite stable

Atif Hussein, MD, MMM

Regulatory and reimbursement issues aside, what third-line treatment would you recommend for a younger patient (PS 0) with metastatic HER2-positive, MS-stable gastric cancer (CPS < 1) with progression on FOLFOX/trastuzumab and then paclitaxel/ramucirumab?

a. TAS-102
b. Other chemotherapy
c. Pembrolizumab
d. Nivolumab
e. Trastuzumab deruxtecan
f. Palliative care
g. Other

Regulatory and reimbursement issues aside, what third-line treatment would you generally recommend for a younger patient (PS 0) with metastatic HER2-positive, microsatellite-stable gastric cancer (PD-L1 CPS < 1) who has experienced disease progression on FOLFOX/trastuzumab and paclitaxel/ramucirumab?

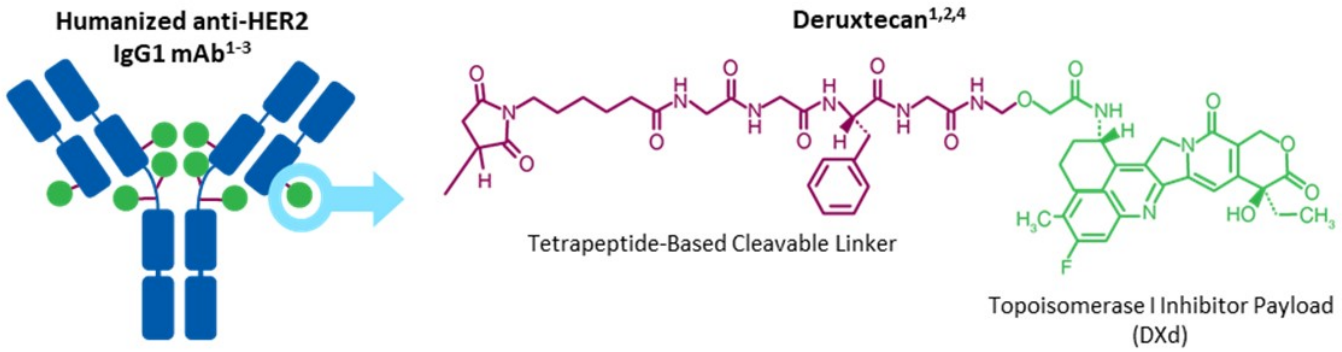


Survey of 50 US-based medical oncologists

Trastuzumab Deruxtecan (T-DXd) is a Novel ADC Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- T-DXd is being clinically evaluated across a number of HER2-expressing or mutated cancers, including breast cancer, CRC, non-small cell lung cancer, and others

Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

Presented By Salvatore Siena at ASCO 2020

Courtesy of Johanna Bendell

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)

Patients

- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- RAS/BRAF wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

T-DXd 6.4 mg/kg q3w

Cohort A (n = 53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n = 7)
HER2 IHC 2+/ISH−

Cohort C (n = 18)
HER2 IHC 1+

Primary endpoint

- Confirmed ORR by independent central review (ICR) in Cohort A

Data cutoff: August 9, 2019

- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

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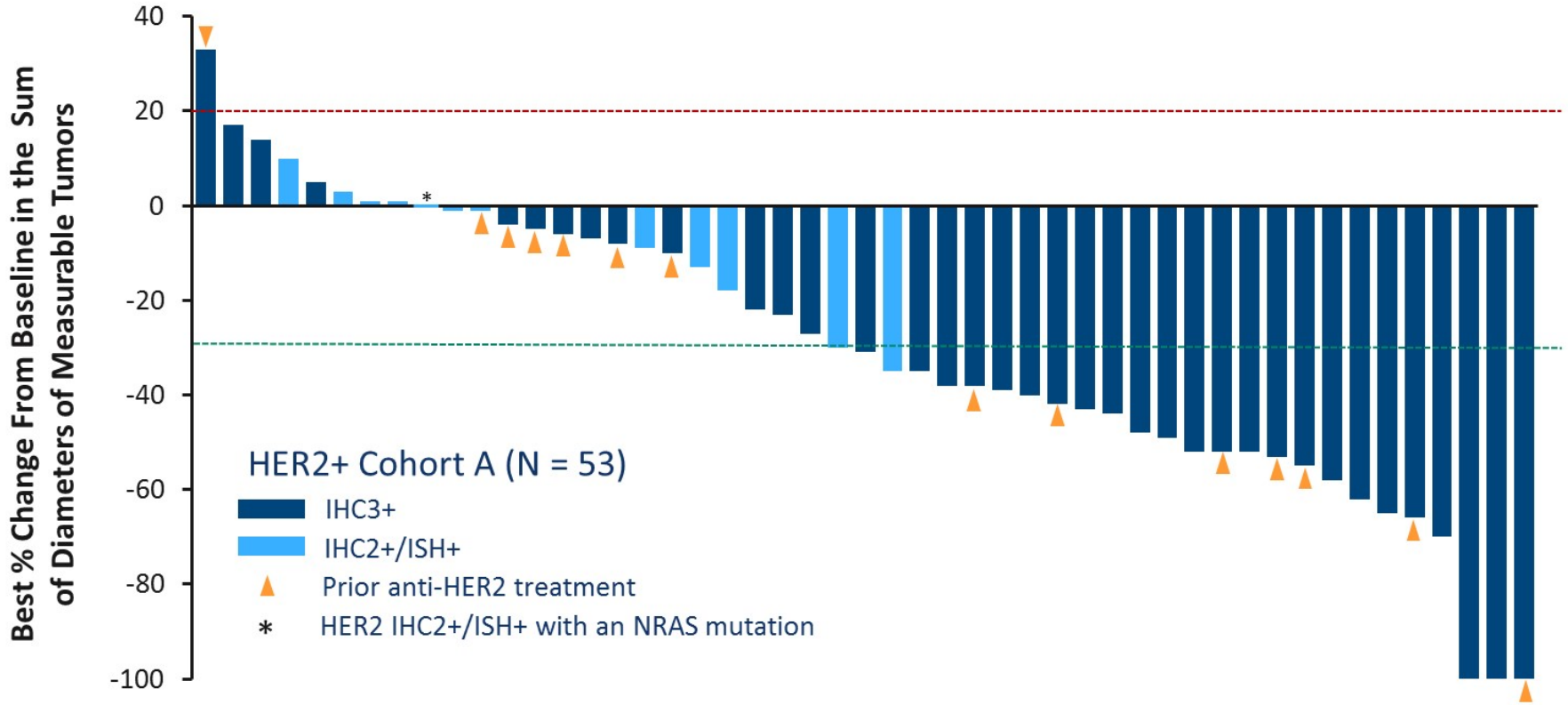
Courtesy of Johanna Bendell

DESTINY-CRC01

Best Change in Tumor Size



PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

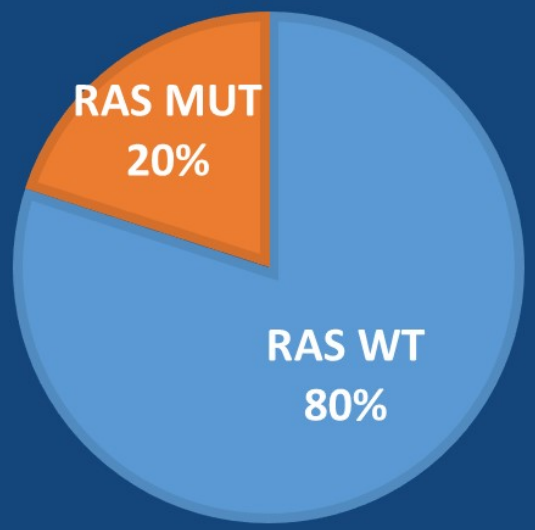
Presented By Salvatore Siena at ASCO 2020

Courtesy of Johanna Bendell

Anti-HER2 targeted therapy is only effective if RAS WT

HER2 amplified in 5-12% of RAS WT CRC

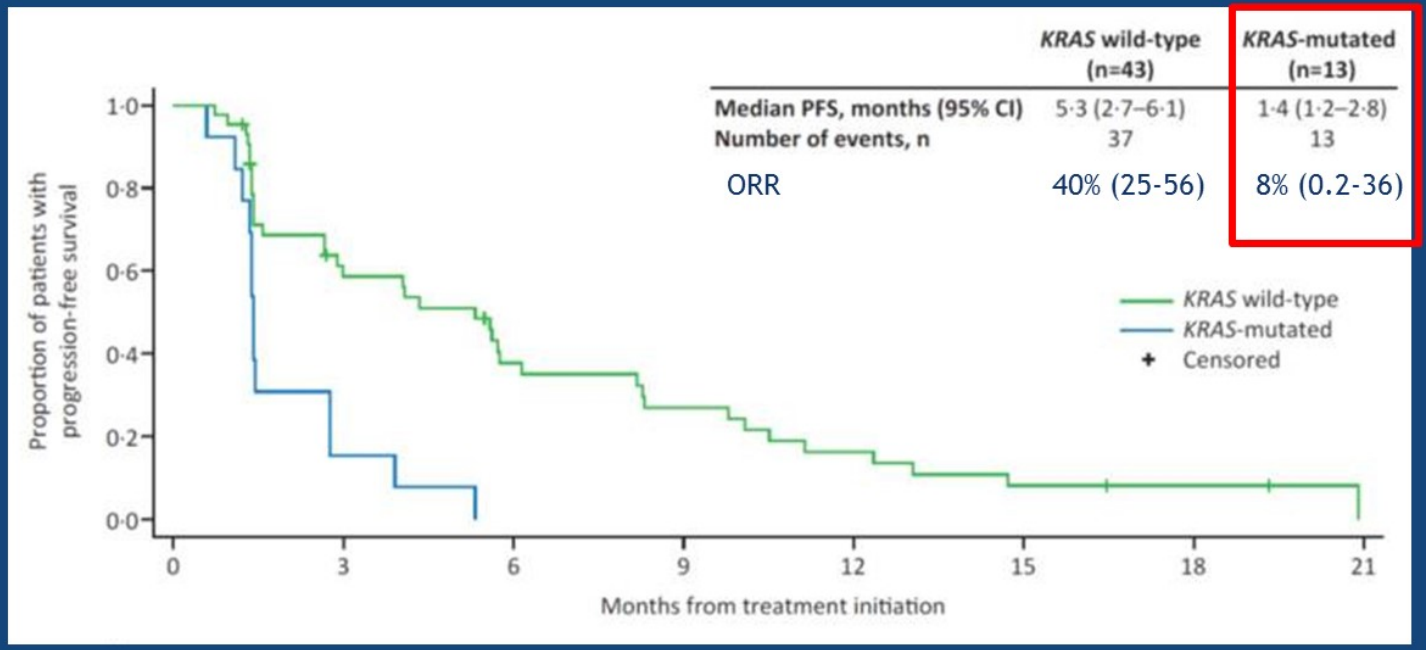
(Sartore-Bianchi A, Lancet Oncol 2016; Raghav KP, J Precision Oncol 2019)



Yaeger R, Cancer Cell 2018

HER2 targeted therapy ineffective for RAS mutant

MyPathway (Trastuzumab + Pertuzumab) PFS



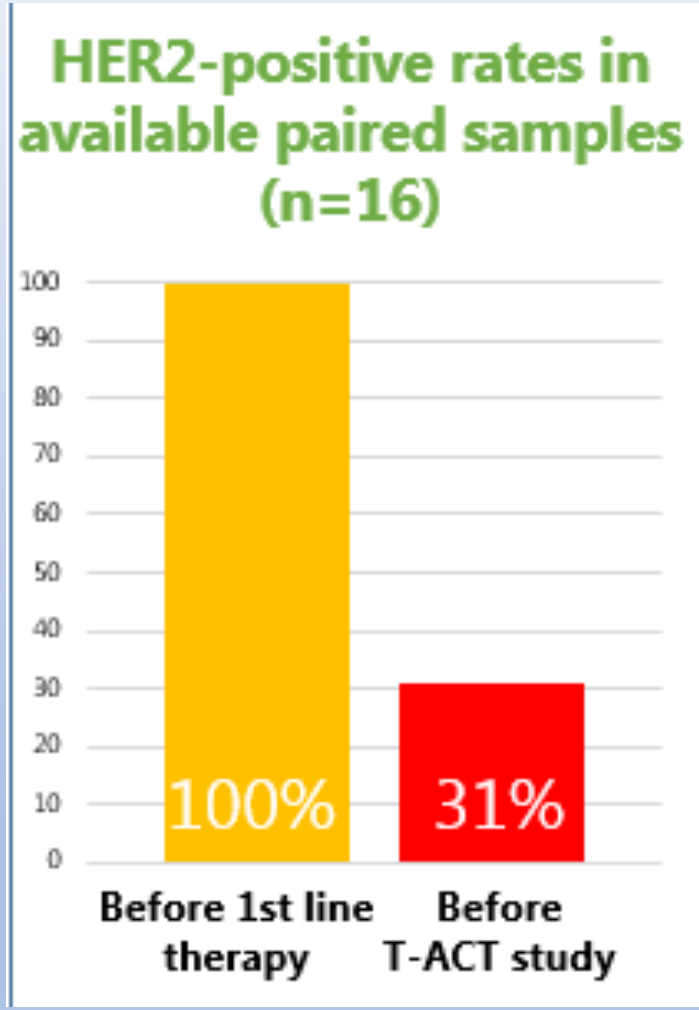
Meric-Bernstam F, Lancet Oncol 2019

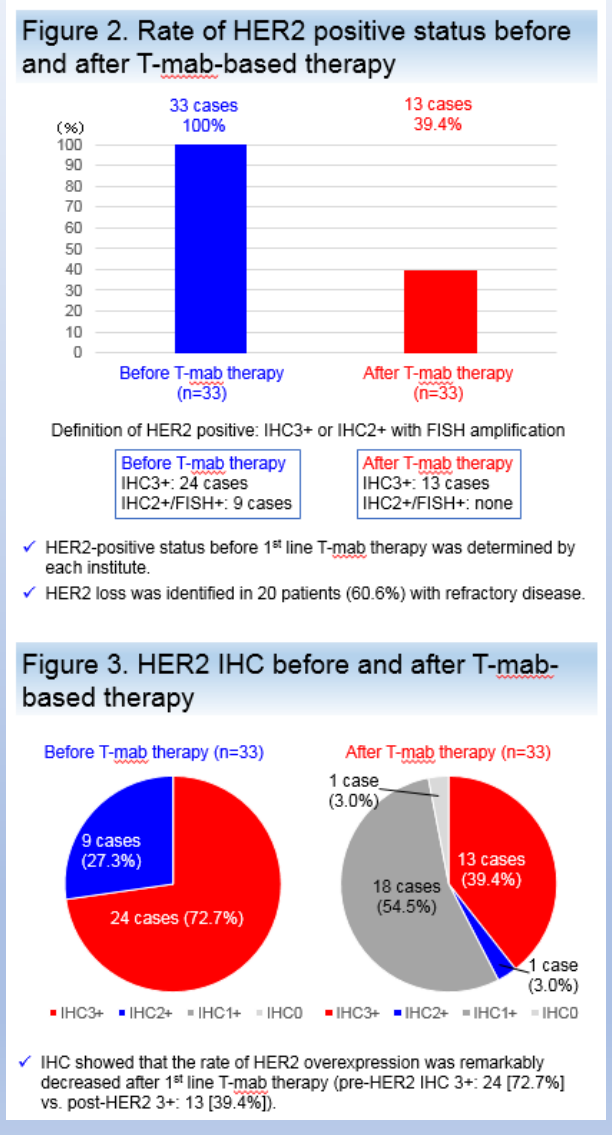
Case Presentation -- Dr Bendell: A 67-year-old man with HER2-positive mCRC

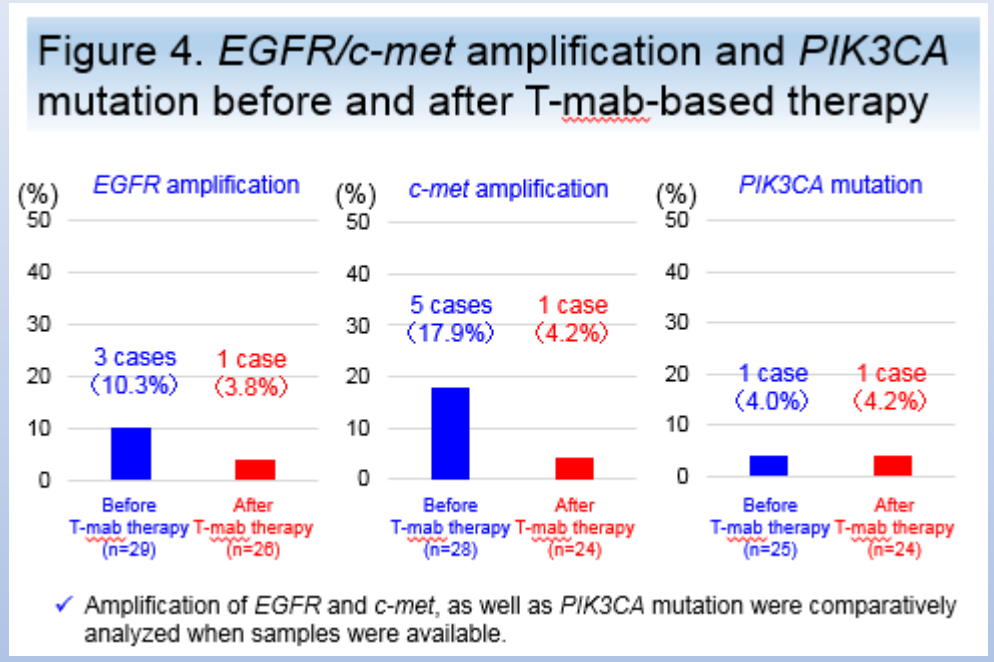
- 67 year old man who presented originally with intermittent abdominal pain, nausea, and vomiting.
- Abdominal CT showed a sigmoid colon mass.
- Colonoscopy showed a sigmoid colon mass and he was taken to the OR for resection. Pathology showed a T3 N2 moderately differentiated adenocarcinoma. MSS, RAS WT, BRAF WT.
- He was treated with adjuvant FOLFOX for 6 months.
- He did well initially, but then had a surveillance CT scan that showed multiple liver lesions 9 months later.
- He was started on FOLFIRI-bev, to which he had stable disease but then had progression 6 months later.
- His tumor was tested for HER2 by IHC, and he was found to be HER2 3+.
- He was started on a clinical trial with trastuzumab and pertuzumab. He had a partial response to this regimen and remains on 10 months later.

HER2-Positive Gastroesophageal Cancer

Why No Benefit for HER2 Therapy in 2nd Line?







Kashiwada T et al, 2018 ASCO Annual Meeting abstract 4038
Makiyama A et al 2018 ASCO Annual Meeting Abstract 4011

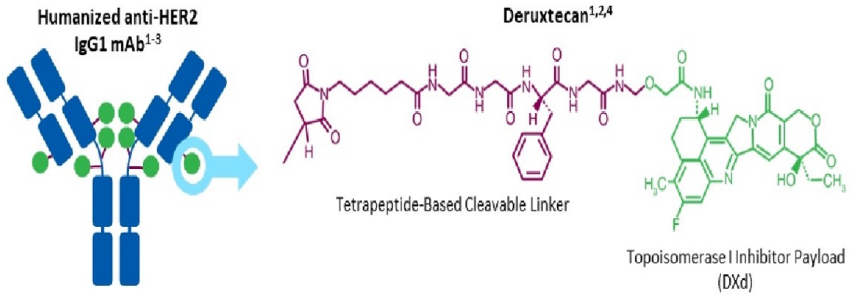
Figures courtesy of Dr. Kashiwada and Dr. Makiyama

Courtesy of Crystal Denlinger, MD, F.A.C.P.

Trastuzumab deruxtecan (T-DXd)

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



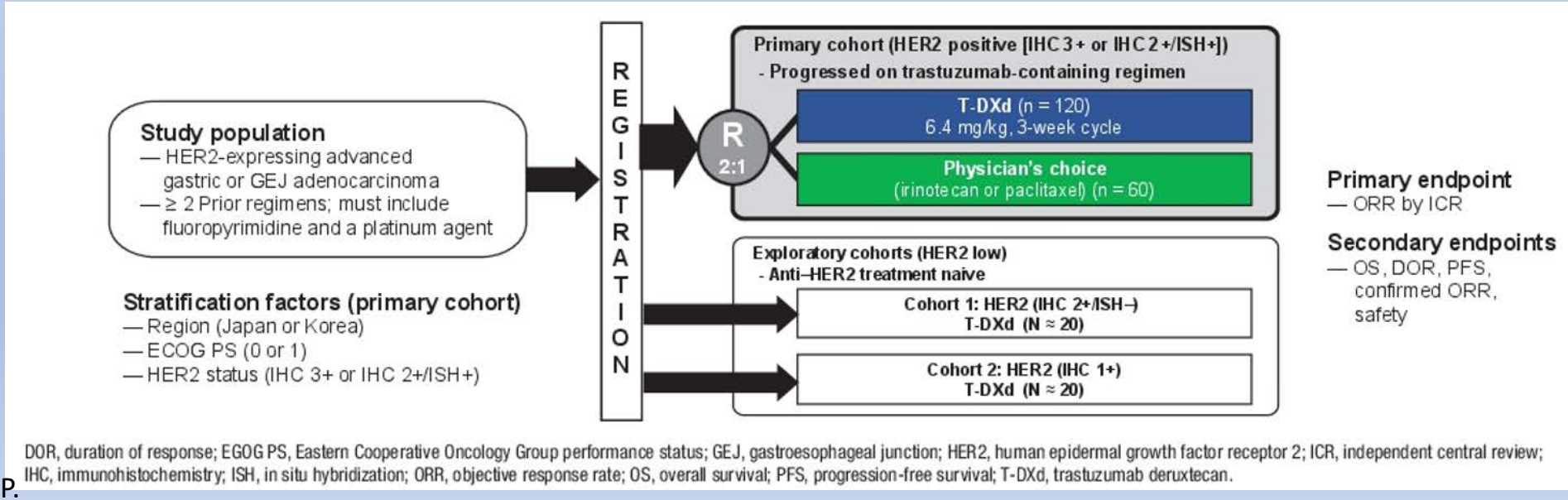
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

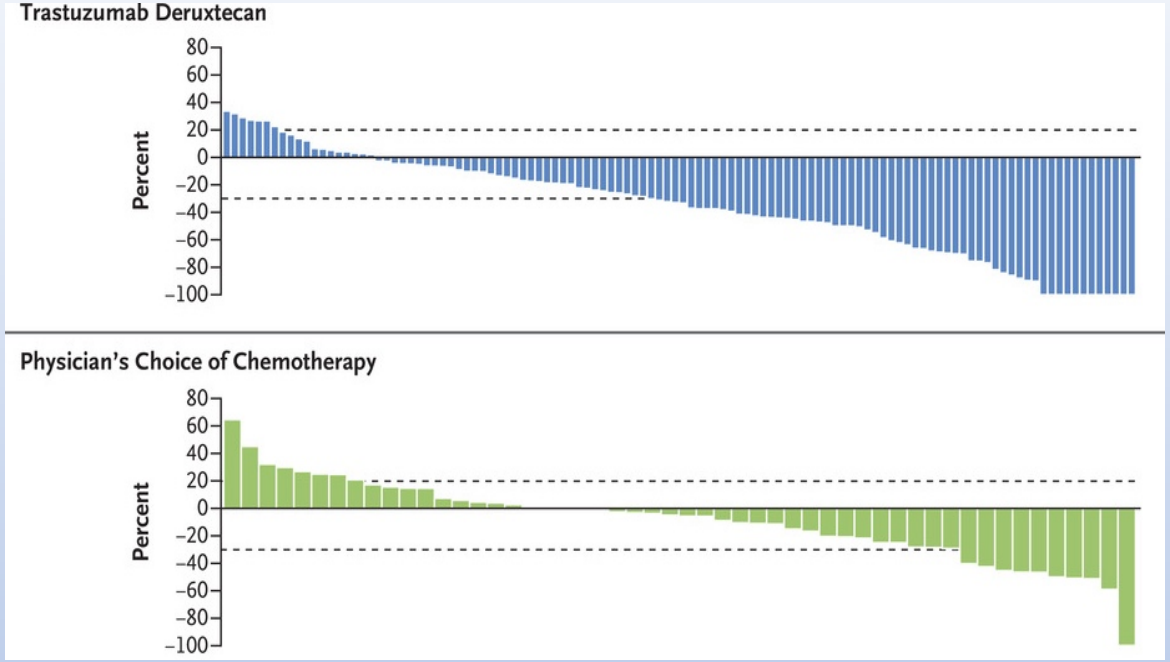
Shitara K et al, NEJM 2020
382: 2419-2430



DOR, duration of response; EGOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Courtesy of Crystal Denlinger, MD, F.A.C.P.

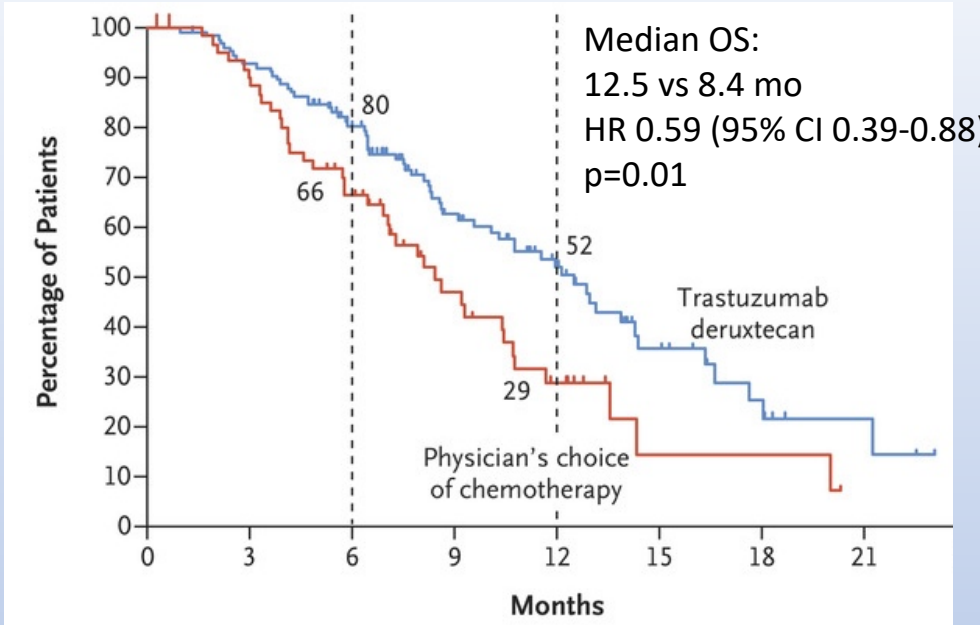
DESTINY-Gastric01: A Potential Option for Refractory GEC?



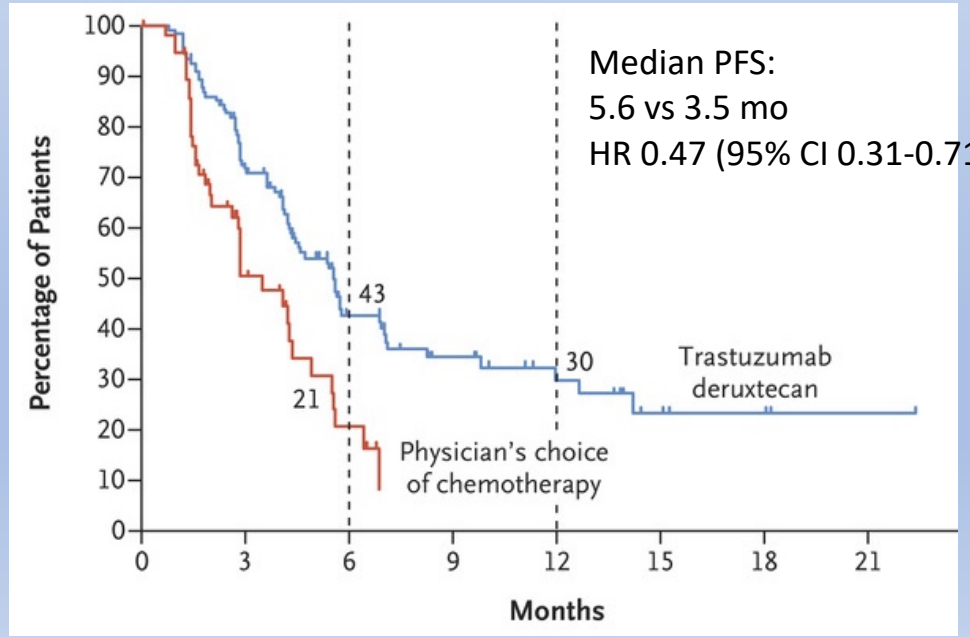
	T-DXd (n=119)	PC (n=56)
ORR	**51.3%**	**14.3%**
Confirmed ORR	**42.9%**	**12.5%**
CR	8.4%	0%
PR	34.5%	12.5%
SD	42.9%	50.0%

Disease control:

- T-DXd: 86% with median 11.3 mo
- PC: 62% with median 3.9 mo



Median OS:
12.5 vs 8.4 mo
HR 0.59 (95% CI 0.39-0.88)
p=0.01

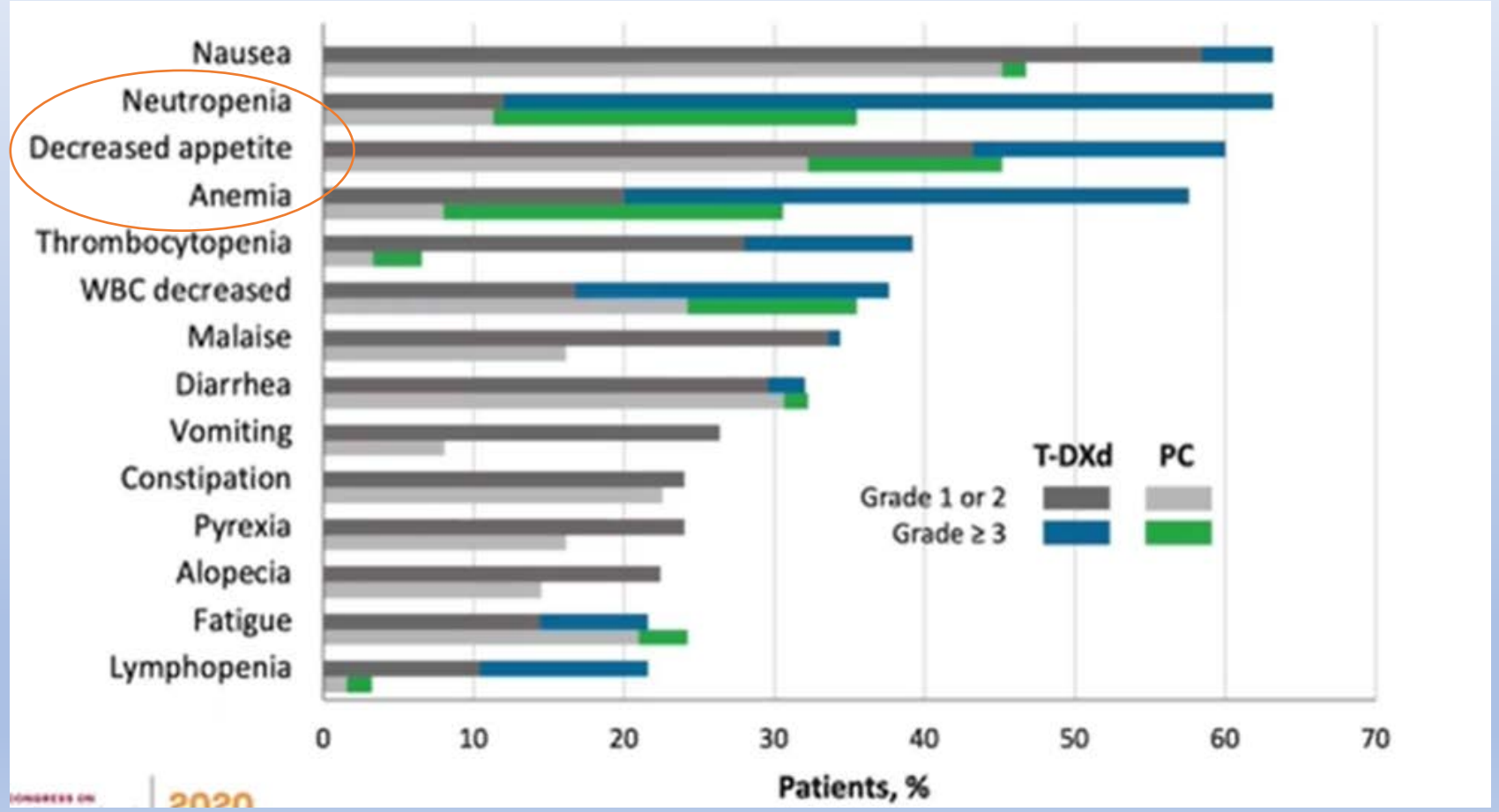


Median PFS:
5.6 vs 3.5 mo
HR 0.47 (95% CI 0.31-0.71)

Shitara et al, *NEJM* (2020), Slide courtesy of Yelena Jangigian

Courtesy of Crystal Denlinger, MD, F.A.C.P.

T-Dxd Adverse Events



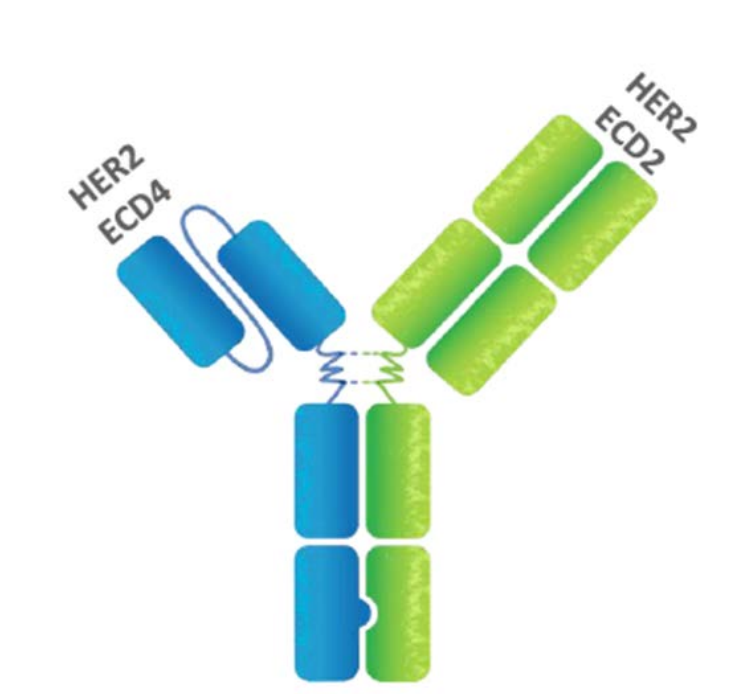
	Interstitial Lung Disease	
	Any (%)	Gr 5 (%)
DESTINY-Gastric01	9.6	0
DESTINY-Lung01	11.9	0
DESTINY-CRC01	6.4	2.6
DESTINY-Breast01	13.6	2.2

- Median time to onset: 84.5 days
- Mostly grade 1 & 2
  - 2 grade 3; 1 grade 4
- Management: Hold T-Dxd and start steroids

Yamaguchi et al, World GI 2020; Shitara NEJM 2020; Table courtesy of Yelena Jangigian

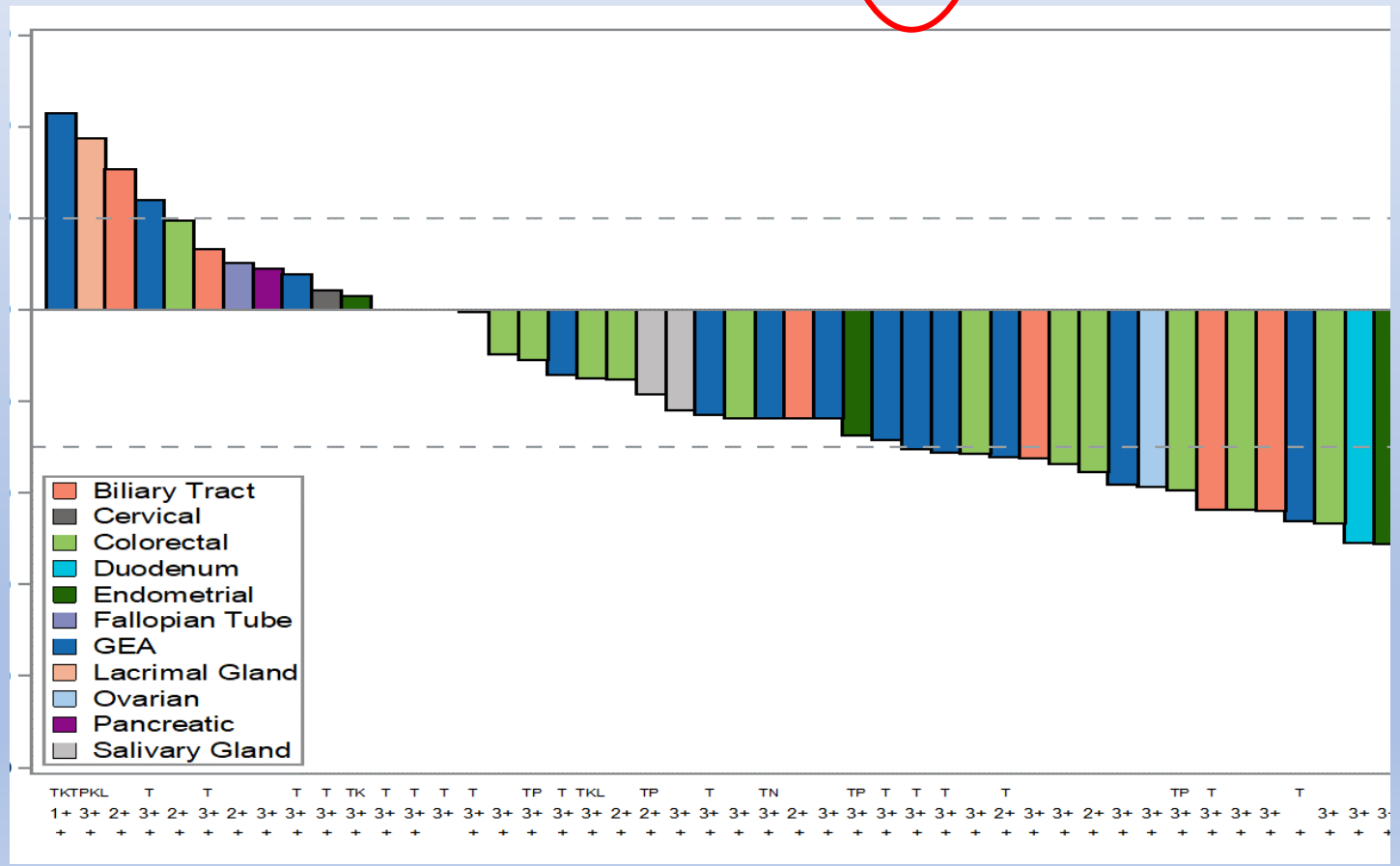
Courtesy of Crystal Denlinger, MD, F.A.C.P.

Zanidatamab (ZW25): Bispecific Antibody Against HER2



- Binds to the ECD4 and ECD2 domains of HER2
- Mechanism of action:
  - Increased receptor binding
  - HER2 receptor clustering
  - Enhanced internalization

Disease response per investigator assessment (using RECIST 1.1)					
	Biliary (N = 9)	CRC (N = 13)	GEA (N = 23)	All others (N = 12)	Total (N = 57)
Partial response (n [%])	6 (66.7)	6 (46.2)	9 (39.1)	4 (33.3)	25 (43.9)
Stable disease	1 (11.1)	5 (38.5)	4 (17.4)	5 (41.7)	15 (26.3)
Progressive disease	2 (22.2)	2 (15.4)	10 (43.5)	3 (25.0)	17 (29.8)
Disease control rate	7 (77.8)	11 (84.6)	13 (56.5)	9 (75.0)	40 (70.2)



Courtesy of Crystal Denlinger, MD, F.A.C.P.

Oh et al, ESMO Asia 2019

Agenda

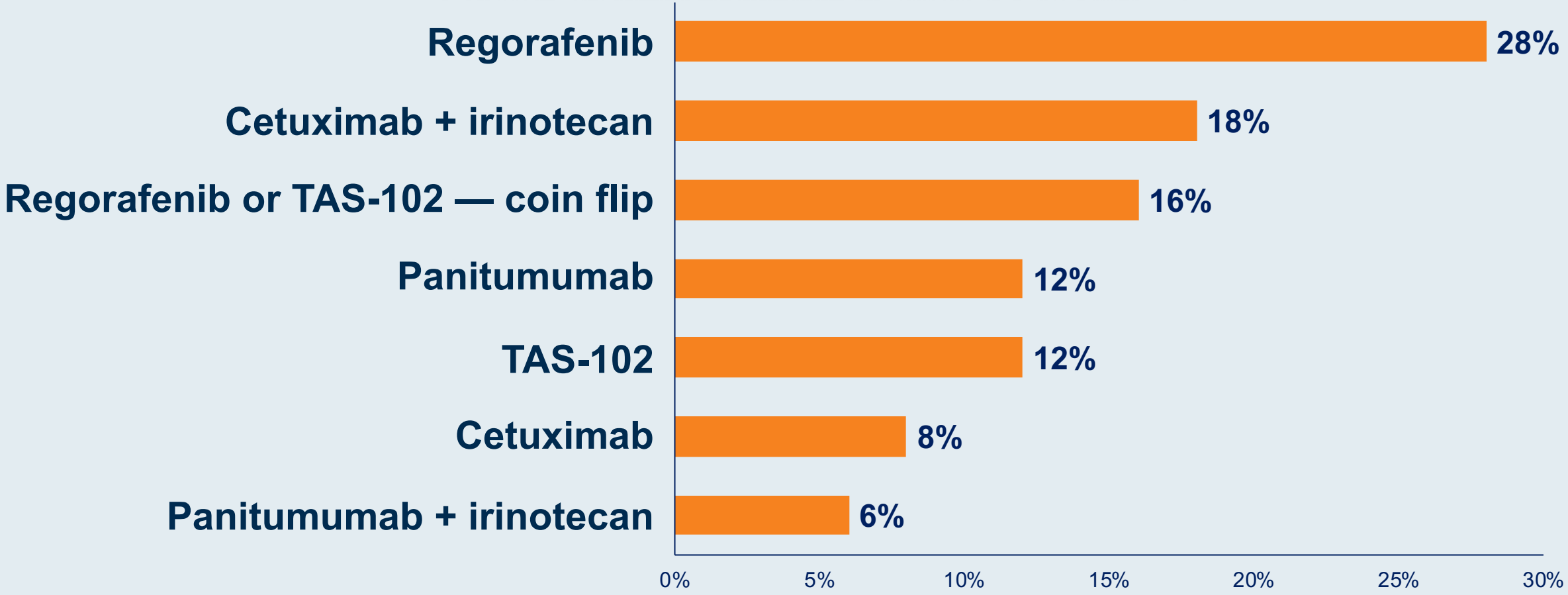
Module 1: BRAF-Mutated Colorectal Cancer

Module 2: Checkpoint Inhibitors in Colorectal and Gastroesophageal Cancer

Module 3: HER2-Positive Colorectal and Gastroesophageal Cancer

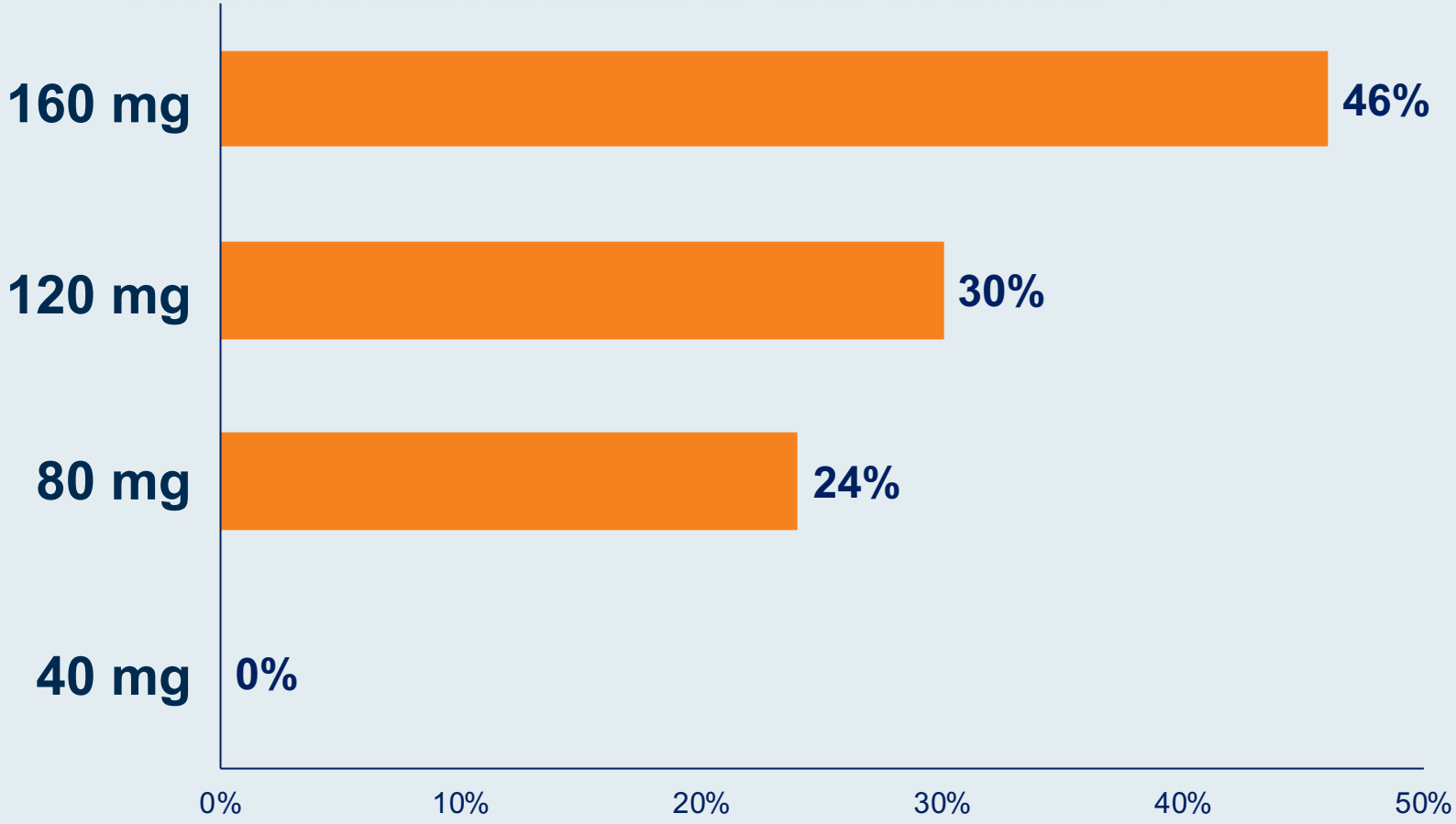
Module 4: Other Treatment Strategies for Advanced Colorectal and Gastroesophageal Cancer

A 65-year-old patient with right-sided, pan-RAS wild-type, BRAF wild-type, microsatellite-stable mCRC receives first-line FOLFOX/bevacizumab and second-line FOLFIRI/bevacizumab and is now experiencing disease progression with a PS of 0. What would be your most likely third-line treatment recommendation?



Survey of 50 US-based medical oncologists

In general, for a younger patient with mCRC, what is your usual starting dose of regorafenib?

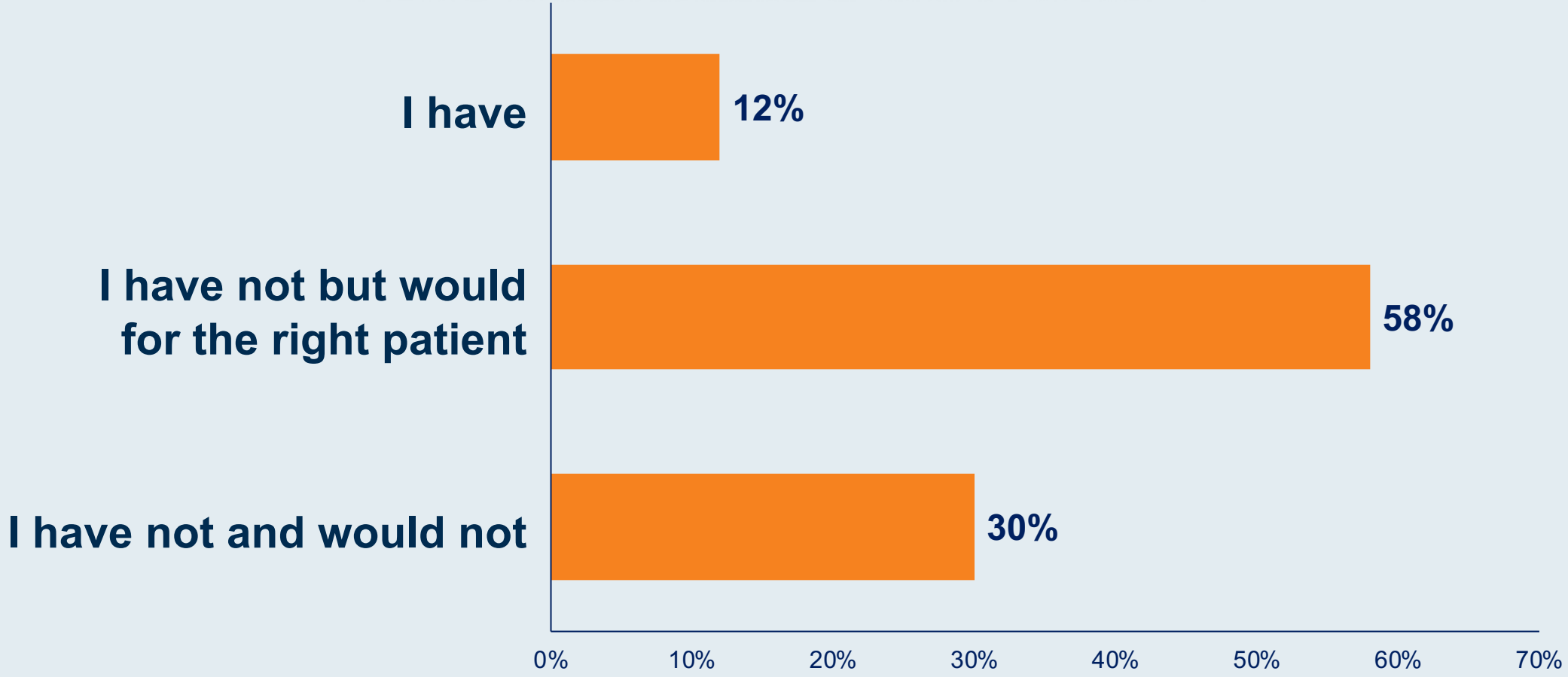


Survey of 50 US-based medical oncologists

Have you or would you use TAS-102 in combination with bevacizumab outside of a clinical trial setting for a patient with mCRC?

a. I have
b. I have not but would for the right patient
c. I have not and would not

Have you or would you use TAS-102 in combination with bevacizumab outside of a clinical trial setting for a patient with mCRC?

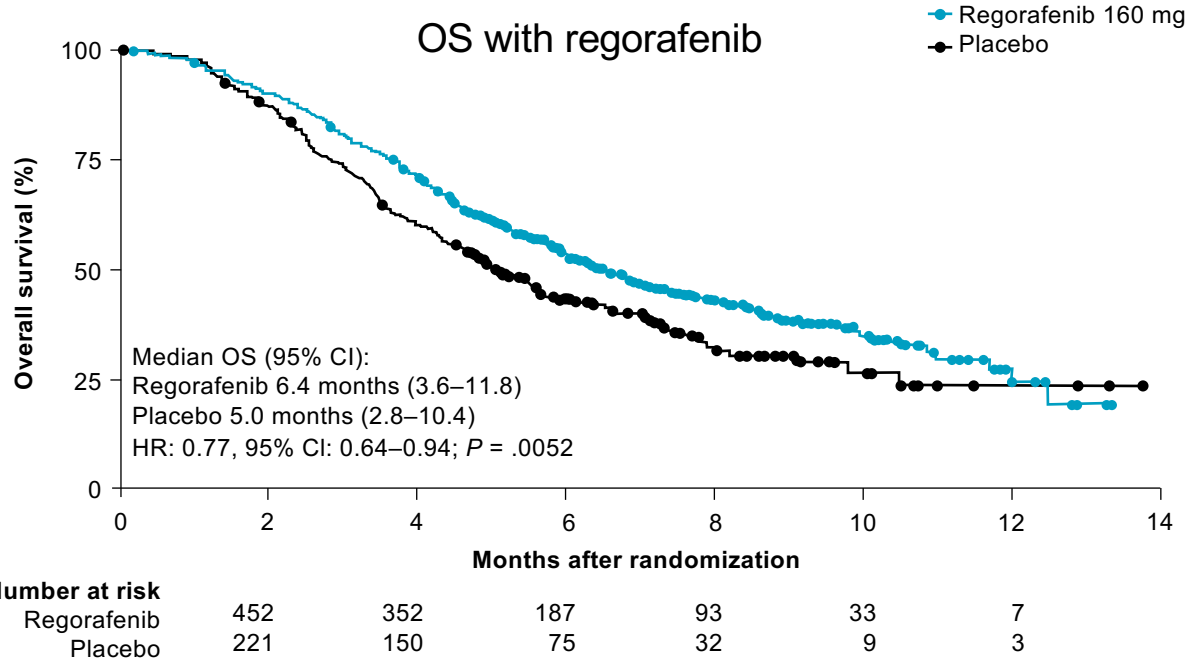


Survey of 50 US-based medical oncologists

Regorafenib Significantly Improved Outcomes in mCRC Phase III RCTs That Used a Daily Starting Dose of 160 mg

6.4 months

OS with regorafenib

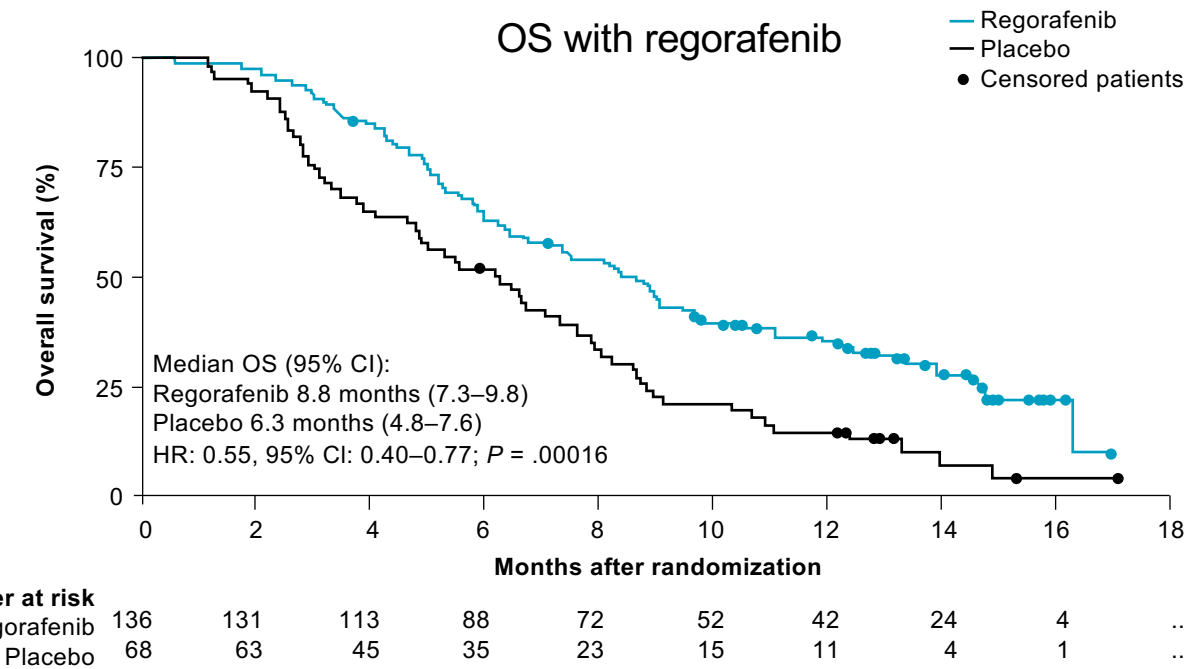


Number at risk						
Regorafenib	452	352	187	93	33	7
Placebo	221	150	75	32	9	3

CORRECT[1]: 23% reduction in the risk of death (primary endpoint)

8.8 months

OS with regorafenib



Number at risk										
Regorafenib	136	131	113	88	72	52	42	24	4	..
Placebo	68	63	45	35	23	15	11	4	1	..

CONCUR[2]: 45% reduction in the risk of death (primary endpoint)

1. Grothey A, Van Cutsem E, et al. *Lancet*. 2013;381:303-312; 2. Li J, et al. *Lancet Oncol*. 2015;16:619-629.

Courtesy of Axel Grothey, MD

Regorafenib Adverse Events Can Be Challenging for Patients

Some of the most common regorafenib-related AEs include HFSR, fatigue, hypertension, and diarrhea[1,2]

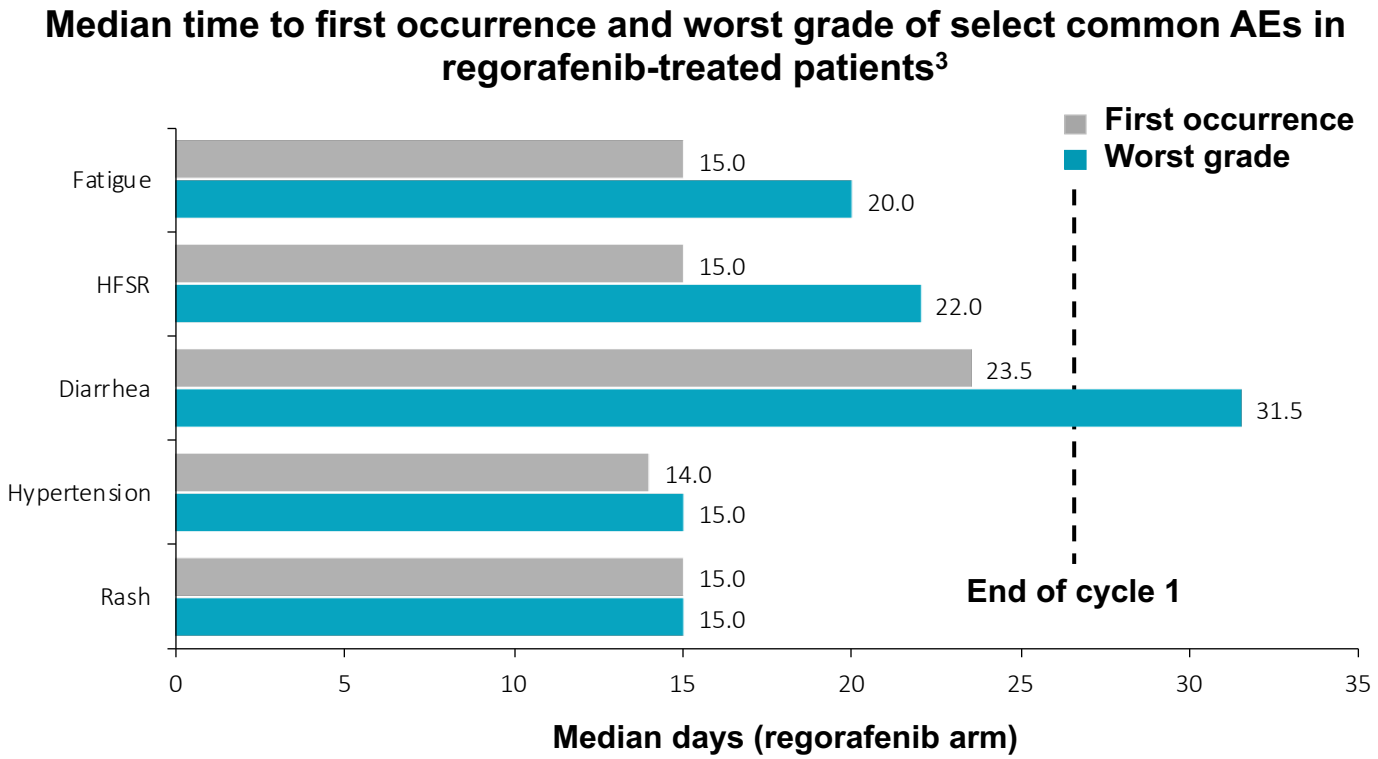
Drug-Related AEs, %	CORRECT[1]				CONCUR[2]			
	Regorafenib (n = 500)		Placebo (n = 253)		Regorafenib (n = 136)		Placebo (n = 68)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
HFSR	47	17	8	<1	74	16	4	0
Fatigue	47	10	28	5	17	3	7	1
Hypertension	28	7	6	1	23	11	4	3
Diarrhea	34	7	8	1	18	1	3	1
Rash/desquamation*	26	6	4	0	9	4	1	0
Anorexia	30	3	15	3	7	1	4	0
Mucositis, oral	27	3	4	0	NR	NR	NR	NR
Hyperbilirubinemia	9	2	2	1	37	7	7	1
ALT increased	NR	NR	NR	NR	24	7	7	0
AST increased	NR	NR	NR	NR	24	6	9	0
Thrombocytopenia	13	3	2	<1	10	3	1	0
Fever	10	1	3	0	NR	NR	NR	NR
Nausea	14	<1	11	0	NR	NR	NR	NR
Voice changes†	29	<1	6	0	21	1	0	0
Weight loss	14	0	2	0	NR	NR	NR	NR

***Maculopapular rash in CONCUR; †Hoarseness in CONCUR. Adverse events were graded using the NCI-CTCAE version 3.0 (CORRECT) and version 4.0 (CONCUR).**
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFSR, hand-foot skin reaction; NR, not reported.
1. Grothey A, Van Cutsem E, et al. *Lancet*. 2013;381:303-312; 2. Li J, et al. *Lancet Oncol*. 2015;16:619-629.

Courtesy of Axel Grothey, MD

Regorafenib AEs Frequently Occur Early in Treatment[1,2]

- **The incidence and severity of HFSR, hypertension, liver abnormalities, fatigue, diarrhea, and oral mucositis did not increase over time[2]**
- **AEs associated with regorafenib are noncumulative[3]**

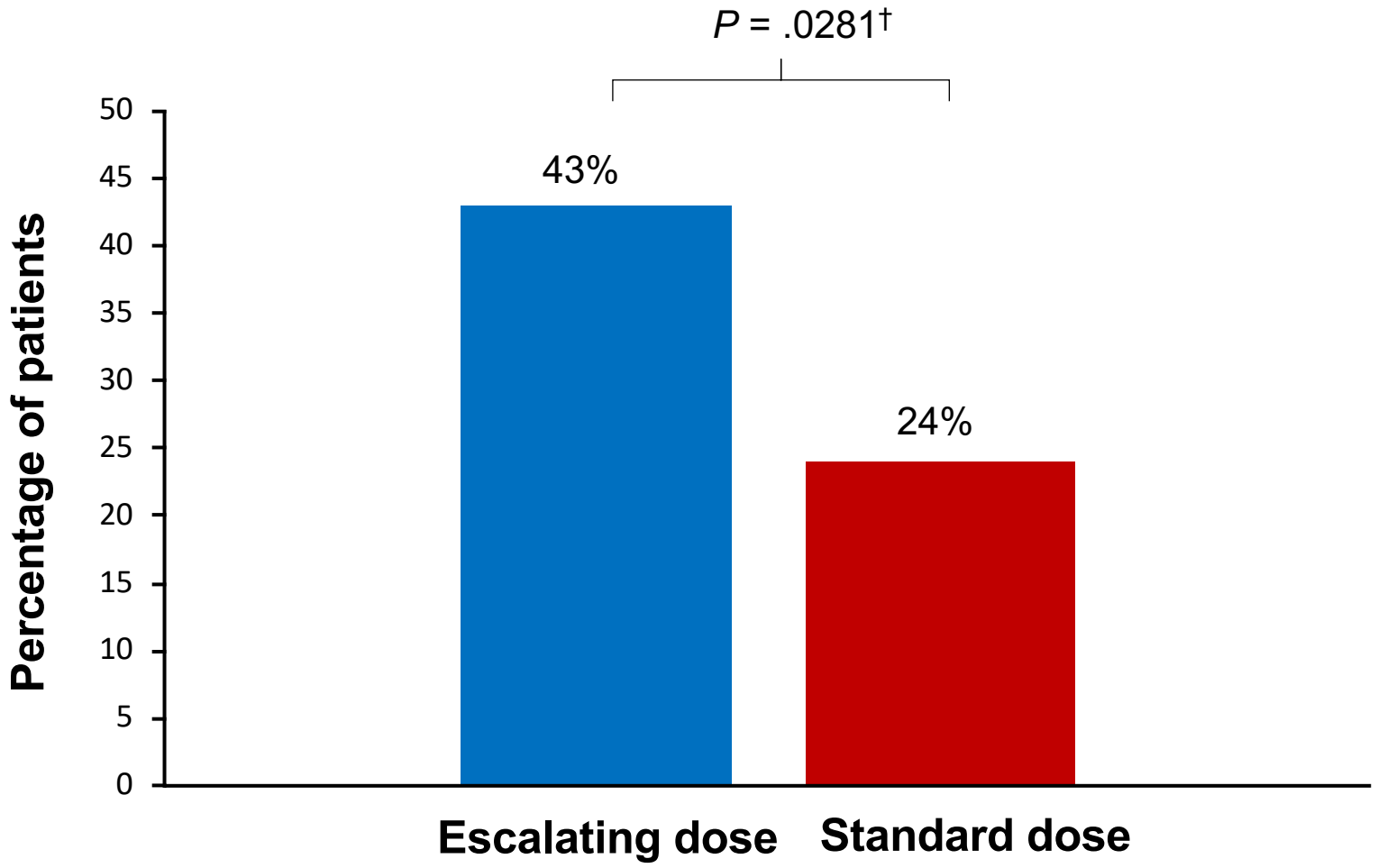


1. Stivarga [summary of product characteristics]. Berlin, Germany: Bayer Pharma AG; 2018; 2. Grothey A, et al. *Oncologist.* 2014;19:669-680; 3. Grothey A, et al. ASCO 2013. Abstract 3637.*

*Information presented at ASCO 2013 congress; only the abstract is available. Information provided for discussion purposes with the advisors. Not to be shown externally. Not for distribution.

Courtesy of Axel Grothey, MD

ReDOS (primary endpoint): Percentage of Patients Starting Cycle 3*



*The primary endpoint is a composite endpoint integrating efficacy (patients needed to have at least stable disease at the planned disease evaluation) and safety (patients need to tolerate the drug with no unacceptable toxicity issues); †Fisher's exact test (1-sided).

Bekaii-Saab T, et al. *Lancet Oncol*. 2019;20:1070-1082.

Courtesy of Axel Grothey, MD

Comparison of Phase III Trials of Regorafenib, TAS-102 in mCRC

Agent	Regorafenib				TAS-102			
Trial	**CORRECT[1]**		**CONCUR[2]**		**RECOURSE[3]**		**TERRA[4]**	
Prior biologics	100% BEV 100% EGFR mAbs		60%		100% BEV 53% EGFR mAbs 18% Prior REGO		20% BEV 18% EGFR mAbs	
	REGO (n = 505)	BSC + PL (n = 255)	REGO (n = 136)	BSC + PL (n = 68)	TAS-102 (n = 534)	BSC + PL (n = 266)	TAS-102 (n = 271)	BSC + PL (n = 135)
Prior lines ≤2 3 ≥4	 27% 25% 49%	 25% 28% 47%	 35% 24% 38%	 35% 25% 40%	 18% 22% 60%	 17% 20% 63%	 23% 27% 50%	 19% 27% 55%
Median OS, mo	6.4	5.0	8.8	6.3	7.1	5.3	7.8	7.1
	HR: 0.77 *P* = .0052		**HR: 0.55** *P* = .0002		**HR: 0.68** *P* <.0001		**HR: 0.79** *P* = .0035	
Median PFS, mo	1.9	1.7	3.2	1.7	2.0	1.7	2.0	1.8
	HR: 0.49 *P* <.0001		HR: 0.31 *P* <.0001		HR: 0.48 *P* <.0001		HR: 0.43 *P* <.0001	
RR, %	1.0	0.4	4.4	0	1.6	0.4	1.1	0

1. Grothey A, et al. *Lancet*. 2013;381:303-312; 2. Li J, et al. *Lancet Oncol*. 2015;16:619-629; 3. Mayer RJ, et al. *N Engl J Med*. 2015;372:1909-1919; 4. Kim TW, et al. ESMO 2016. Abstract 465PD.

Courtesy of Axel Grothey, MD

Why Regorafenib Before TAS-102?

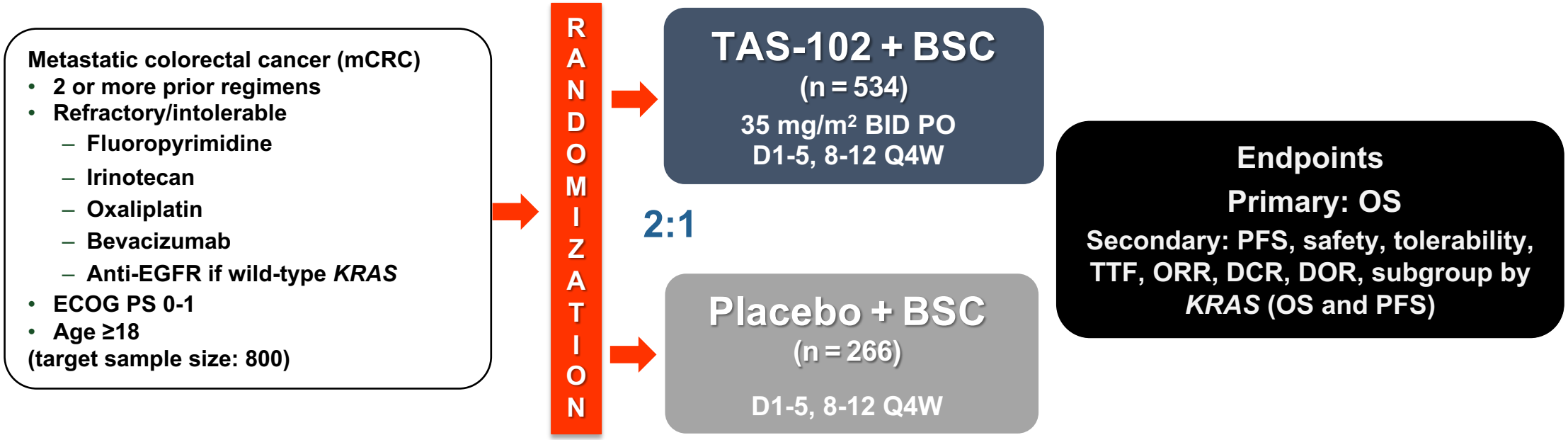
- **Patients benefit from access to all active agents, ie, regorafenib AND TAS-102**
- **Regorafenib appears to provide greater benefit in less-pretreated patients**
- **Regorafenib should not be used in PS 2+ patients**
  - Do not let PS deteriorate before regorafenib
- **Side effects can be managed (and QOL can be maintained – see ReDOS)**
- **Cytotoxic therapy (eg, TAS-102) can be active after regorafenib**
- **We have data on TAS-102 after regorafenib**

Riechelmann R, Grothey A. *Lancet Oncol.* 2015;16:596-597.

Courtesy of Axel Grothey, MD

TAS-102 Global, Randomized Phase III Study RECOURSE: Refractory Colorectal Cancer Study

(NCT01607957)

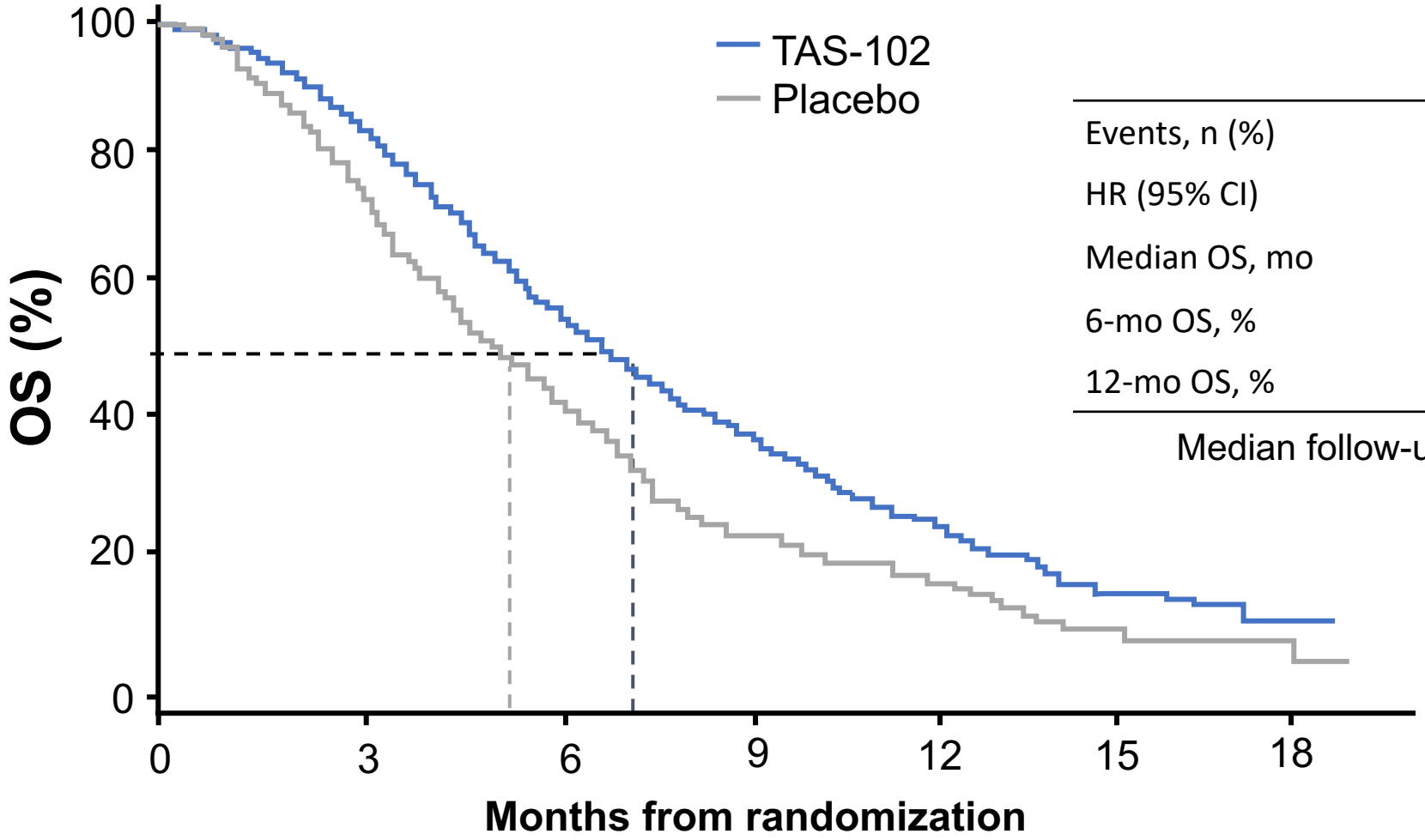


- Treatment continuation until progression, intolerable toxicity, or patient refusal
- Multicenter, randomized, double-blind, placebo-controlled phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographic region
- Sites: 13 countries, 114 sites
- Enrollment: June 2012 to October 2013

Mayer RJ, et al. *N Engl J Med*. 2015;372:1909-1919.

Courtesy of Axel Grothey, MD

RECOURSE: OS



	TAS-102 (n = 534)	Placebo (n = 266)
Events, n (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81); *P* <.001	
Median OS, mo	7.1	5.3
6-mo OS, %	58	44
12-mo OS, %	27	18

Median follow-up: 11.8 mo

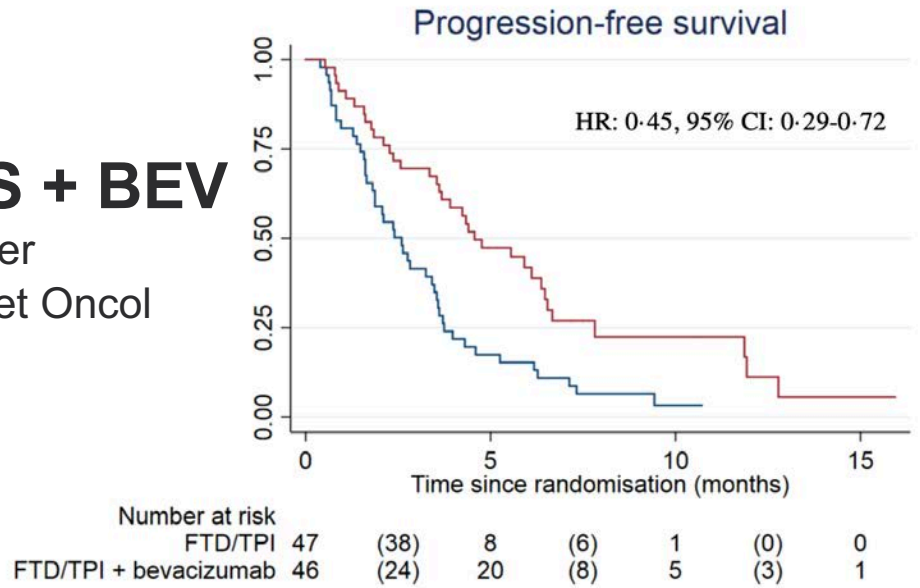
Mayer RJ, et al. *N Engl J Med*. 2015;372:1909-1919.

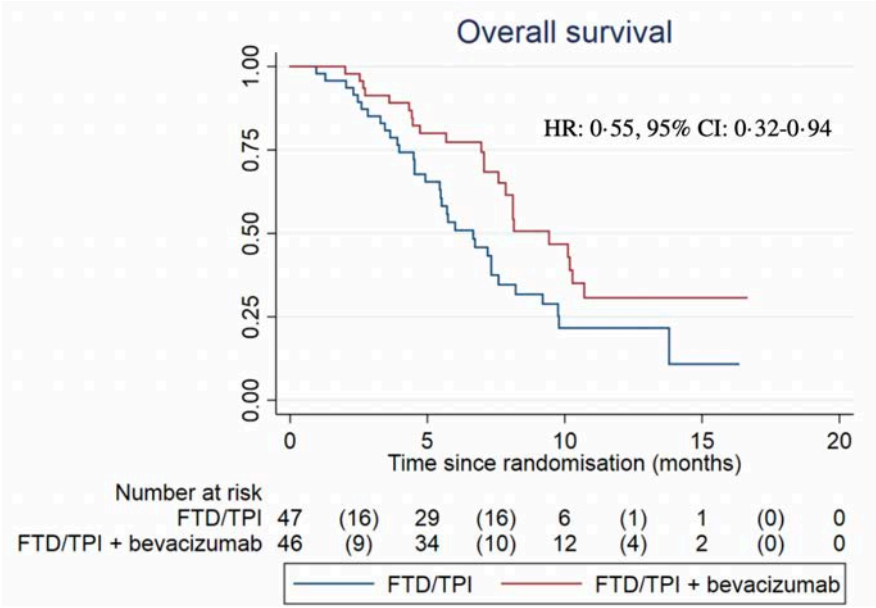
Courtesy of Axel Grothey, MD

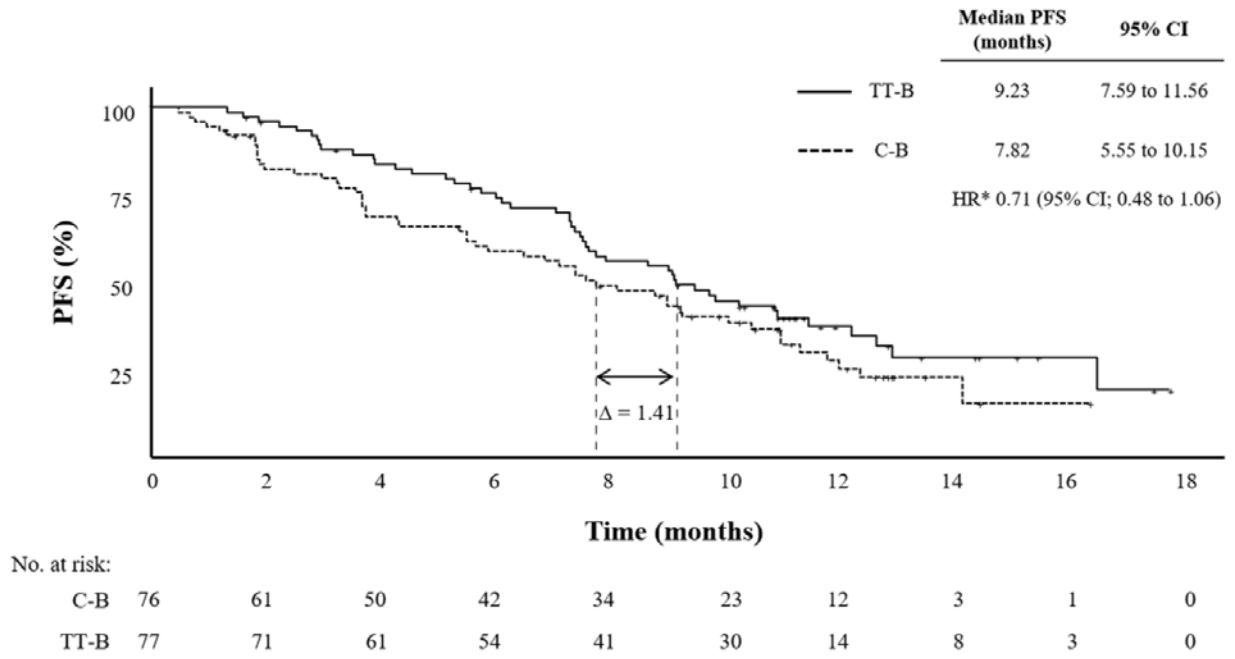
Interesting Combination: TAS-102 + BEV

TAS + BEV

Pfeiffer
Lancet Oncol
2020





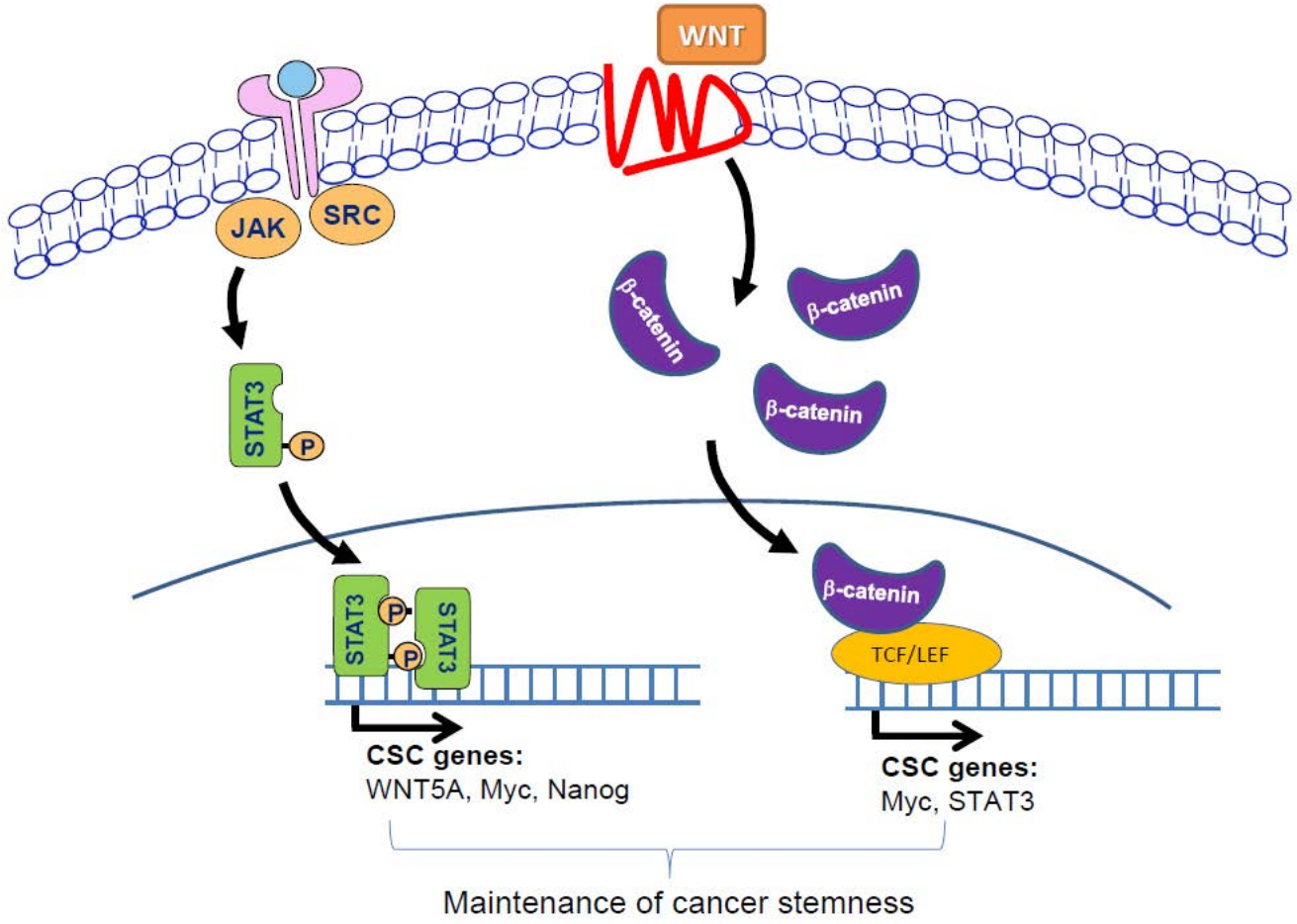


TASCO1 trial:
TAS-BEV vs Cape-BEV
as first-line therapy
N=154
Van Cutsem et al., Ann Oncol 2020

Courtesy of Axel Grothey, MD

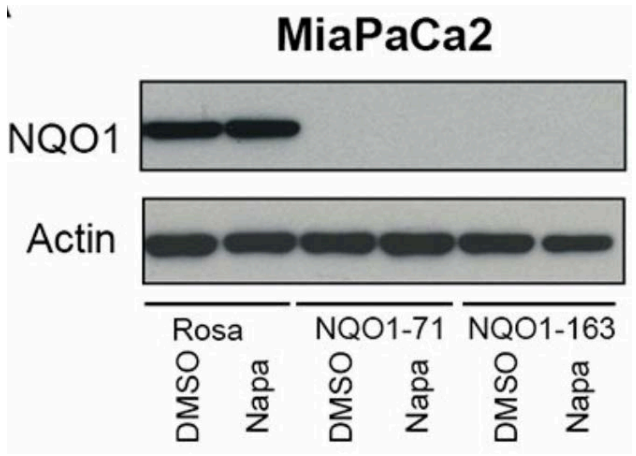
STAT-3/β-catenin/Nanog in CRC

- Elevated expression by IHC of p-STAT-3, Nanog and cytoplasmic β-catenin associated with poor prognosis

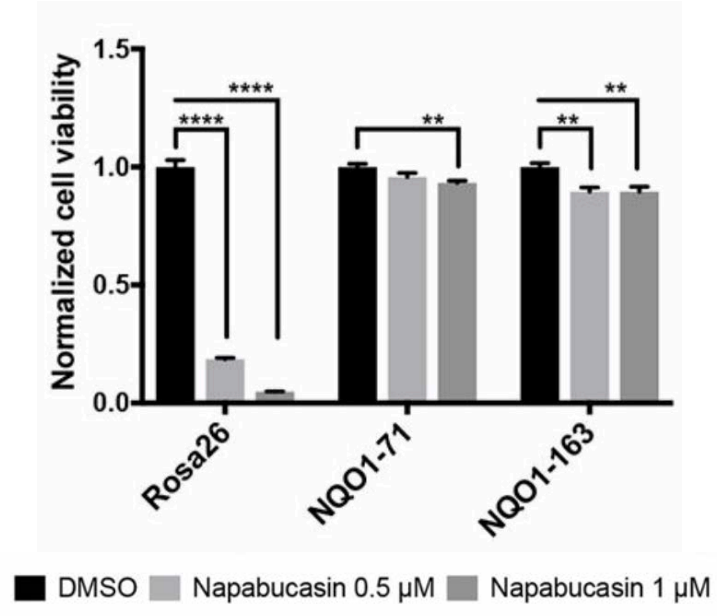


Courtesy of Axel Grothey, MD

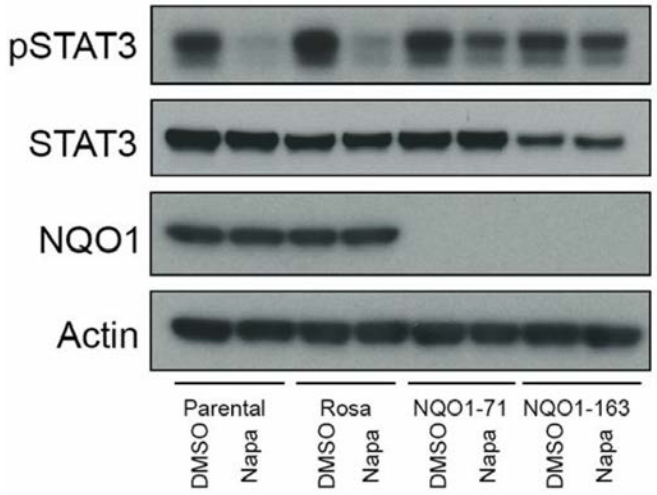
Napabucasin: Mechanism of Action



NQO1-71 and NQO1-163 are NQO1 knock-out clones



NAPA's cytotoxic activity depends on intact NQO1

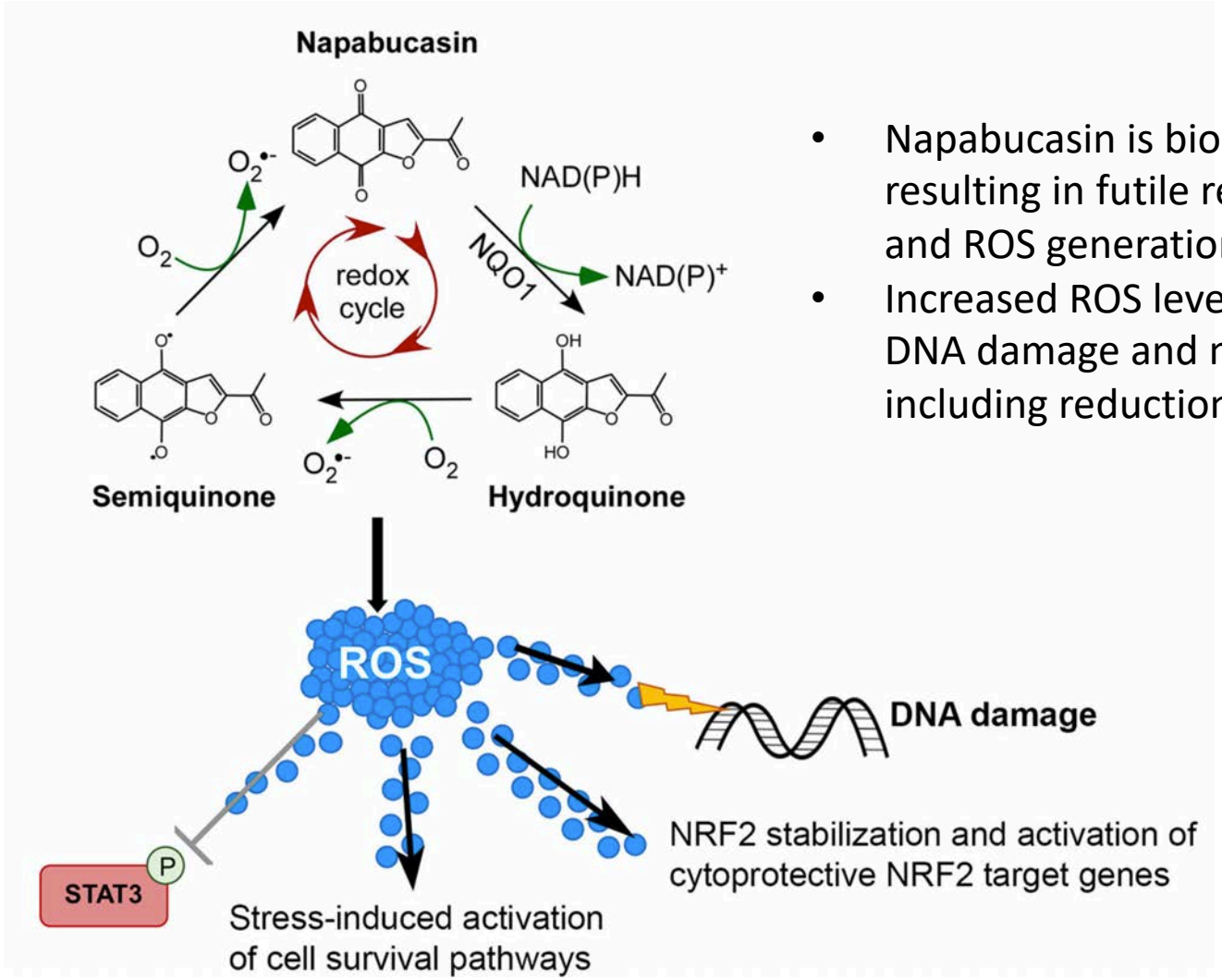


NAPA inhibits STAT3 phosphorylation in NQO1 positive cells

Froeling et al., Clin Cancer Res 2019

Courtesy of Axel Grothey, MD

Napabucasin: Mechanism of Action



- Napabucasin is bioactivated by NQO1 resulting in futile redox cycling and ROS generation
- Increased ROS levels result in DNA damage and multiple cell changes, including reduction in STAT3 phosphorylation

NQO1: NAD(P)H:quinone oxidoreductase-1
ROS: reactive oxygen species

Froeling et al., Clin Cancer Res 2019

Courtesy of Axel Grothey, MD

Napabucasin (BBI-608): Activity

- 94% (16 of 17 evaluable pts) had partial response (PR) or stable disease (SD)
- Median PFS was 5.72 months
- 59% (10 of 17 evaluable pts) had prolonged SD (≥ 6 months)

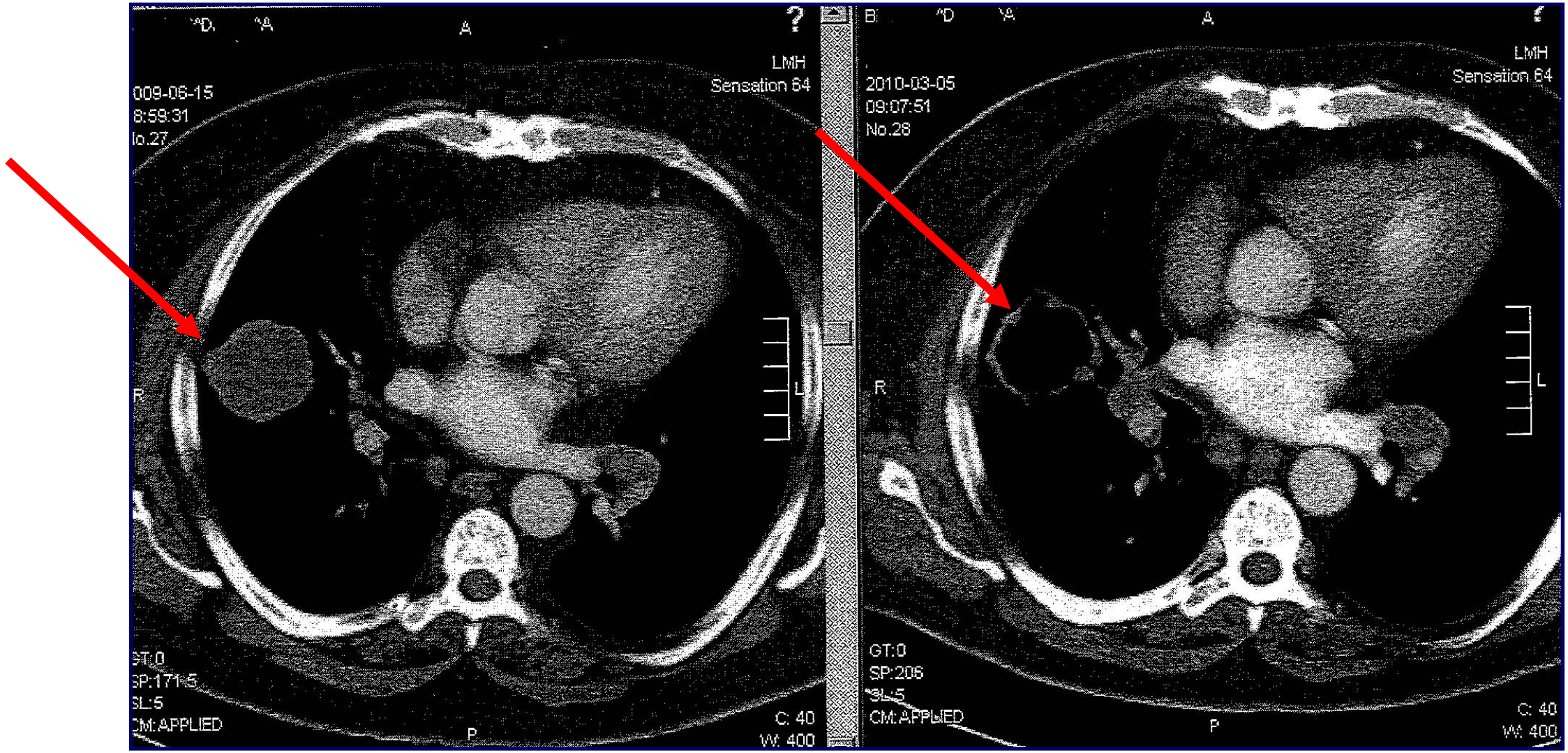
Hubbard et al., ASCO GI 2016

Courtesy of Axel Grothey, MD

Case Presentation – Dr Grothey: A 45-year-old man with mCRC

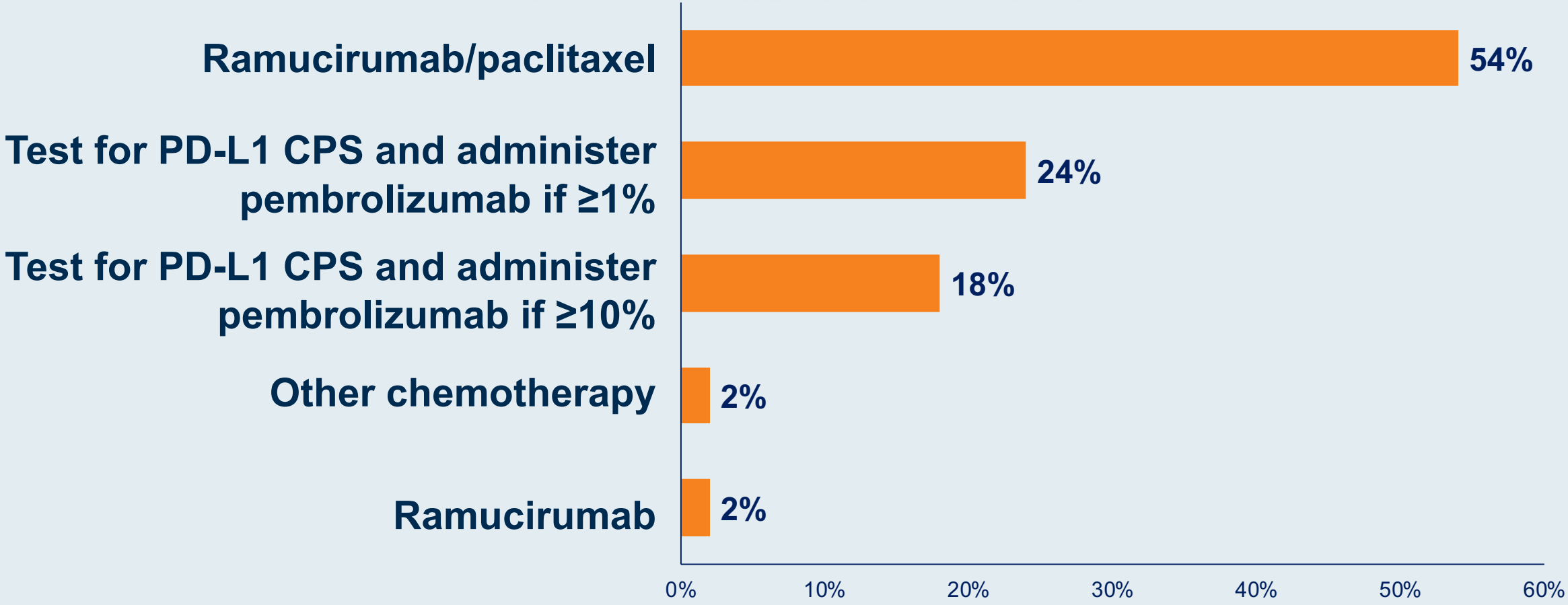
- 45 yo male patient without comorbidities
- 07/11 Dx of rectal cancer, KRAS mut with synchronous liver, lung, and retroperitoneal LN metastases
- Until 2013 received FOLFOX plus BEV (OPTIMOX with 5-FU/LV + BEV maintenance), then upon PD FOLFIRI + BEV
- Subsequently treated with regorafenib in escalating dose (80-120-160 mg daily weeks 1, 2, and 3 of first cycle)
- At first scan at 8 weeks SD of liver and retroperitoneal metastases, cavitation of lung metastasis
- SD on regorafenib for 6 months, then PD

Case Presentation – Dr Grothey: A 45-year-old man with mCRC -- Cavitation of lung metastasis on regorafenib



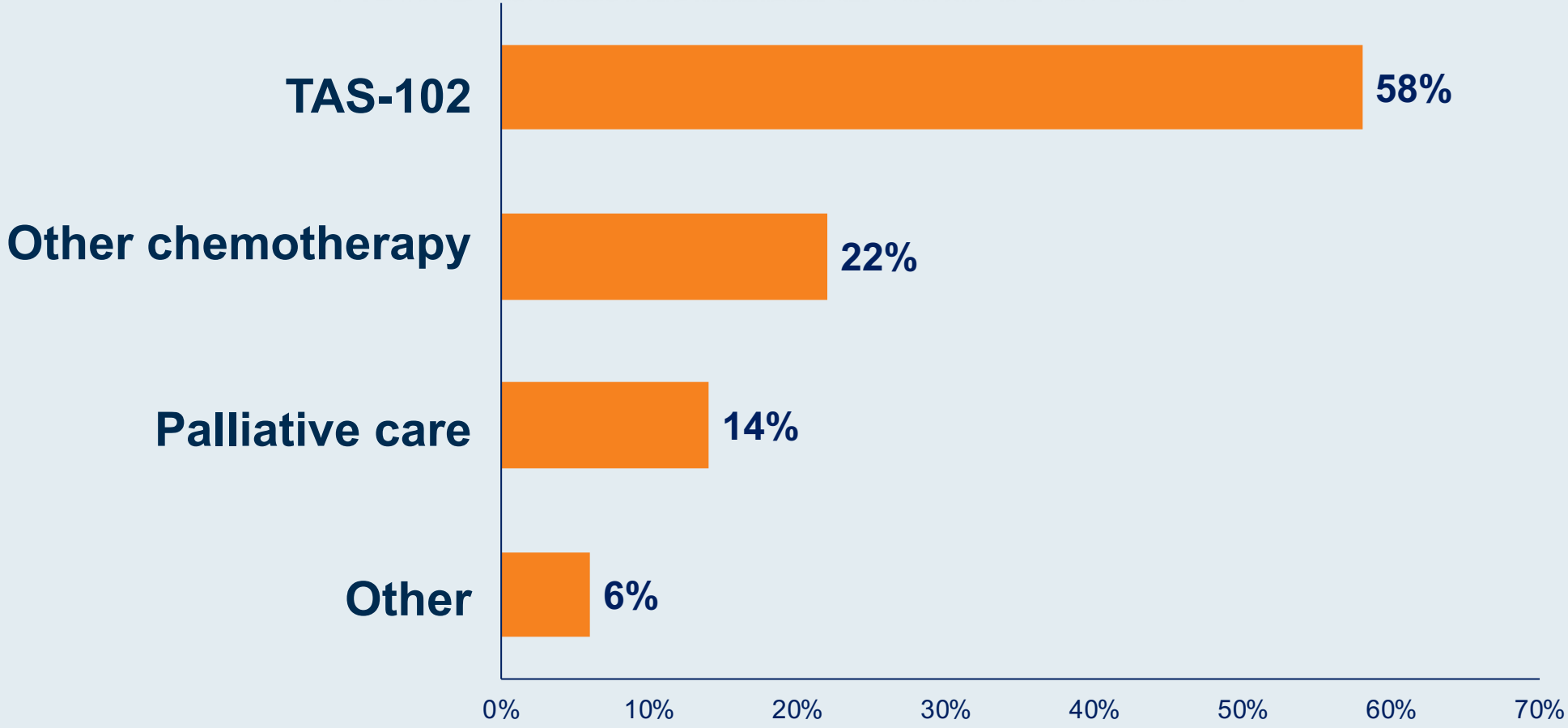
Metastatic Gastroesophageal Cancers

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-negative, microsatellite-stable gastric adenocarcinoma who has experienced disease progression on first-line FOLFOX?



Survey of 50 US-based medical oncologists

What is your usual next treatment for a younger patient (PS 0) with metastatic HER2-negative, microsatellite-stable gastric cancer who has experienced disease progression on FOLFOX, paclitaxel/ramucirumab and an anti-PD-1/PD-L1 antibody?



Survey of 50 US-based medical oncologists

Conclusions

- Therapy for gastroesophageal cancer is becoming more complex and personalized
  - Check biomarkers early!
- Ramucirumab-based cytotoxic combinations are appropriate second-line treatment
- Trifluridine/tipiracil is an appropriate third line option
- Trastuzumab deruxtecan may be an option for refractory HER2+ disease
- Targeted agents against HER2, FGFR, VEGF, CLDN 18.2 are in development
  - Rebiopsy at time of progression to re-evaluate biomarkers may be necessary

Courtesy of Crystal Denlinger, MD, F.A.C.P.

FOLFIRI and Ramucirumab: A Non-Taxane Option

Inclusion (selection)

- Histologically proven metastatic or locally advanced adenocarcinoma stomach/EGJ
- progression during / within 6 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline or docetaxel
- ECOG ≤ 1

STRATIFICATION

Previous docetaxel-containing therapy
yes vs. no
Time of progression during or after end of first-line therapy
≤3 months vs. >3 months

RANDOMISATION

2:1

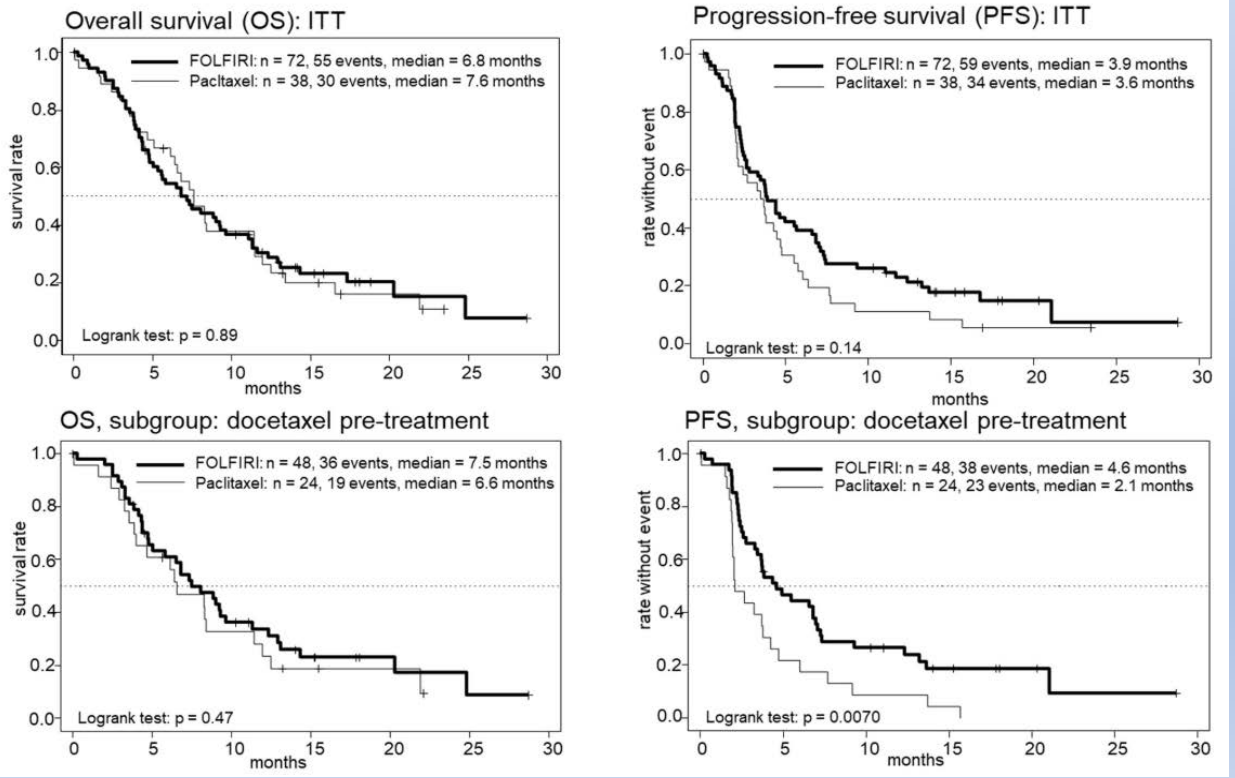
Arm A
Irinotecan 180 mg/m²
5-FU bolus 400 mg/m²
Leucovorin* 400 mg/m²
5-FU 2400 mg/m² 46-hour continuous administration
day 1 and 15, qd28
plus
Ramucirumab 8 mg/kg i.v. infusion
day 1 and 15, qd28
67 patients

Arm B
Paclitaxel 80 mg/m²
day 1, 8, 15
plus
Ramucirumab 8mg/kg
day 1 and 15
qd28
34 patients

Table 3: Objective Response Rate (ORR) and Disease Control Rate (DCR)

Event	FOLFIRI+ Ramucirumab	Paclitaxel+ Ramucirumab
ORR %	22% (16/72)	11% (4/38)
ORR % in Docetaxel pre-treated pts	25% (12/48)	8% (2/24)
DCR %	61% (44/72)	58% (21/38)
DCR % in Docetaxel pre-treated pts	65% (31/48)	37% (9/24)

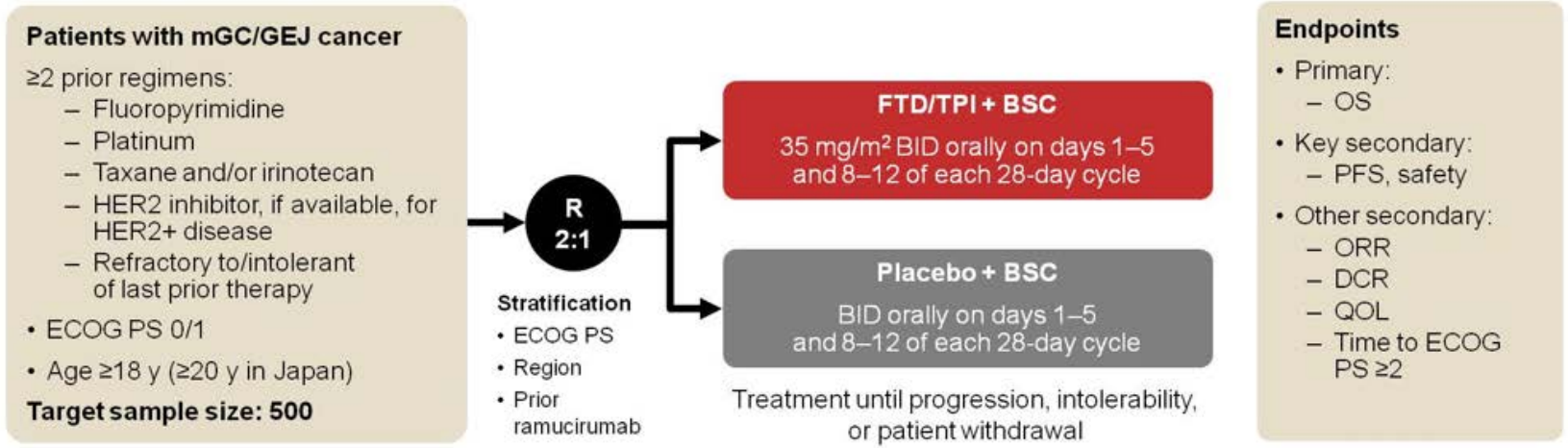
Figure 2: Overall and Progression-free Survival



Lorenzen ASCO 2020 abs 4514

Courtesy of Crystal Denlinger, MD, F.A.C.P.

TAGS – Multicenter, Randomized, Double-blind, Phase 3 Study



	Trifluridine/Tipiracil	Placebo	P value
Overall Survival	5.7 months	3.6 months	P=0.00058
	HR 0.69 (95% CI 0.56-0.85)		
12-month OS	21%	13%	
Progression-Free Survival	2.0 months	1.8 months	P< 0.0001
	HR 0.57 (95% CI 0.47-0.70)		
6-month PFS	15%	6%	
Overall Response Rate	4%	2%	P=0.28
Disease Control Rate	44%	14%	P<0.0001

Shitara et al Lancet Oncology 2018, 19: 1427-1448

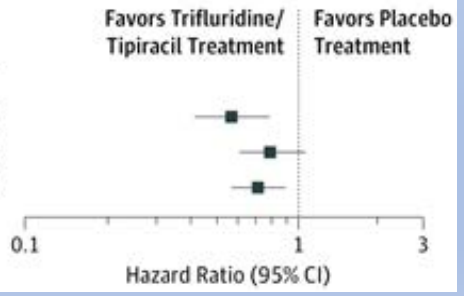
Courtesy of Crystal Denlinger, MD, F.A.C.P.

Trifluridine/Tipiracil and Prior Gastrectomy

Trifluridine/Tipiracil Safety Profile:

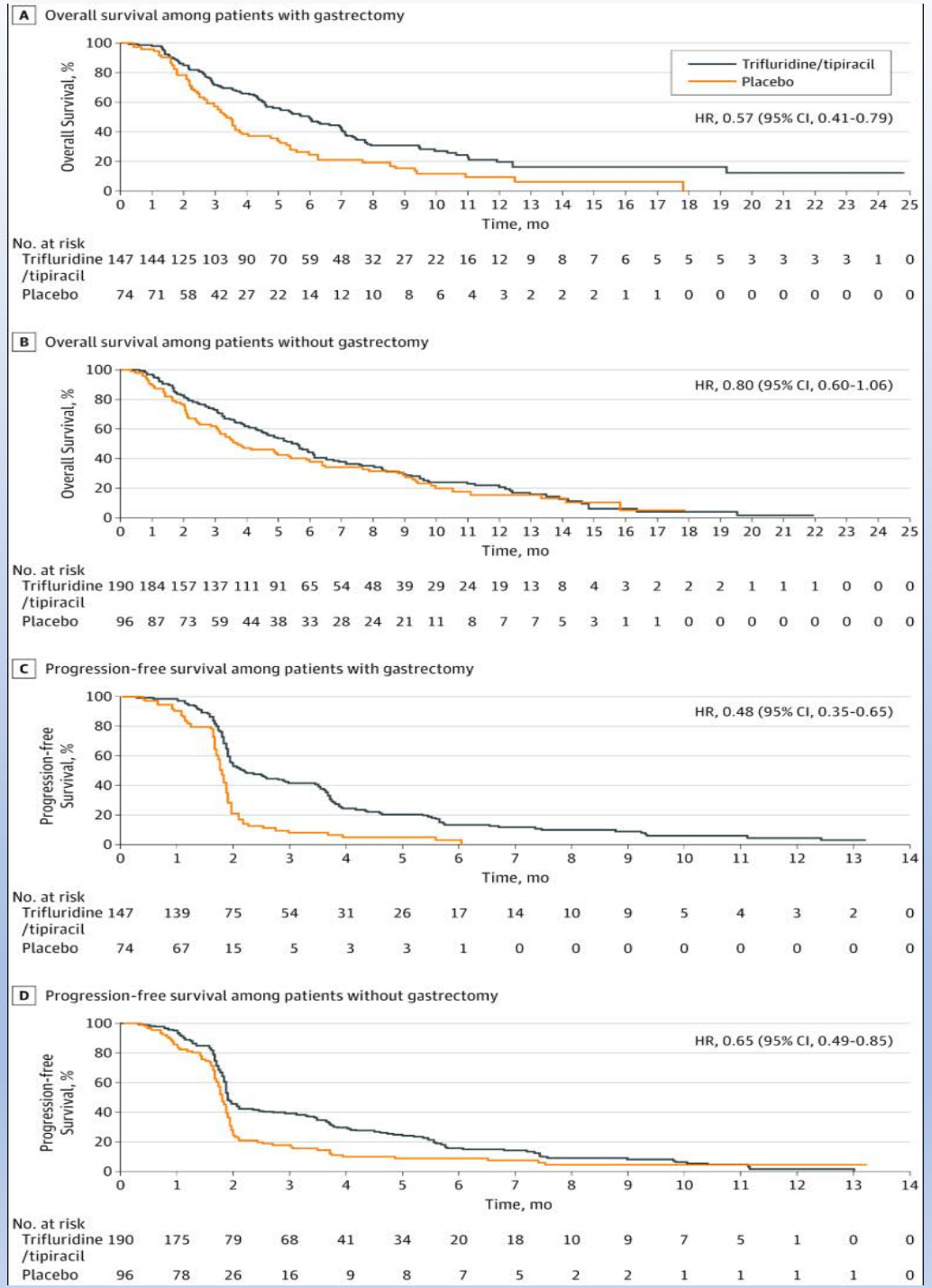
- Adverse events: Cytopenias most common
- Dose modifications due to adverse events: 58%
- Dose discontinuation due to adverse events: 13%
- Prior gastrectomy:
  - Higher incidence of neutropenia and anemia
  - Higher rates of dose modifications

Subgroup	Trifluridine/ Tipiracil Treatment, No. of Events/No. of Patients	Placebo, No. of Events/ No. of Patients	Hazard Ratio (95% CI)
Previous gastrectomy			
Yes	102/147	64/74	0.57 (0.41-0.79)
No	142/190	76/96	0.80 (0.60-1.06)
All Patients	244/337	140/170	0.69 (0.56-0.85)



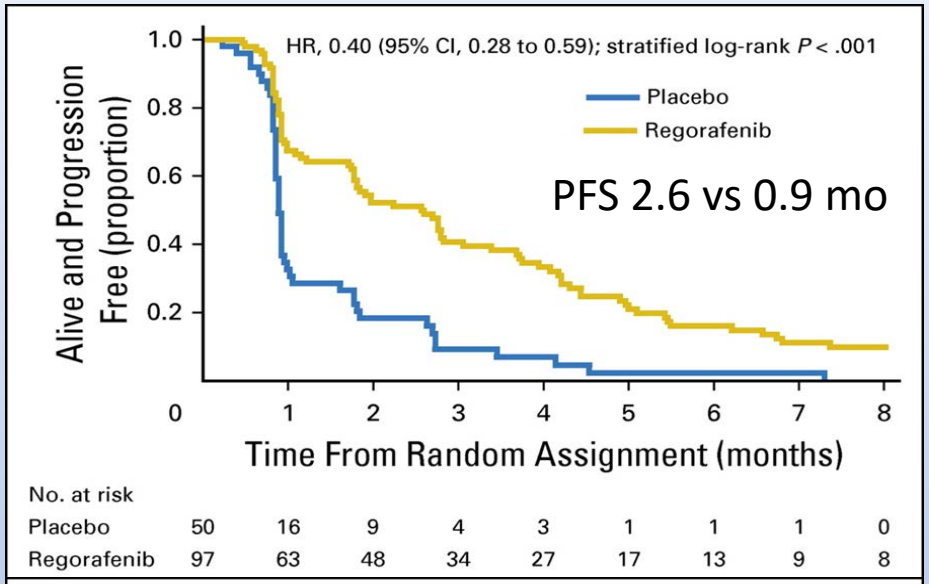
Ilson DH et al, JAMA Oncology 2020; 6: e193531

Courtesy of Crystal Denlinger, MD, F.A.C.P.

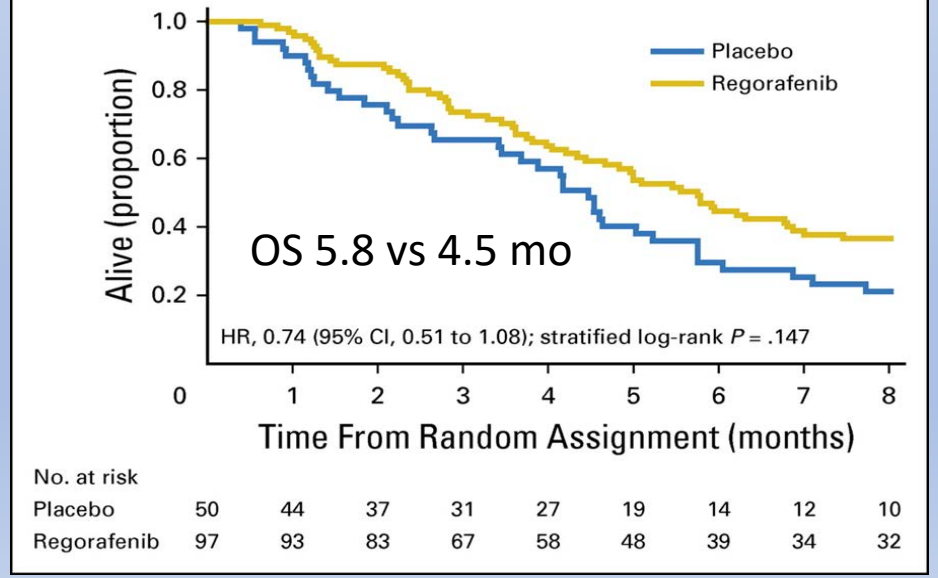


Regorafenib in Refractory Disease

Regorafenib monotherapy

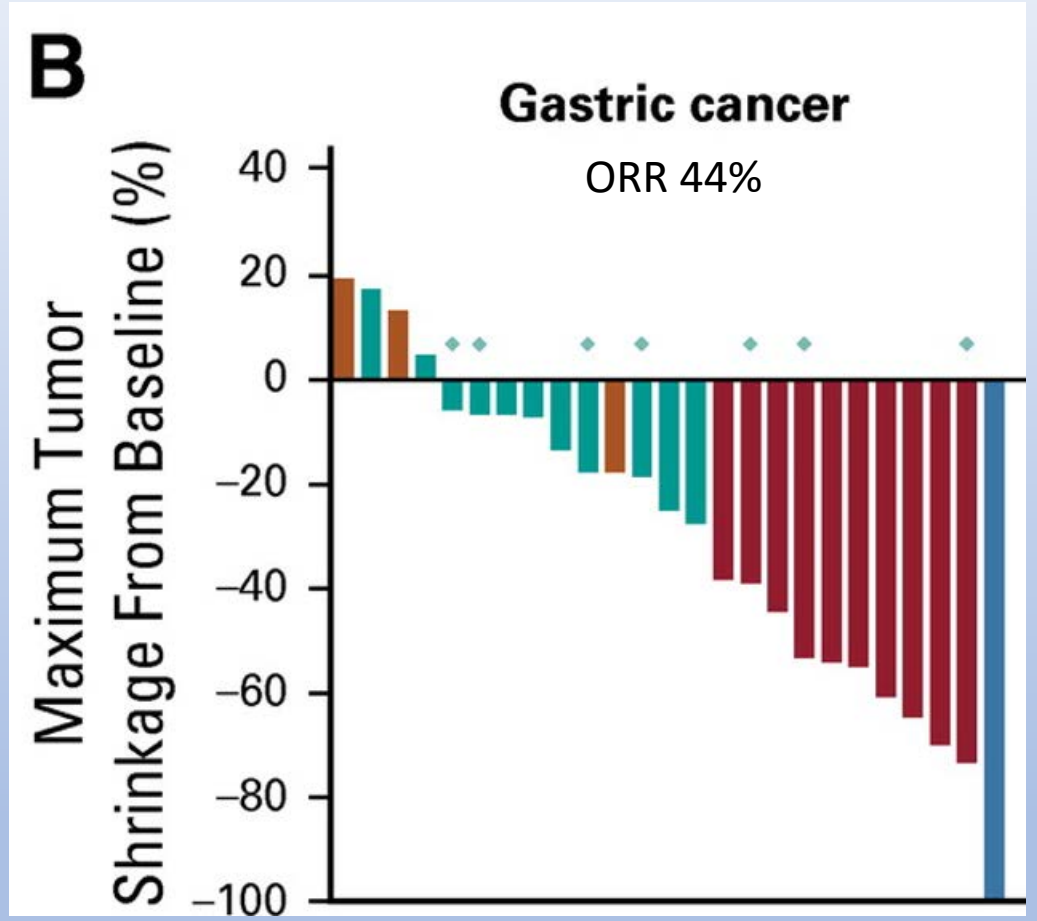


PFS 2.6 vs 0.9 mo



OS 5.8 vs 4.5 mo

Regorafenib + Nivolumab



Median PFS: 5.6 months
Median OS: 12.3 months

Pavlakis et al, Journal of Clinical Oncology 2016 34: 2728-2735

Courtesy of Crystal Denlinger, MD, F.A.C.P.

Fukuoka S et al, JCO 2020 38: 2053-2061

Case Presentation – Dr Denlinger: A 62-year-old man with metastatic GEJ cancer (2018-present)

- 62 year old man
  - Mild dysphagia with pills
  - ECOG PS 0
- Upper endoscopy: ulcerated, thickened distal esophagus extending through GE junction and into cardia
- Biopsy: Adenocarcinoma
  - HER2 negative by FISH
  - Microsatellite stable
  - CPS 5
- Staging: + multiple hepatic metastases, indeterminant pulmonary nodules
- ROS: Negative
- Physical exam: No abnormal findings

Case Presentation – Dr Denlinger: A 62-year-old man with metastatic GEJ cancer (Treatment History)

1. 9/2018: Capecitabine/Oxaliplatin, complicated by weight loss, dehydration, and diarrhea. Significant partial response to therapy. Oxaliplatin discontinued 4/2019 secondary to intolerance.
2. 4/2019-11/2019: Maintenance dose-reduced capecitabine with tolerance, discontinued for progressive disease.
3. 11/2019-present: Paclitaxel/ramucirumab with significant partial response to therapy. Held due to diverticular abscess with microperforation
4. Next planned therapy: pembrolizumab upon PD on taxane therapy

Recent Advances in Medical Oncology: Ovarian Cancer

Wednesday, July 29, 2020

5:00 PM – 6:00 PM ET

Faculty

Mansoor Raza Mirza, MD
Kathleen Moore, MD
Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 days.