Oncology Grand Rounds

New Agents and Strategies in Gastrointestinal Cancers

Thursday, May 28, 2020

5:00 PM – 6:30 PM ET

Faculty

Melony Avella-Howell, NP
Wells A Messersmith, MD
Philip A Philip, MD, PhD, FRCP
Tammy Triglianos, RN, MS, ANP-BC, AOCNP

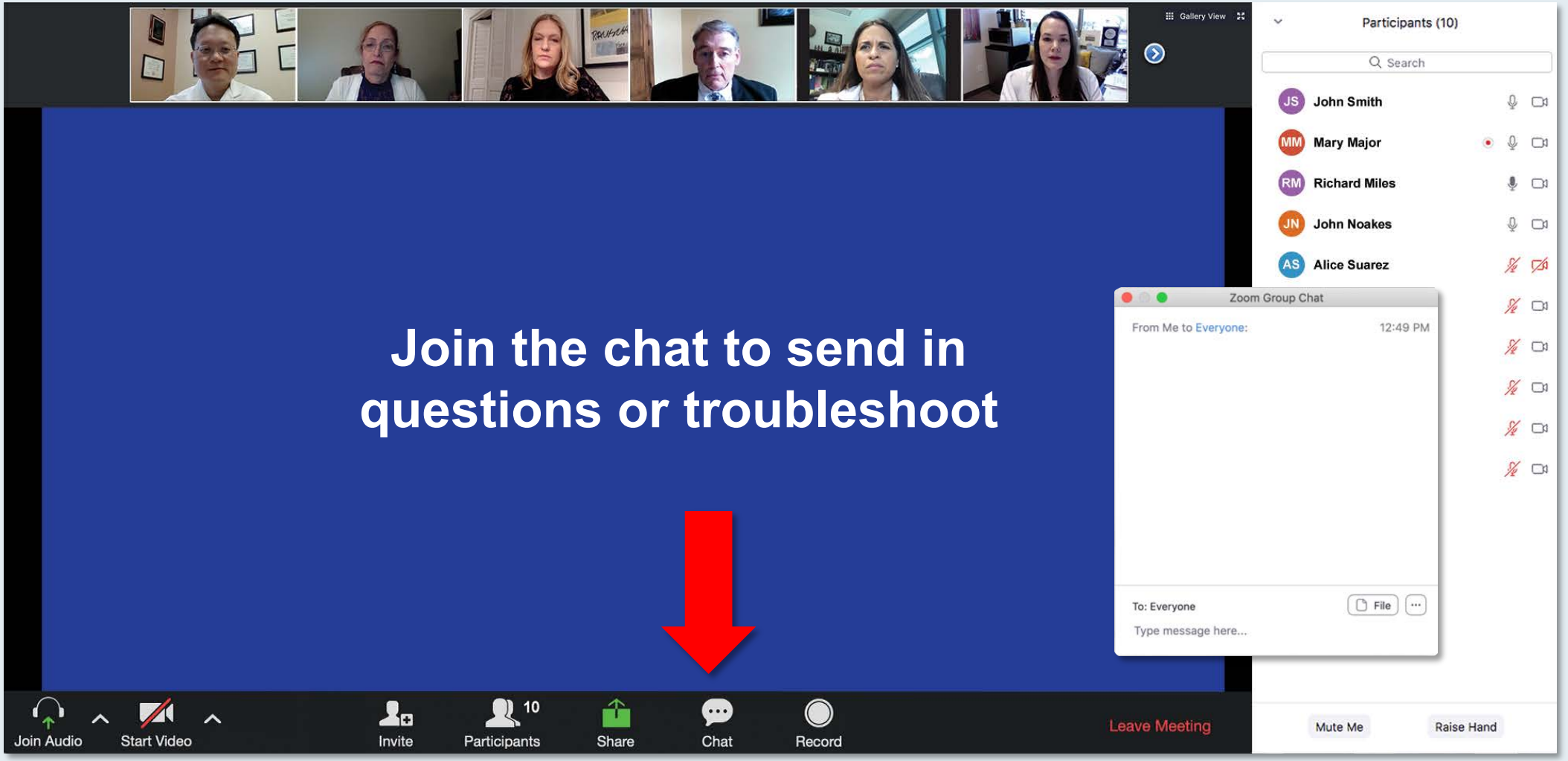
Moderator

Neil Love, MD

Research To Practice®

Familiarizing yourself with the Zoom interface

How to participate in the chat



RTP Live Webinar Nursing Series

Monday	Tuesday	Wednesday	Thursday	Friday
25	May 26 **Breast Cancer** 5:00 PM – 6:30 PM	27	May 28 **Gastrointestinal Cancers** 5:00 PM – 6:30 PM	29
Jun 1	June 2 **Hodgkin and Non-Hodgkin Lymphomas** 5:00 PM – 6:30 PM	3	June 4 **Chronic Lymphocytic Leukemia** 5:00 PM – 6:30 PM	5
8	June 9 **Gynecologic Cancers** 5:00 PM – 6:30 PM	10	June 11 **Metastatic Lung Cancer** 5:00 PM – 6:30 PM	12
15	June 16 **Locally Advanced Non-Small Cell Lung Cancer** 5:00 PM – 6:30 PM	17	June 18 **Urothelial Bladder Carcinoma** 5:00 PM – 6:30 PM	19
22	June 23 **Chimeric Antigen Receptor T-Cell Therapy** 5:00 PM – 6:30 PM	24	June 25 **PARP Inhibition in the Management of Common Cancers** 5:00 PM – 6:30 PM	26
29	June 30 **Prostate Cancer** 5:00 PM – 6:30 PM	Jul 1	2	3
6	7	8	9	10

Oncology Grand Rounds

New Agents and Strategies in Hodgkin and Non-Hodgkin Lymphomas

Tuesday, June 2, 2020

5:00 PM – 6:30 PM ET

Faculty

Kim Leake, MSN, FNP-C, APN-1
Mollie Moran, MSN, CNP, AOCNP
Craig Moskowitz, MD
Michael E Williams, MD, ScM

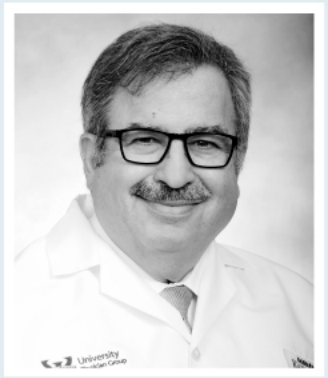
Moderator

Neil Love, MD

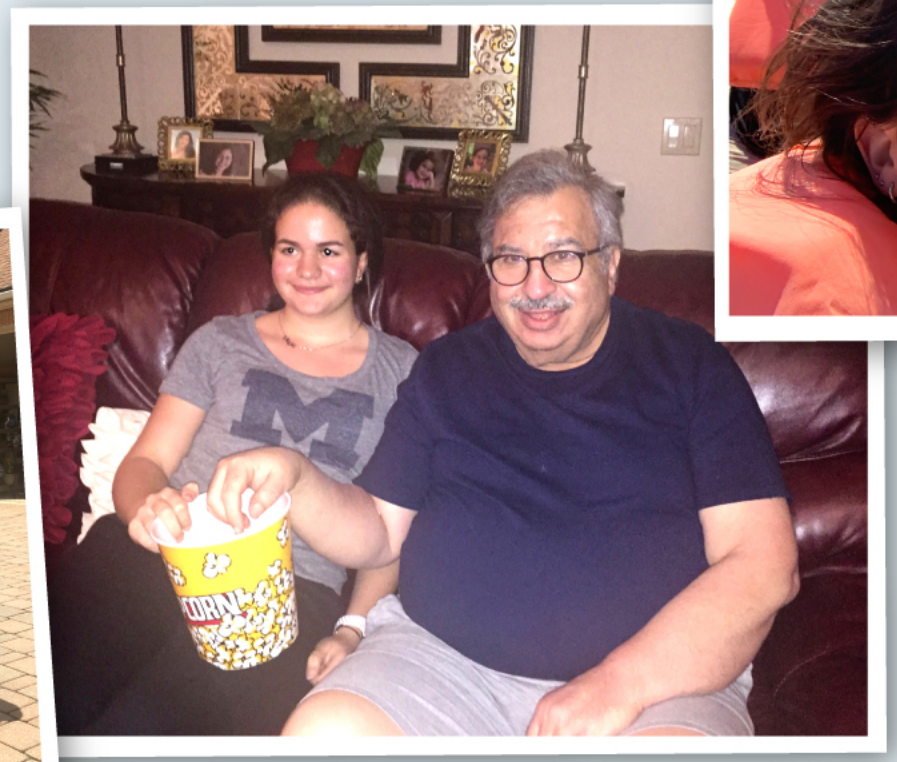
Research To Practice®

Melony Avella-Howell, NP
Aurora, Colorado

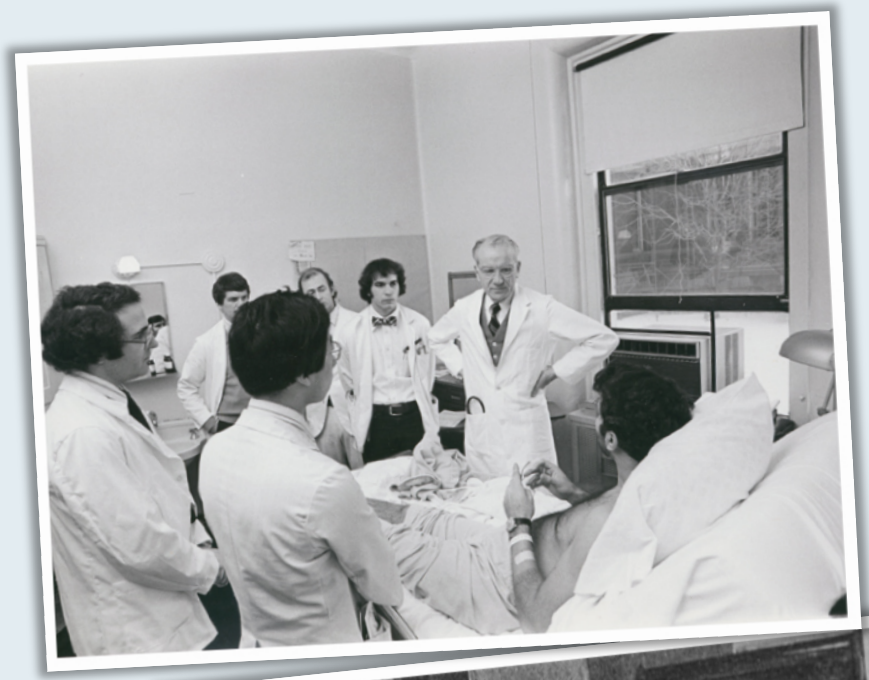
Wells A Messersmith, MD
University of Colorado Cancer Center
Aurora, Colorado

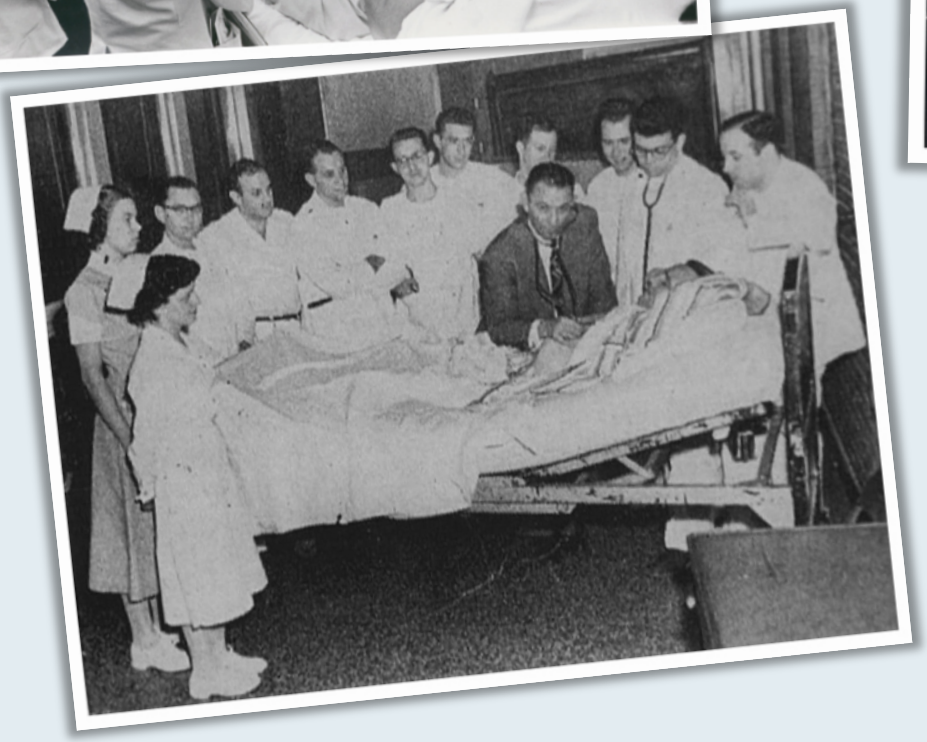


Philip A Philip, MD, PhD, FRCP
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan



Tammy Triglianos, RN, MS, ANP-BC, AOCNP
Lineberger Comprehensive Cancer Center
The University of North Carolina Division of Oncology
Chapel Hill, North Carolina

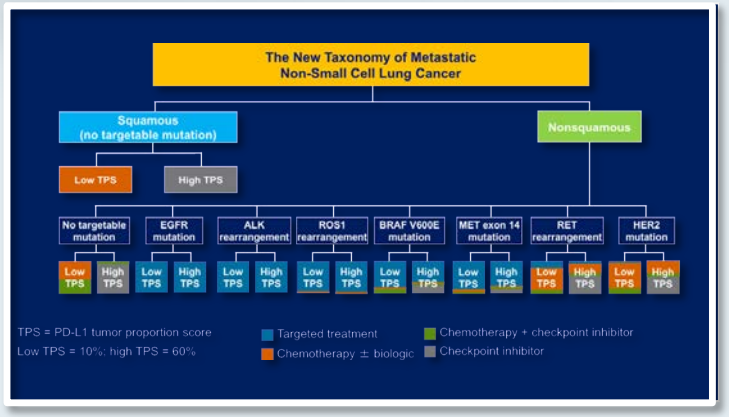


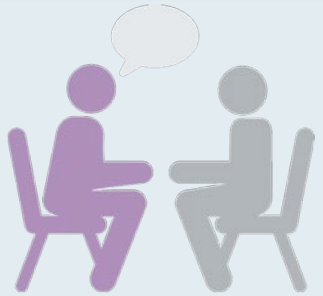



The Birmingham News

Oncology Grand Rounds: Format

- **Personalized oncology strategy**
  - New markers and agents
- **Patient counseling and education as a component of that strategy**
  - Symptom management
- **Discussion of actual cases from nurse faculty**
  - The bond that heals; trust and integrity
  - Supporting family and loved ones





The Core Oncology Triad
Developing an Individualized Oncology Strategy

Day in the Life: NURSE 8

- 72 M, Lung cancer, Pemetrexed, carboplatin, Socioeconomic status
- 31 F, Benign hematology, transfusion exchange, Depression
- 72 F, AML and HCC, Pembrolizumab, Acceptance of disease
- 73 F, Mantle Cell Lymphoma, Study drug, Acceptance of disease
- 30 F, Breast cancer, AC, Young age
- 61 F, Colorectal cancer, completed FOLFOX, Language barrier
- 63 F, Multiple myeloma, Daratumumab, Language barrier
- 56 F, Head and neck cancer, Pembrolizumab, Socioeconomic status
- 79 F, Multiple myeloma, Surveillance, Culture
- 58 M, Multiple myeloma, Zoledronic acid, poor attitude
- 85 F, Ovarian cancer, will receive study drug, had multiple lines of therapy

Day in the Life: NURSE 8

- 80 F, AML and Lung cancer, Pembrolizumab, venetoclax, azacitidine, family support
- 70 F, Lung cancer, Pemetrexed/carbo/pembrolizumab, Acceptance of disease
- 37 F, Benign hematology, Opioid addiction
- 26 F, Hodgkin lymphoma, Nivolumab, Family support
- 63 M, Colorectal cancer, Surveillance, Socioeconomic status
- 91 M, Myeloproliferative neoplasm, Surveillance, ETOH use
- 31 M, Testicular cancer, Surveillance, Anxiety/depression
- 67 F, Multiple myeloma, Bortezomib, Positive outlook
- 50 F, Breast cancer, AC, Family support

Agenda

Module 1: Up-Front Management of Advanced Hepatocellular Carcinoma (HCC)

- IMbrave150: Atezolizumab plus bevacizumab versus sorafenib in unresectable HCC
  ESMO Asia 2019, November 23, 2019

Module 2: Current Clinical Algorithms for Patients with Metastatic Colorectal Cancer (mCRC)

- Clinical implications of tumor sidedness, MSI status, RAS and BRAF in mCRC

Module 3: Sequencing of Systemic Therapy in Patients with Metastatic Gastric Cancer

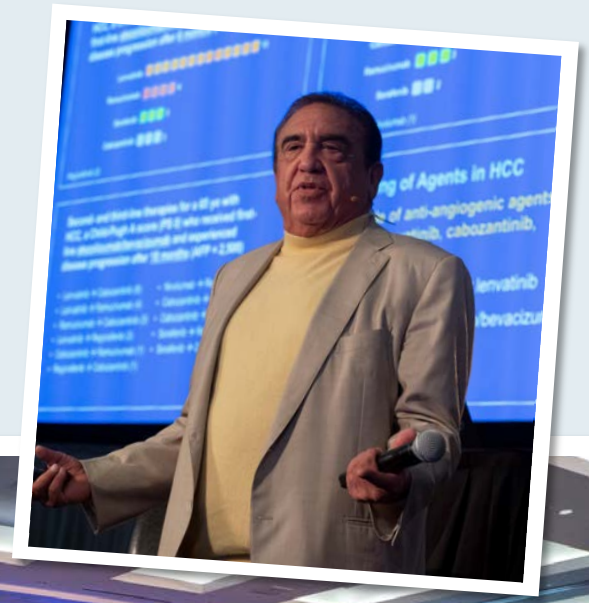
- Impact of MSI status, PD-L1 level and HER2 status on treatment choice

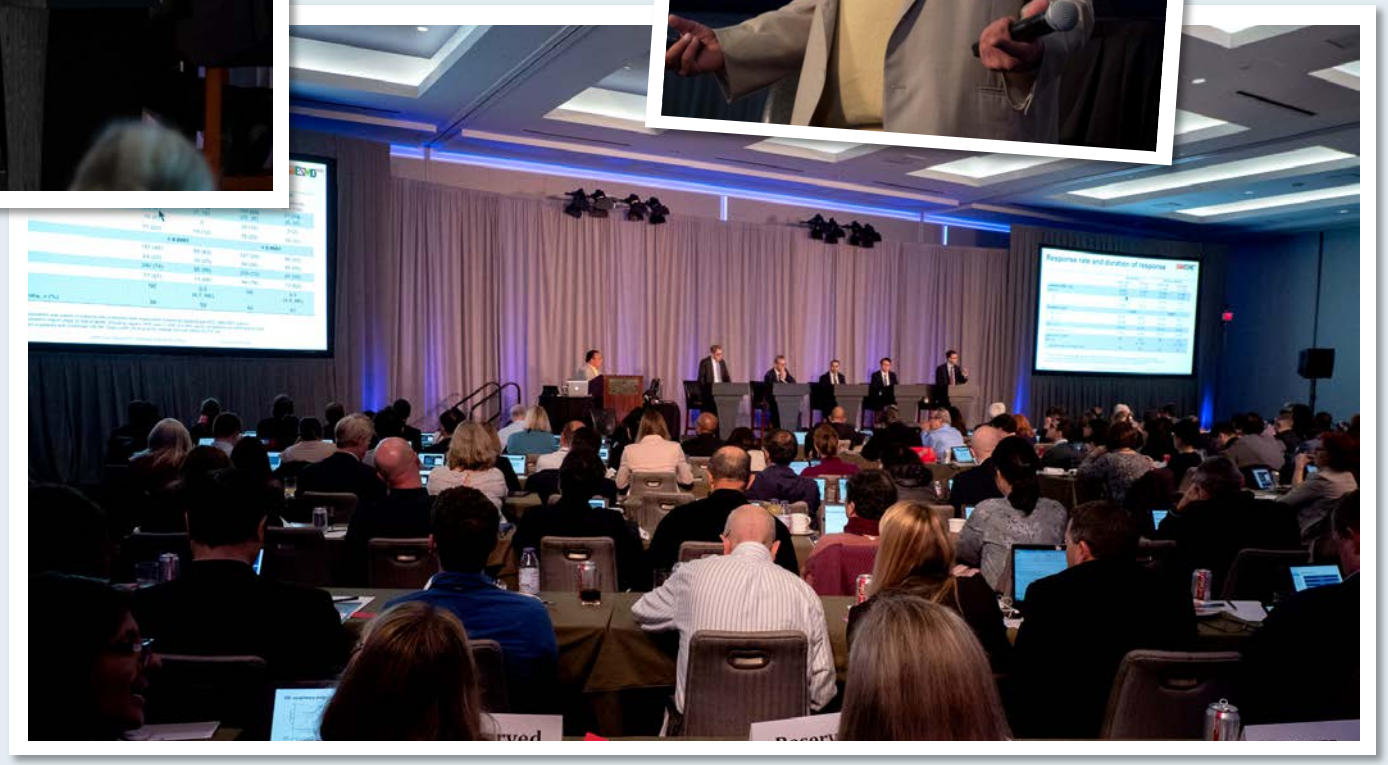
Module 4: Management of Gastrointestinal Cancers in the Era of COVID-19

- Telemedicine, minimization of surgeries, reduced infusions and clinic visits

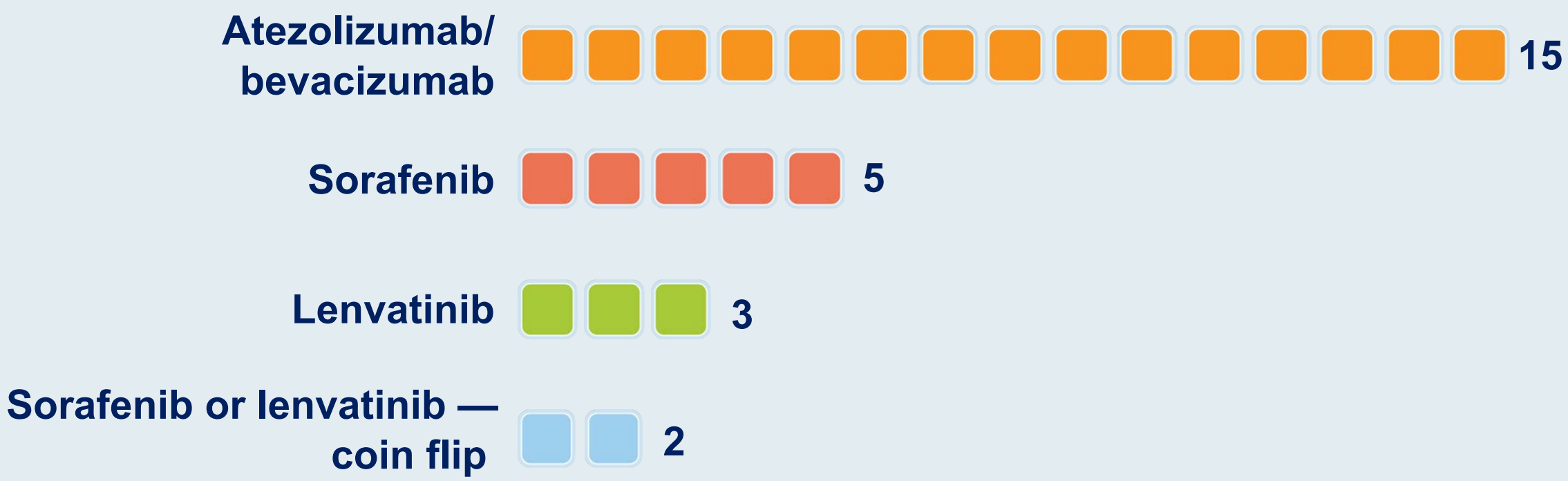
Module 1: Up-Front Management of Advanced Hepatocellular Carcinoma (HCC)

- IMbrave150: Atezolizumab plus bevacizumab versus sorafenib in unresectable HCC. ESMO Asia 2019, November 23, 2019

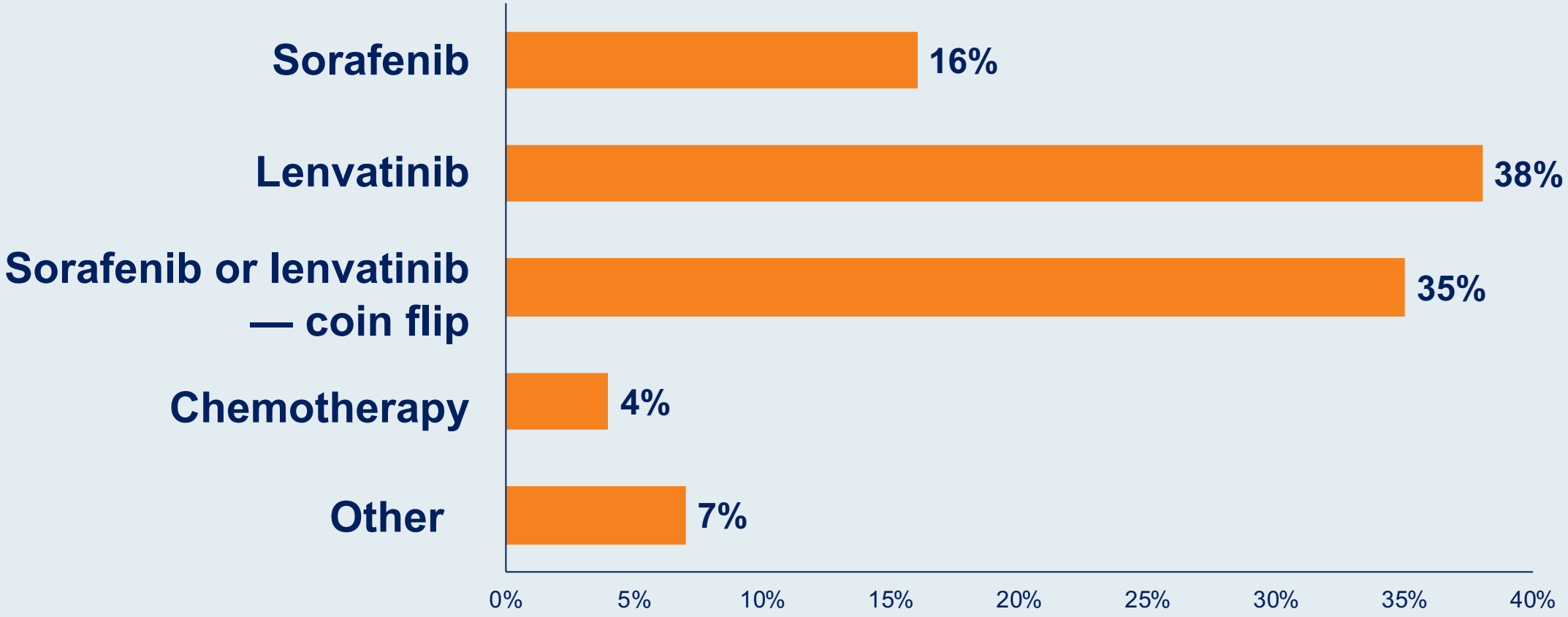




Regulatory and reimbursement issues aside, what would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1?



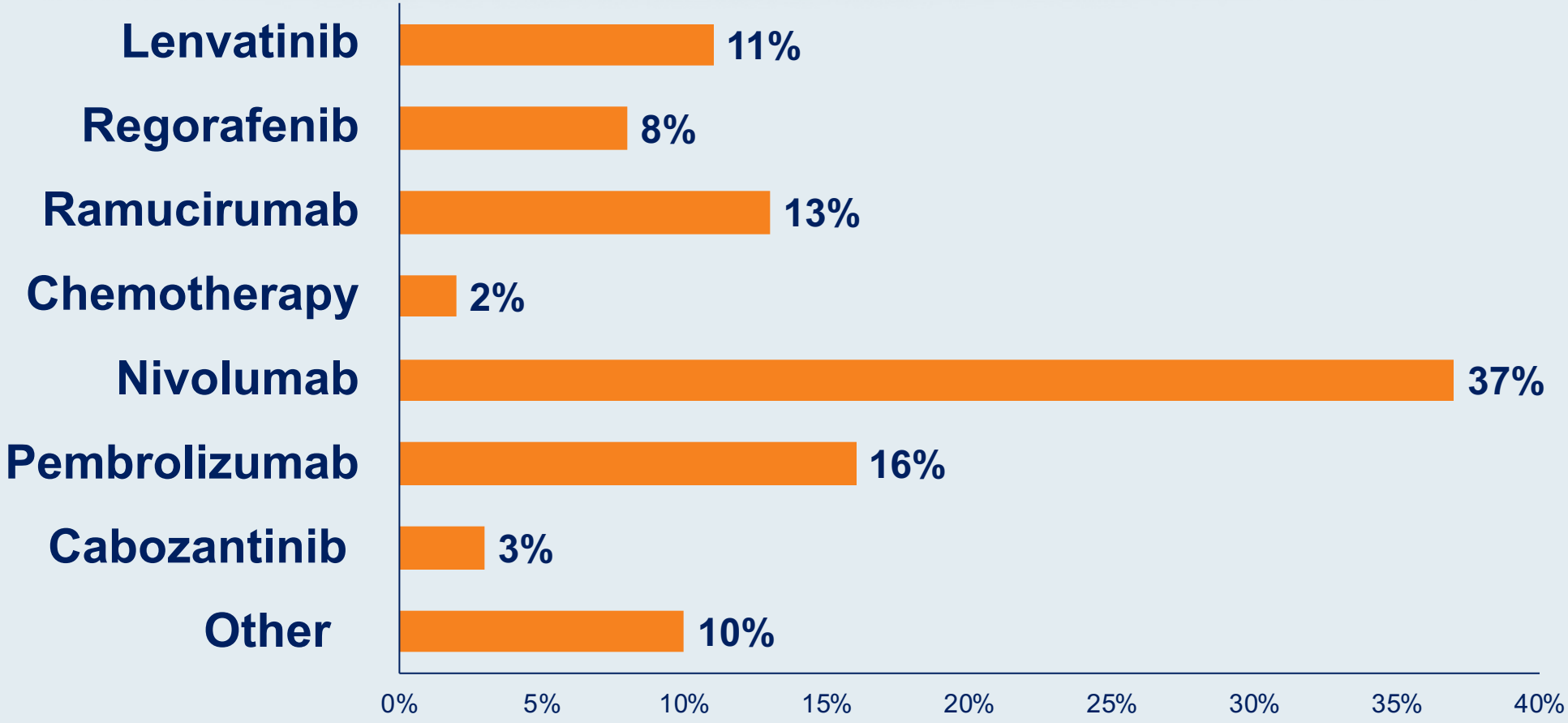
What would be your most likely first-line systemic treatment for a 65-year-old patient with hepatocellular carcinoma (HCC), a Child-Pugh B score and a performance status (PS) of 1?



Year in Review, Orlando FL, October 26, 2019

Regulatory and reimbursement issues aside, what would be your second-line therapy for a 65 yo with HCC, a Child-Pugh A score and a PS of 0 who received first-line sorafenib, had stable disease for 14 months and experienced disease progression (AFP = 2,500)?

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0 who received first-line standard-dose sorafenib with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP = 2,500)?



Year in Review, Orlando FL, October 26, 2019

In addition to sorafenib, what is the other FDA-approved first-line systemic treatment for advanced hepatocellular carcinoma (HCC)?

a. Regorafenib

b. Lenvatinib

c. Ramucirumab

d. An anti-PD-1/PD-L1 antibody

e. I don’t know

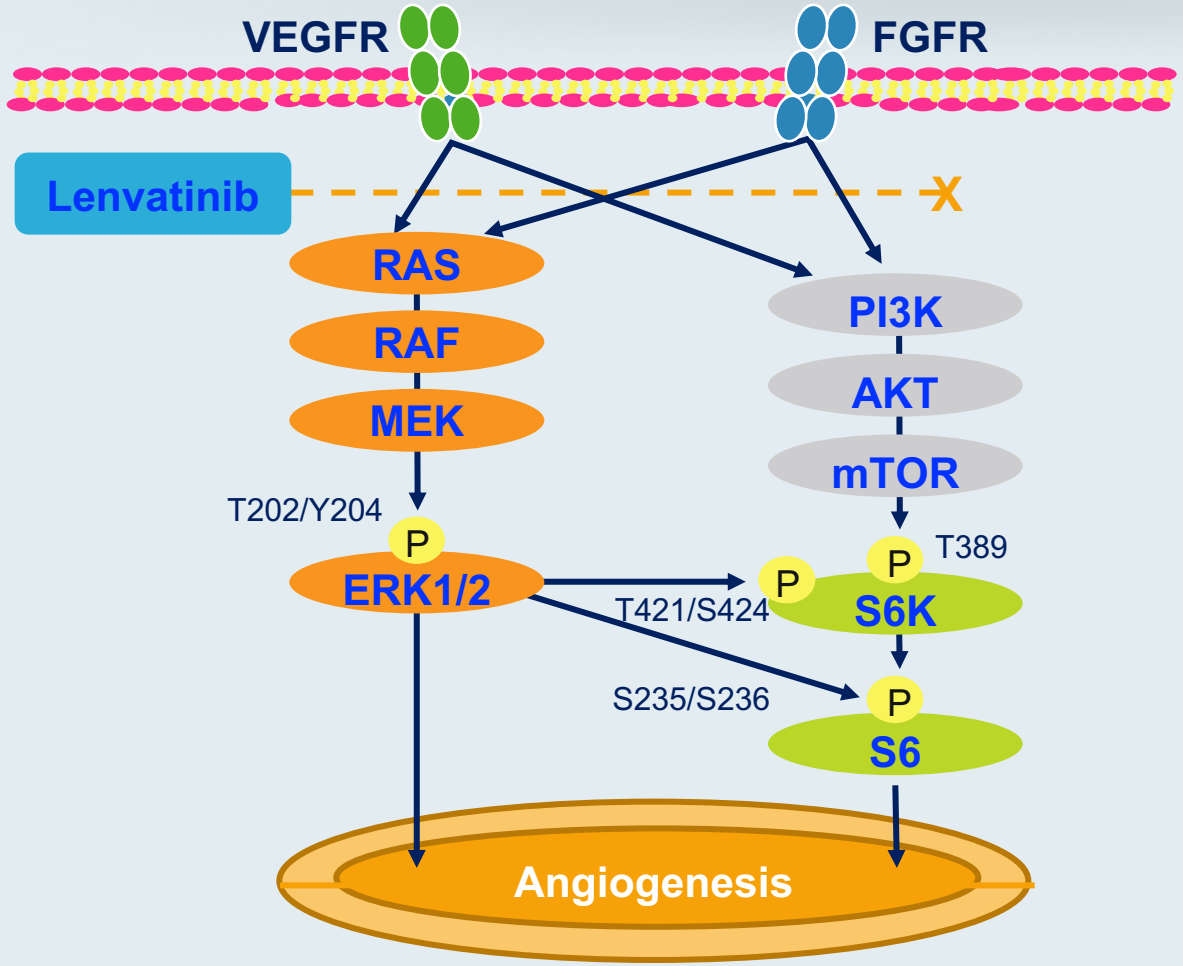
The combination of atezolizumab and bevacizumab as first-line therapy for patients with advanced hepatocellular cancer has been shown in a Phase III trial to result in improved overall survival and quality-of-life outcomes when compared to sorafenib.

a. I agree

b. I disagree

c. I don’t know

Mechanism of Action of Lenvatinib



- Orally available inhibitor of multiple tyrosine kinases including VEGF receptors, FGFR, RET, PDGFR and KIT
- Demonstrated promising radiographic response rates and survival results in Phase II and III trials in HCC

Finn RS et al. *Proc ASCO* 2014;Abstract TPS4153; Stjepanovic N et al. *Biologics* 2014;8:129-39; Cheng AL et al. *Proc ASCO* 2017;Abstract 4001; Ikeda K et al. *J Gastroenterol* 2017;52(4):512-9.

Lenvatinib

Mechanism of action

- Oral multikinase inhibitor

Indication

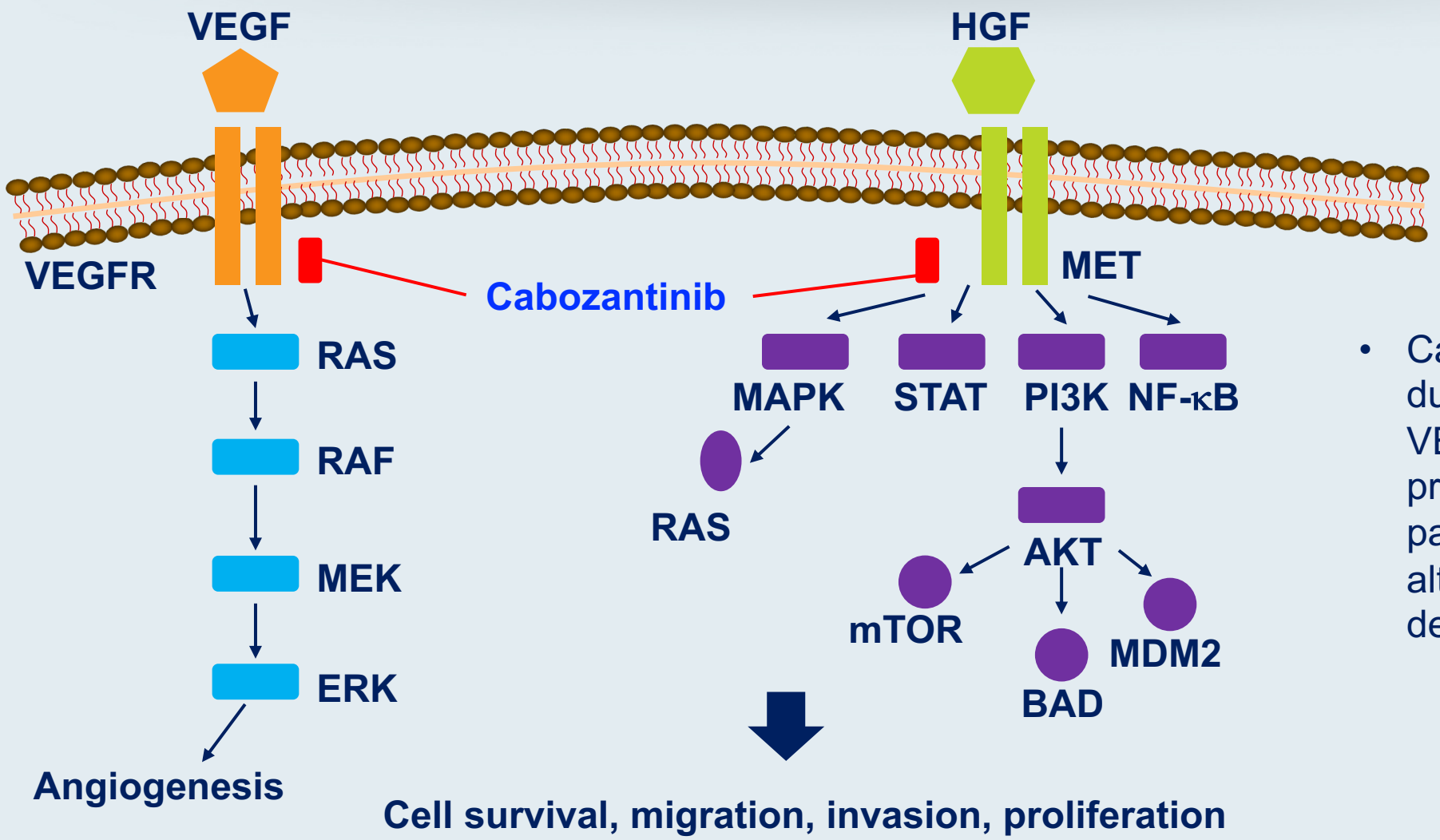
- For patients with unresectable hepatocellular carcinoma as first-line therapy

Recommended dose

- 12 mg orally once daily in patients 60 kg or greater actual body weight
- 8 mg orally once daily in patients less than 60 kg actual body weight

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma

Mechanism of Action of Cabozantinib



- Cabozantinib provides dual inhibition of MET and VEFGR2, thereby preventing the MET pathway from acting as an alternative pathway in the development of VEGF

Cabozantinib

Mechanism of action

- Oral multikinase inhibitor

Indication

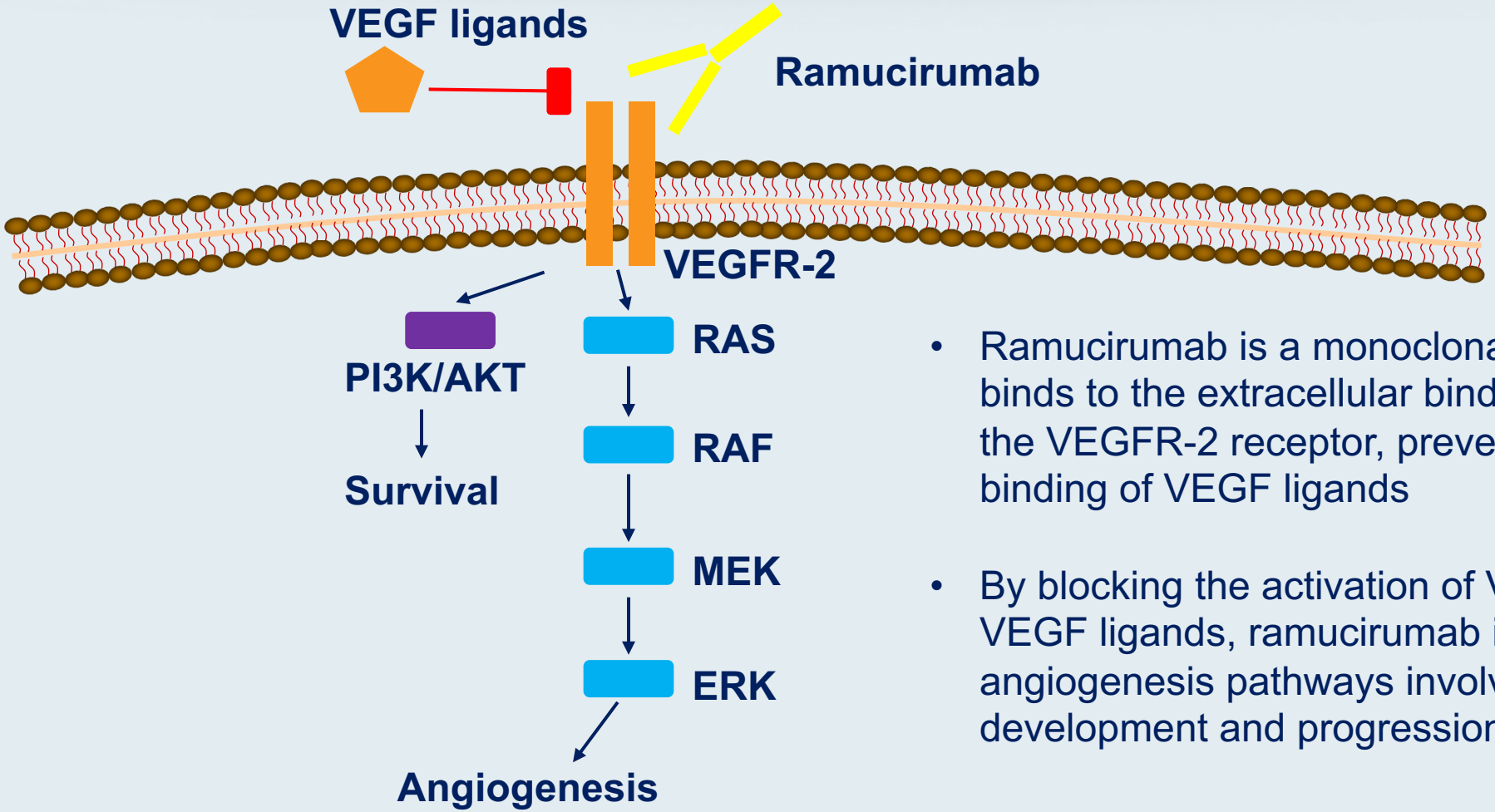
- For patients with unresectable hepatocellular carcinoma as first-line therapy

Recommended dose

- 60 mg once daily without food until disease progression or unacceptable toxicity

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma

Mechanism of Action of Ramucirumab



- Ramucirumab is a monoclonal antibody that binds to the extracellular binding domain of the VEGFR-2 receptor, preventing the binding of VEGF ligands
- By blocking the activation of VEGFR-2 by VEGF ligands, ramucirumab inhibits the angiogenesis pathways involved in the development and progression of cancer

Ramucirumab

Mechanism of action

- Anti-VEGFR2 monoclonal antibody

Indication

- Single agent for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥400 ng/mL and have received sorafenib

Dose/schedule

- 8 mg/kg every 2 weeks

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125477s029lbl.pdf; Ramucirumab package insert.

Atezolizumab/Bevacizumab Regimen

Mechanism of action

- PD-L1 inhibitor
- Anti-VEGF monoclonal antibody

Indication

- Investigational

Phase III study dose

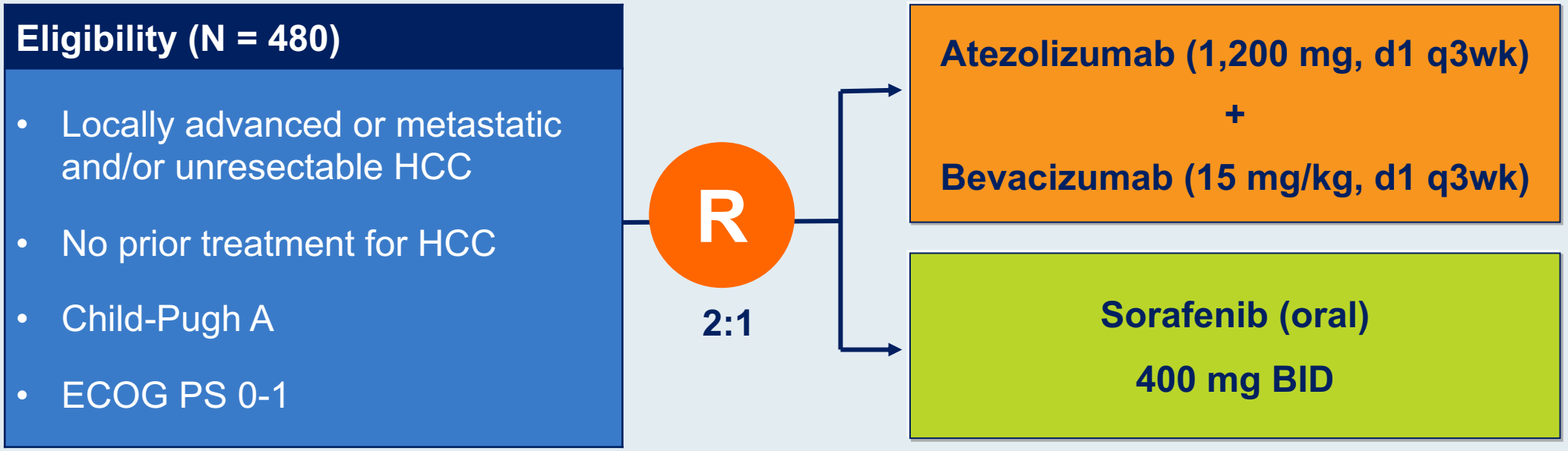
- Atezolizumab: 1,200 mg every 3 weeks
- Bevacizumab: 15 mg/kg every 3 weeks

Key Toxicities

- Grade 3/4 hypertension: 15%

Finn RS et al. *N Engl J Med* 2020;382(20):1894-905.

IMbrave150: A Phase III Trial of Atezolizumab/Bevacizumab



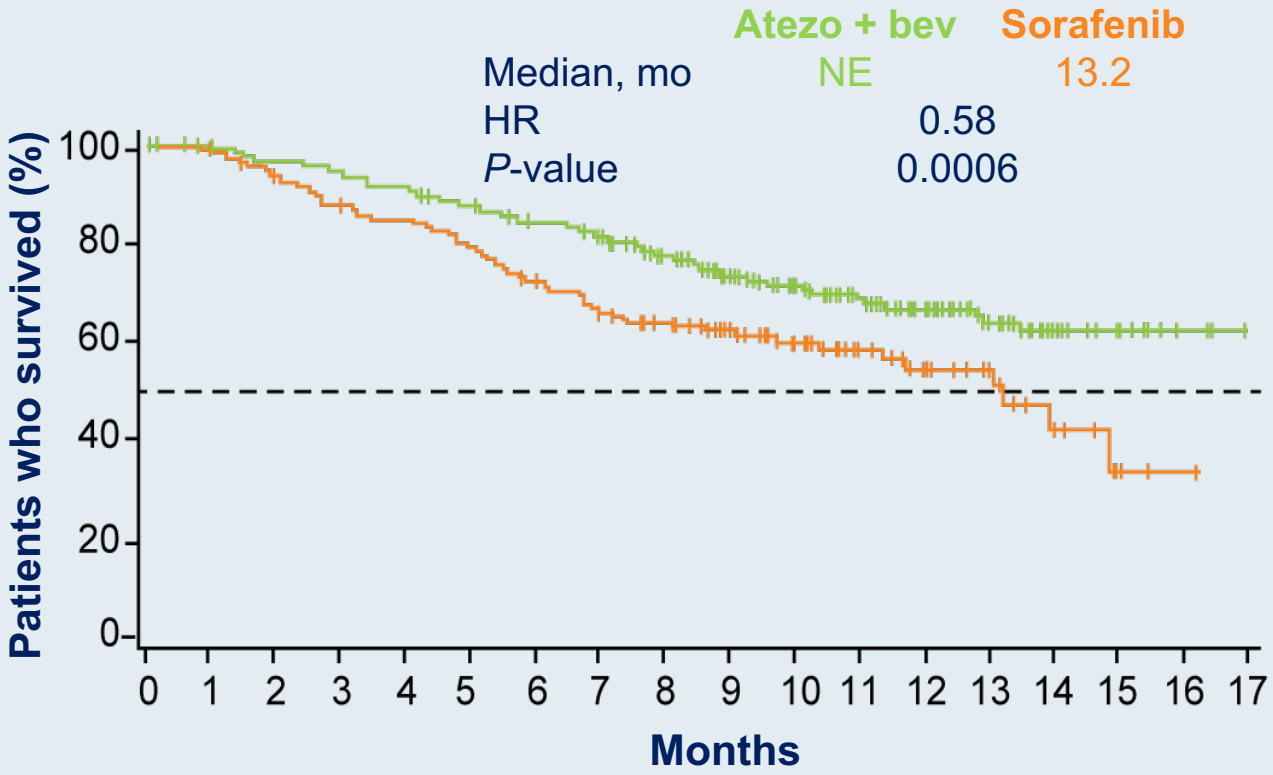
Primary endpoints: Overall survival and progression-free survival

Key secondary endpoints include: Objective response, duration of response and quality of life

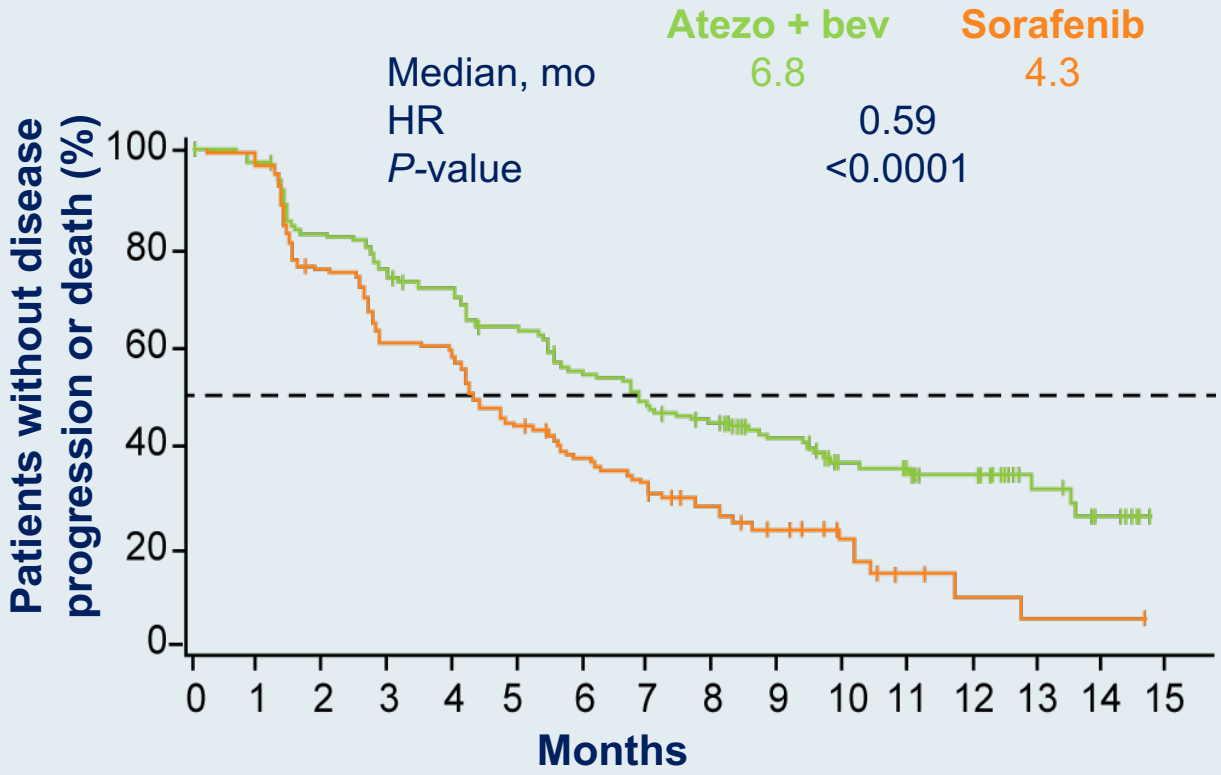
Clinicaltrials.gov; Accessed May 2020.

IMbrave150: Co-Primary Endpoints (OS and PFS)

OS



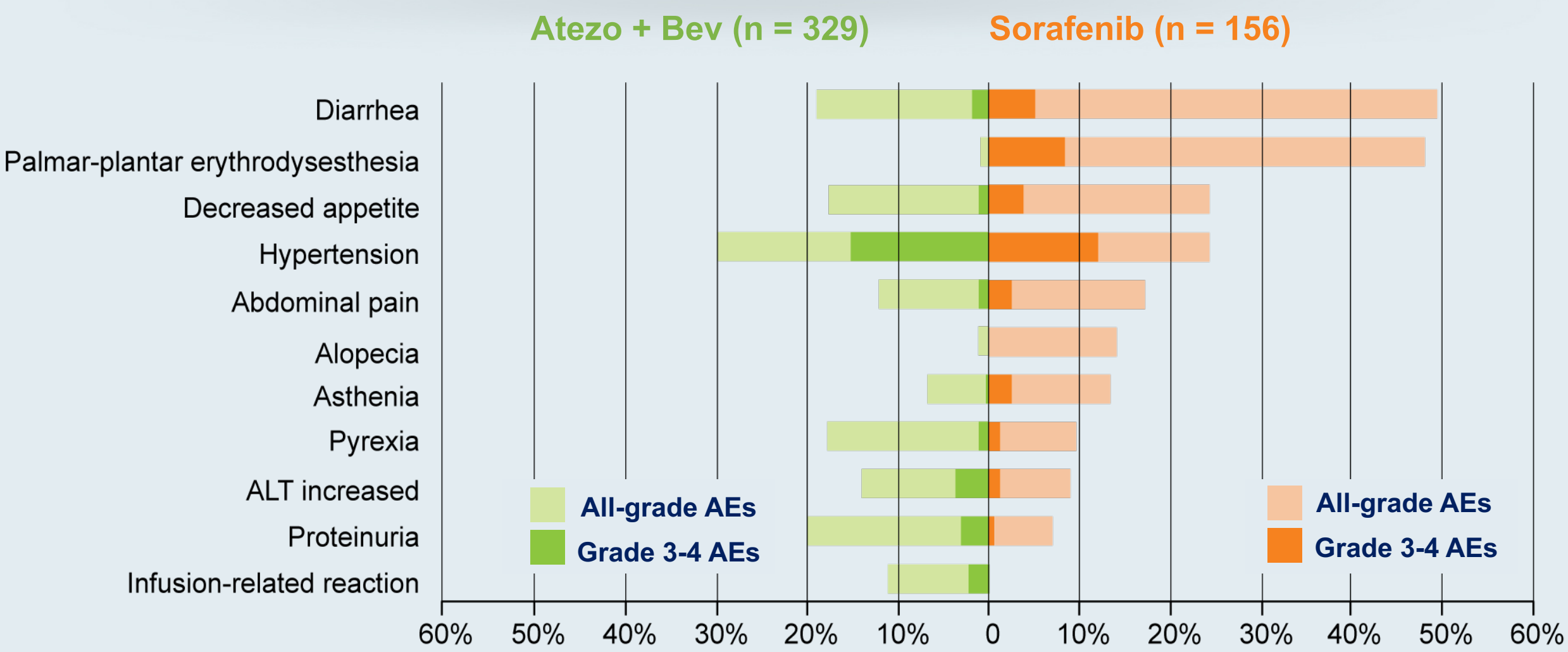
PFS (IRF assessed RECIST 1.1)



- Study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS with atezolizumab/bevacizumab

Galle PR et al. Gastrointestinal Cancers Symposium 2020;Abstract 476

IMbrave150: Safety Results



Galle PR et al. Gastrointestinal Cancers Symposium 2020;Abstract 476

Press Release: Supplemental Biologics License Application to the FDA for Atezolizumab/Bevacizumab for Untreated HCC — January 27, 2020

A supplemental Biologics License Application has been submitted to the FDA for atezolizumab in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy. The FDA is reviewing the application under the Real-Time Oncology Review pilot program, which aims to explore a more efficient review process to ensure safe and effective treatments are available to patients as early as possible.

In July 2018, the FDA granted Breakthrough Therapy Designation for atezolizumab in combination with bevacizumab in HCC based on data from an ongoing Phase Ib trial.

This application is based on the results of the Phase III IMbrave150 study, which demonstrated that atezo/bev reduced the risk of death (OS) by 42% (HR = 0.58; $p = 0.0006$) and reduced the risk of disease worsening or death (PFS) by 41% (HR = 0.59; $p < 0.0001$), compared with sorafenib. Safety for atezo/bev was consistent with the known safety profiles of the individual agents.

https://www.roche.com/media/releases/med-cor-2020-01-27.htm

Press Release: FDA Grants Accelerated Approval to Nivolumab and Ipilimumab Combination for HCC — March 10, 2020

On March 10, 2020, the Food and Drug Administration granted accelerated approval to the combination of nivolumab and ipilimumab for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Efficacy of the combination was investigated in Cohort 4 of CheckMate-040, (NCT01658878) a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. A total of 49 patients received nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

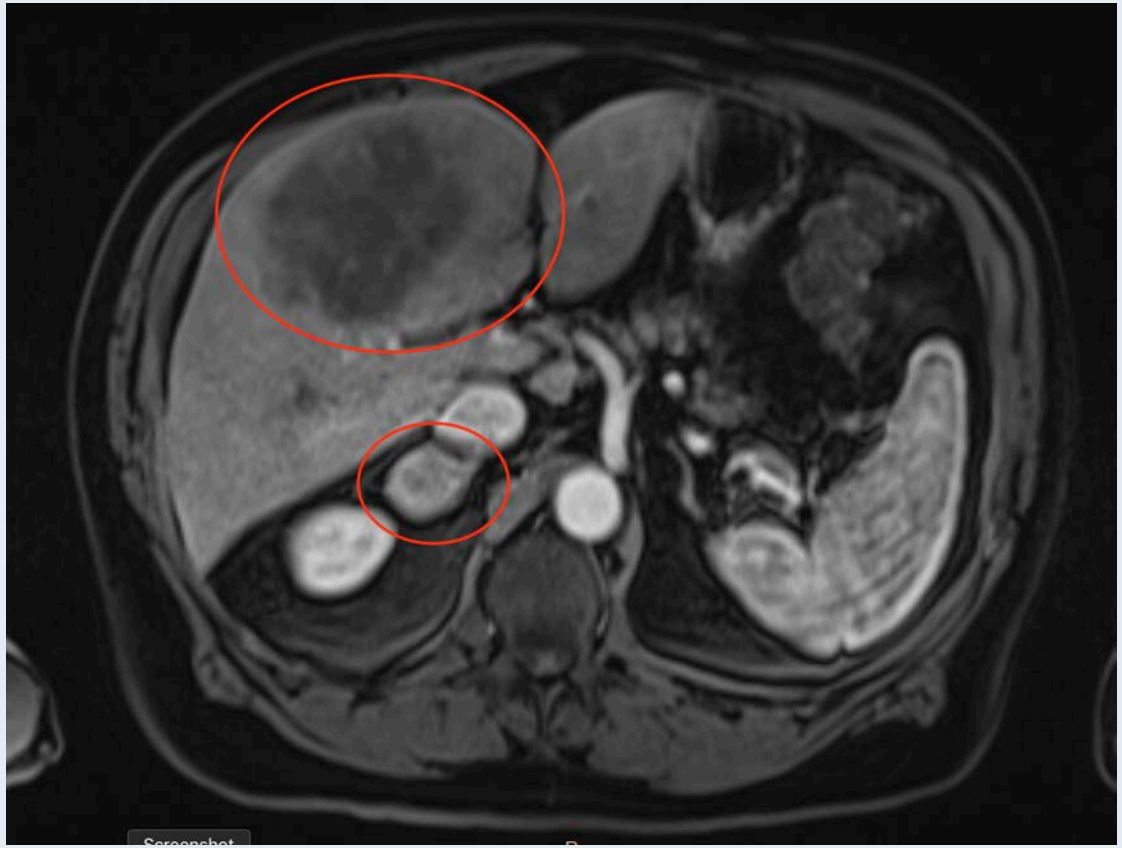
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma

63-year-old previously healthy, active man (from the practice of Ms Triglianos)

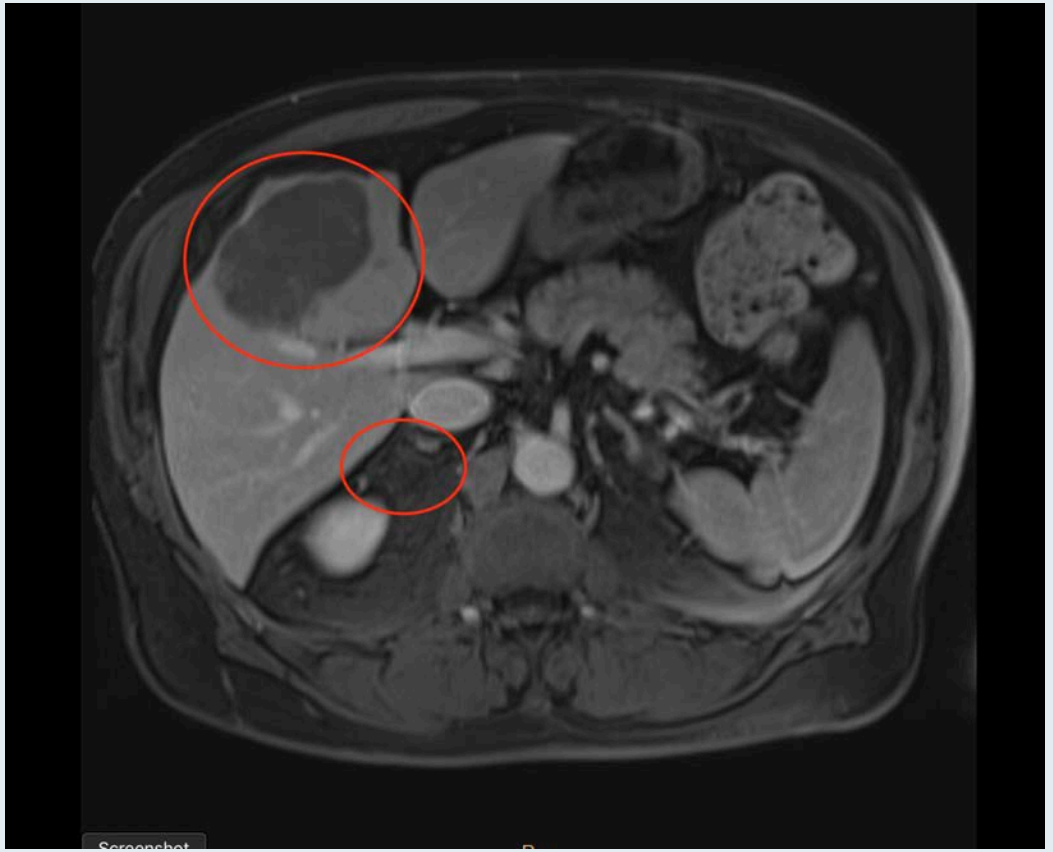
- 2018: Presented to ER with RUQ abdominal pain (CT scan: large liver mass)
  - Hepatitis C (eventually treated with ledipasvir-sofosbuvir)
  - Poorly differentiated 10-cm hepatic and 4.5-cm adrenal adenocarcinoma consistent with HCC (AFP: 193, Ca 19-9 < 1.4)
- 7/2018: Clinical trial (GO30140): Atezolizumab + bevacizumab
  - 11/2018: Decreasing liver and adrenal lesions
  - 10/2019: Stable dominant liver lesion, slight increase in a satellite lesion, adrenal lesion no longer visible
- Hepatectomy, right adrenalectomy
- Bevacizumab discontinued due to proteinuria
- Currently, off therapy on active surveillance every 3 months

63-year-old man (from the practice of Ms Triglianos)

Prior to Atezolizumab/bevacizumab



After Atezolizumab/bevacizumab



63-year-old man with metastatic hepatocellular cancer (from the practice of Ms Triglianos)

Patient education

- Review of side effects of immunotherapy:
  - diarrhea/intestinal issues (colitis)
  - skin reactions/rash or other skin changes/mouth sores
  - lung problems/SOB/cough (pneumonitis)
  - liver problems/yellowing of eyes, bleeding, abd pain (hepatitis)
  - hormone abnormalities (pituitary, thyroid, pancreas, adrenal glands)
  - headaches, nausea/vomiting, rapid heart rate, extreme fatigue, excessive thirst or urination, hair loss, changes in mood
  - brain (encephalitis) – headaches, vision changes, weakness, drooping of eyelids
  - other teaching points: Avoid systemic steroids for nonimmune-related side effects
- Review side effects of bevacizumab:
  - hypertension, proteinuria, increased risk of bleeding / thrombosis and rare risk of intestinal perforation

Module 2: Current Clinical Algorithms for Patients with Metastatic Colorectal Cancer (mCRC)

- Clinical implications of tumor sidedness, MSI status, RAS and BRAF in mCRC

Patients with RAS wild-type metastatic colon cancer generally do not receive an EGFR antibody as part of first-line therapy if their tumor originates on…

a. The left side

b. The right side

c. I don’t know

Patients with metastatic colorectal cancer and a BRAF V600E tumor mutation do not generally respond to targeted treatment with regimens that contain a BRAF inhibitor and an EGFR antibody.

a. Agree

b. Disagree

c. I don’t know

Which of the following regimens recently received FDA approval for the treatment of metastatic colorectal cancer with a BRAF V600E mutation?

a. Dabrafenib/trametinib

b. Vemurafenib/cobimetinib

c. Encorafenib/cetuximab

d. Encorafenib/binimetinib/cetuximab

e. I don’t know

Which of the following descriptions best reflects the mechanism of action of TAS-102?

a. Anti-angiogenic agent

b. PI3 kinase inhibitor

c. Novel antimetabolite/chemotherapy agent

d. Antibody-drug conjugate

e. I don’t know

Patients with metastatic colorectal cancer who experience neutropenia while receiving TAS-102…

a. Have a better clinical response rate than those who do not experience neutropenia

b. Have the same clinical response rate as those who do not not experience neutropenia

c. Have a worse clinical response rate than those who do not experience neutropenia

d. I don’t know

e. I am not familiar with this agent

Based on your clinical experience, how would you compare the tolerability of TAS-102 to that of regorafenib for patients with metastatic colorectal cancer?

a. About the same

b. TAS-102 is more tolerable

c. Regorafenib is more tolerable

d. I don’t know

e. I have not used these agents

Patients with microsatellite instability (MSI)-high/mismatch repair-deficient metastatic cancers have been shown to have a high rate of response to…

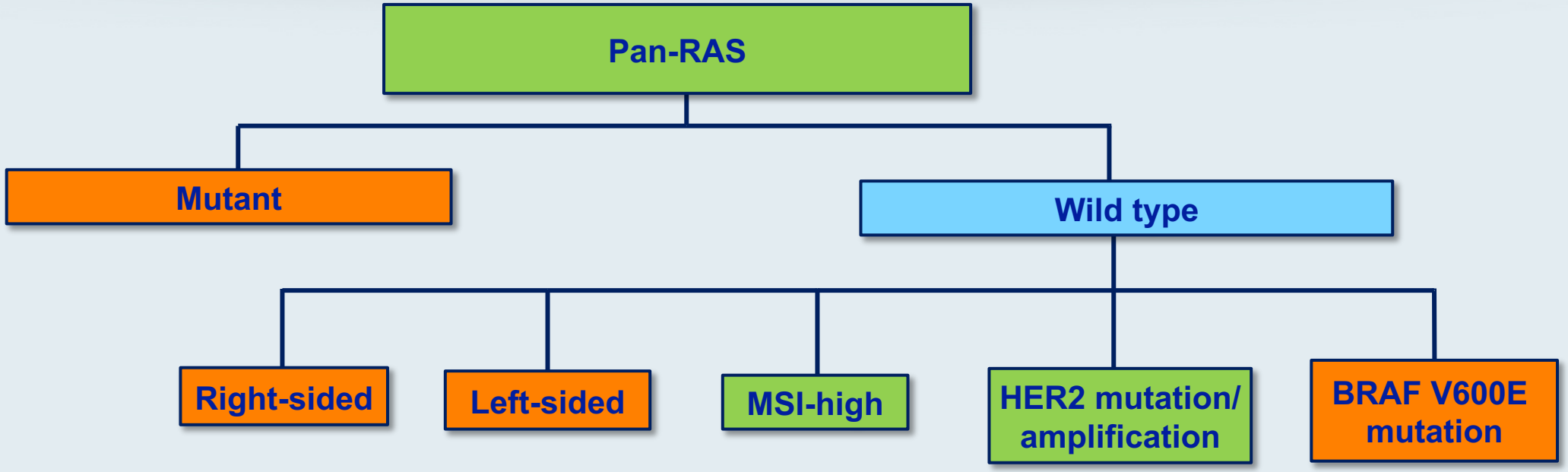
a. EGFR antibodies

b. Bevacizumab

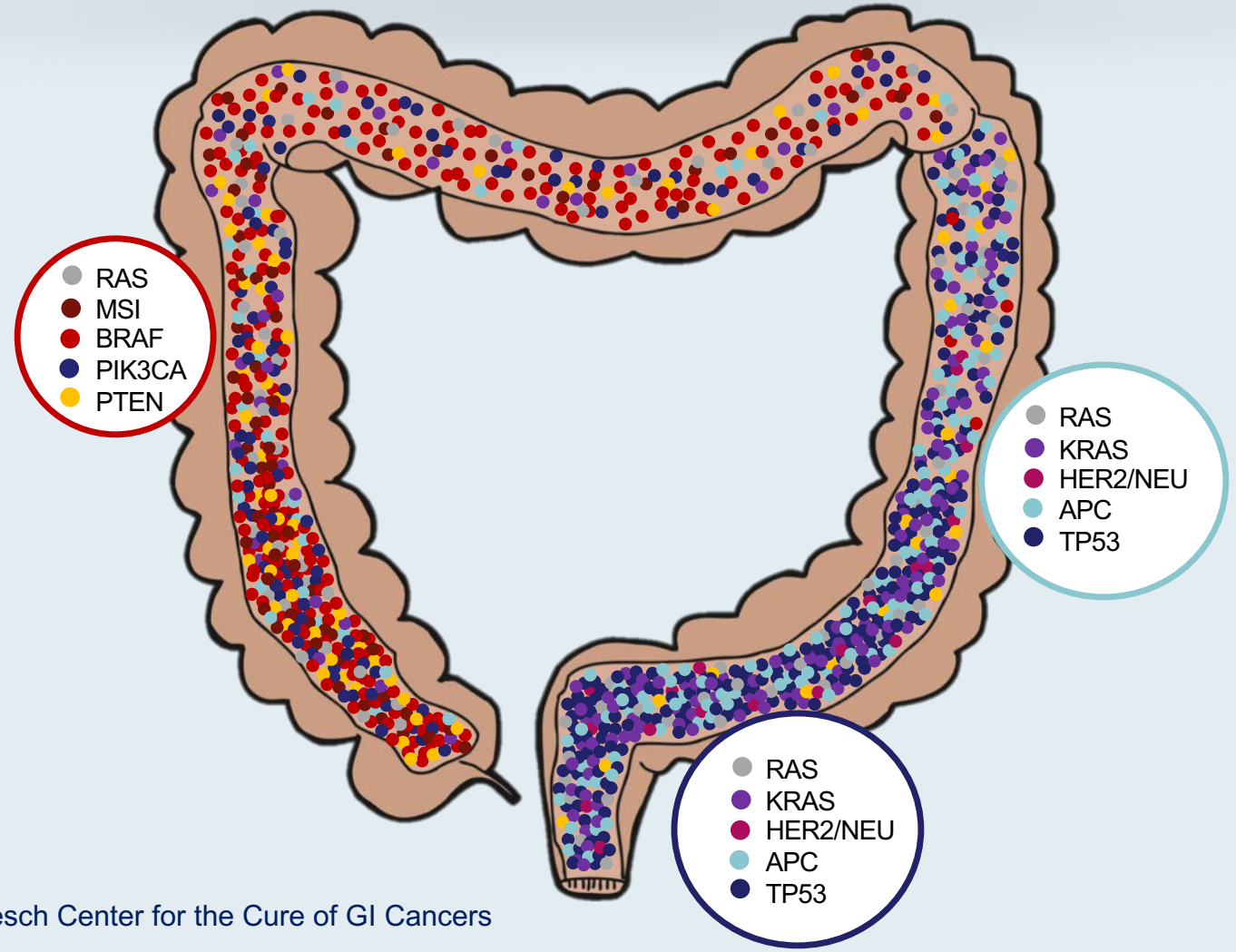
c. Immune checkpoint inhibitors

d. I don’t know

Incurable Metastatic Colorectal Cancer Treatment Subsets



Tumor Sidedness Associated with Genetic Alterations

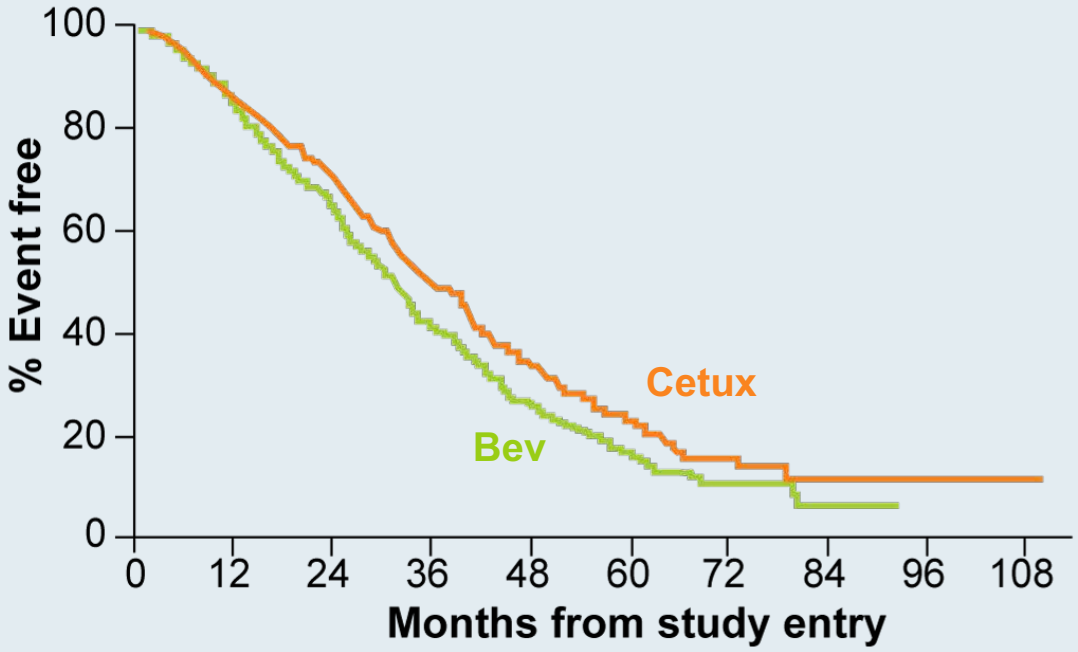


Venook A et al. *Proc ASCO* 2016;Abstract 3504.

CALGB/SWOG 80405: Overall Survival by Biologic Agent and Primary Tumor Sidedness

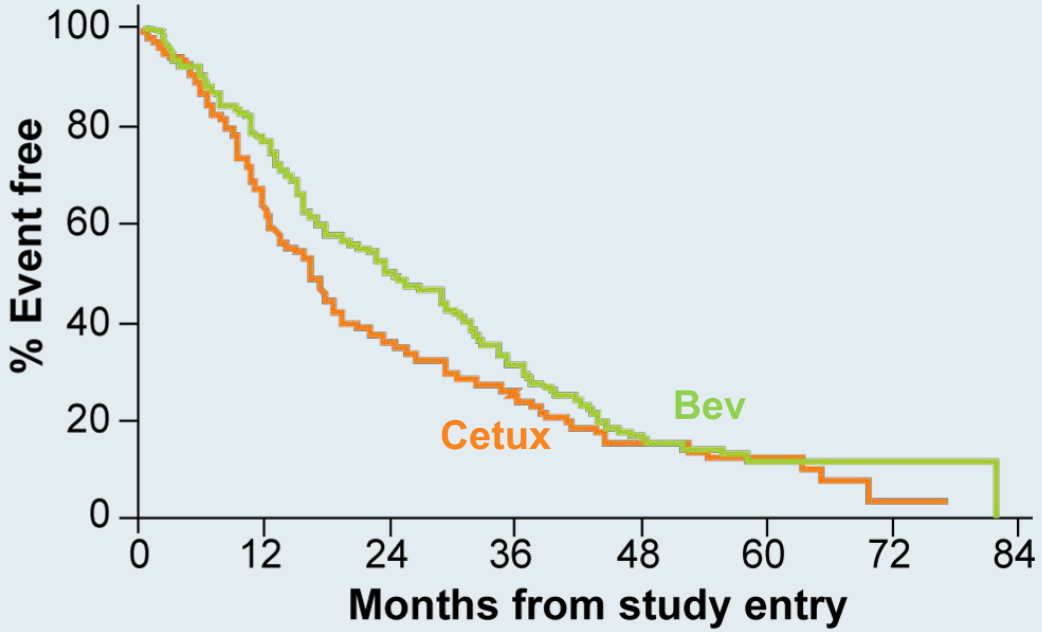
Left-sided primary

Agent	N	Median	HR	*p*-value
Bev	356	31.4	0.817	0.018
Cetux	376	36.0		



Right-sided primary

Agent	N	Median	HR	*p*-value
Bev	150	24.2	1.269	0.065
Cetux	143	16.7		



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CALGB/SWOG 80405: Overall Survival by Biologic Agent and Primary Tumor Sidedness

Left-sided primary

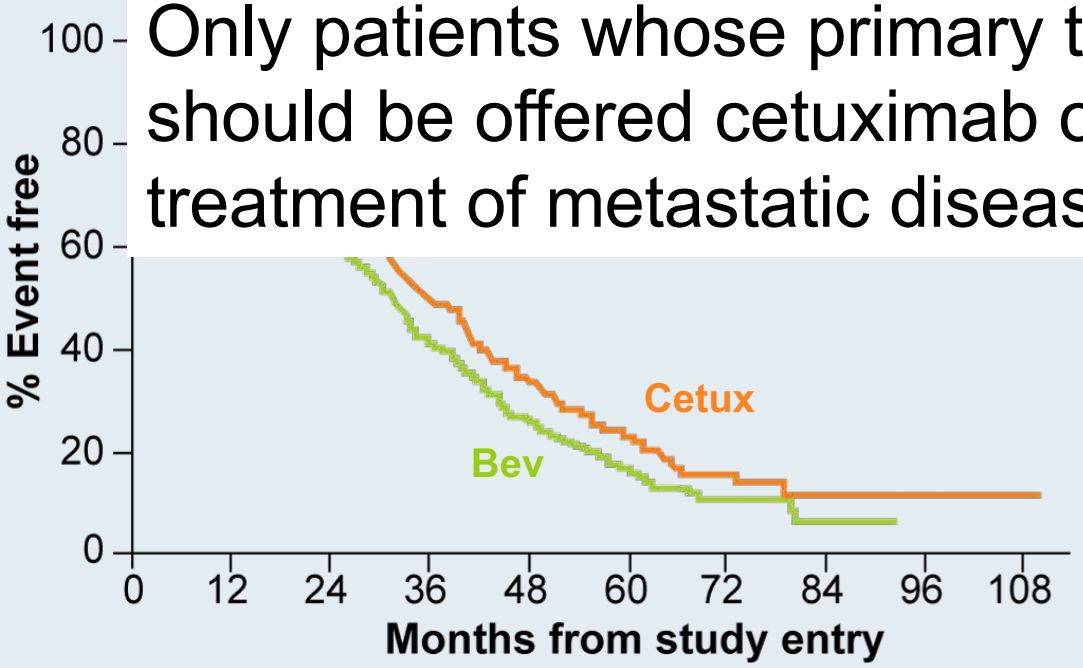
Agent	N	Median	HR	*p*-value

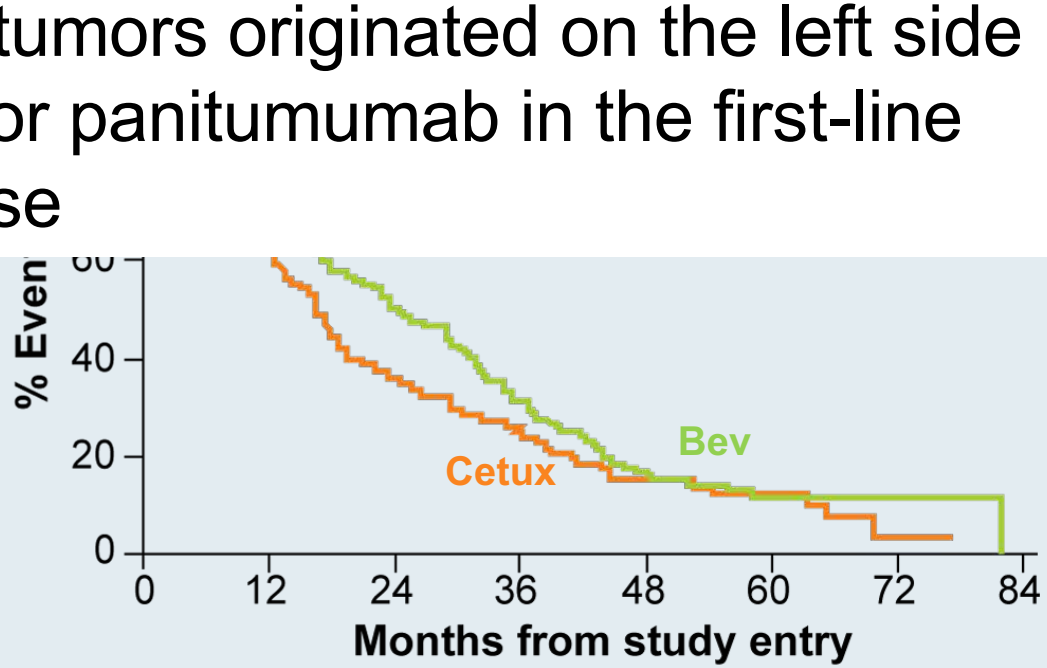
Right-sided primary

Agent	N	Median	HR	*p*-value

NCCN Guidelines:

Only patients whose primary tumors originated on the left side should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease





Venook A et al. *Proc ASCO* 2016;Abstract 3504.

TAS-102

Mechanism of action

- Combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor

Indication

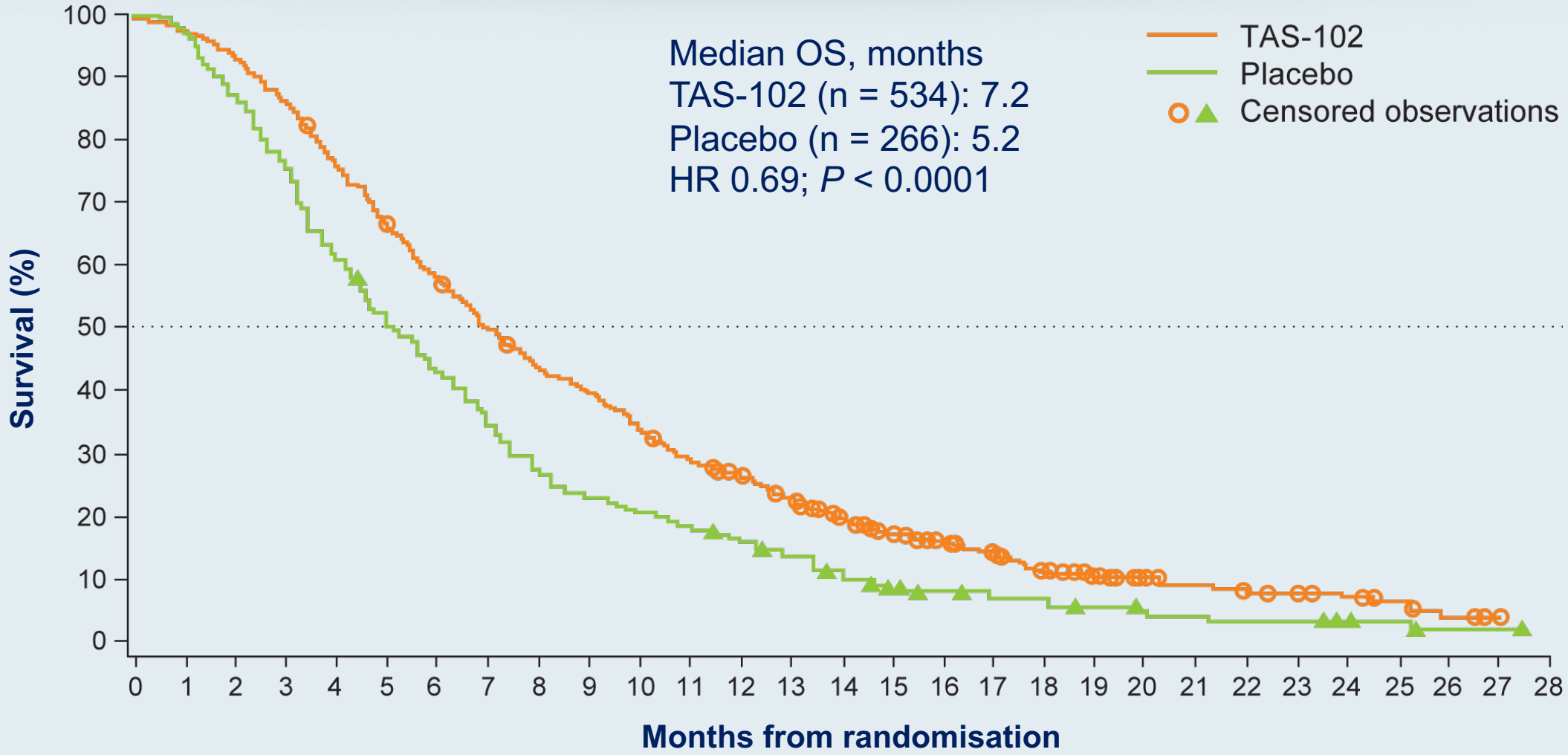
- For patients with mCRC who have previously received fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biologic product and an anti-EGFR therapy, if RAS wild type

Recommended dose

- 35 mg/m^2 per dose PO twice daily on days 1 through 5 and days 8 through 12 of each 28-day cycle

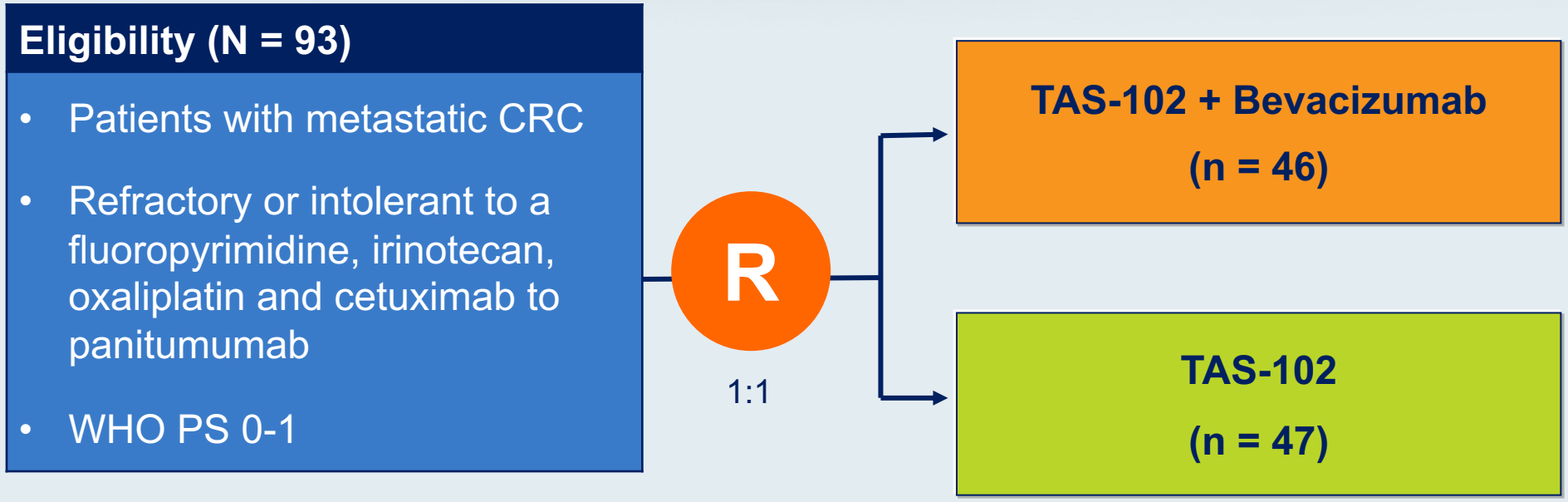
http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm463743.htm
TAS-102 package insert

RECOURSE: Final Overall Survival with TAS-102 versus Placebo



Van Cutsem E et al. *Eur J Ca* 2018;90:62-72.

A Phase II Trial of TAS-102 and Bevacizumab

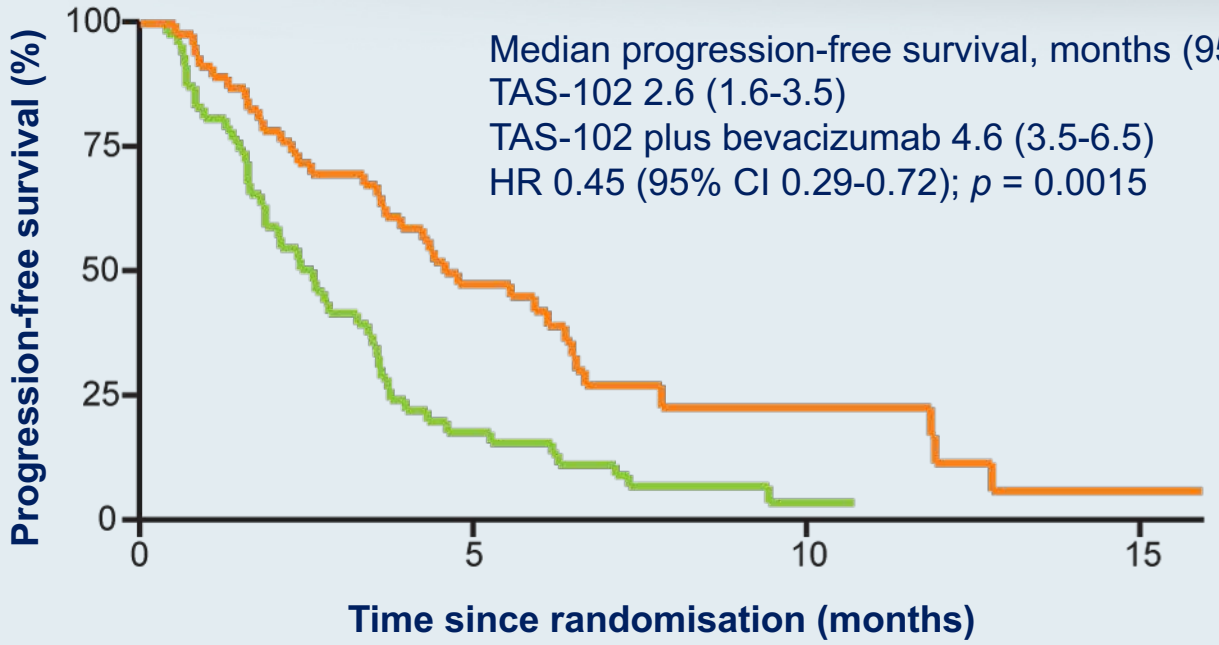


Primary endpoint: Investigator-assessed progression-free survival

Key secondary endpoints include: Overall survival, response rate, toxicity and tumor markers

Pfeiffer P et al. *Lancet Oncol* 2020;21(3):412-20.

TAS-102 +/- Bevacizumab: Efficacy Results



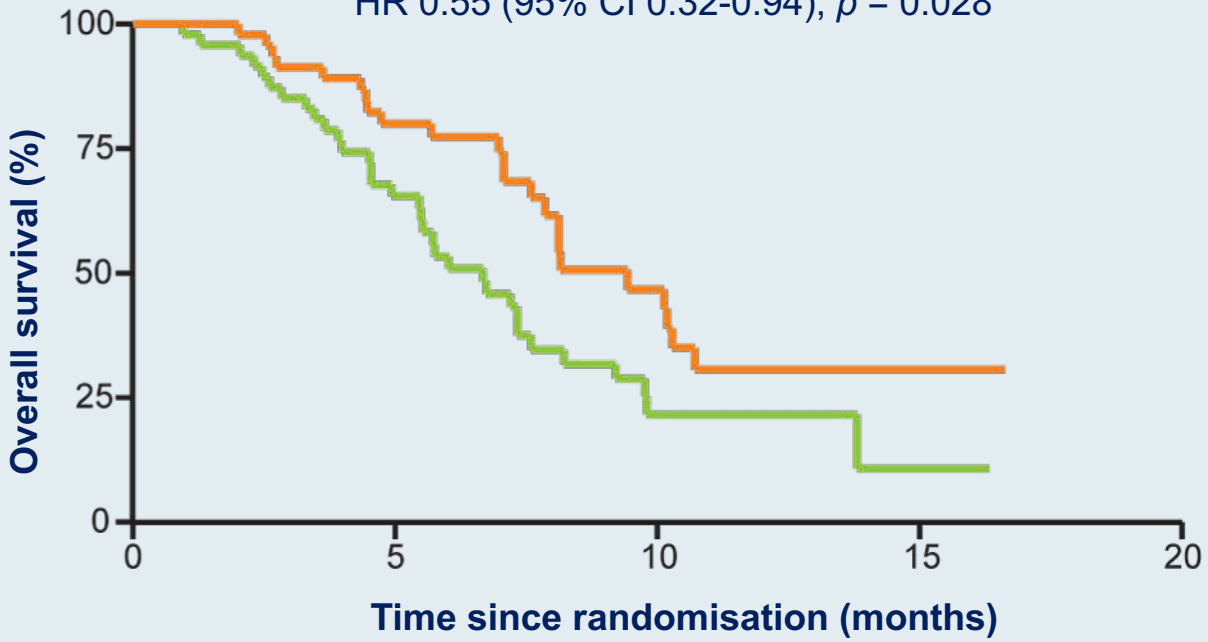
Median progression-free survival, months (95% CI)
TAS-102 2.6 (1.6-3.5)
TAS-102 plus bevacizumab 4.6 (3.5-6.5)
HR 0.45 (95% CI 0.29-0.72); *p* = 0.0015

Disease control rate:

- TAS-102/Bev = 67%
- TAS-102 = 51%

TAS-102
TAS-102 plus bevacizumab

Median overall survival, months (95% CI)
TAS-102 6.7 months (4.9-7.6)
TAS-102 plus bevacizumab 9.4 months (7.6-10.7)
HR 0.55 (95% CI 0.32-0.94); *p* = 0.028



Pfeiffer P et al. *Lancet Oncol* 2020;21(3):412-20.

TAS-102 +/- Bevacizumab: Select AEs

Adverse event, n (%)	TAS-102 (n = 47)		TAS-102 + bev (n = 46)	
	Grade 1-2	Grade 3-5	Grade 1-2	Grade 3-5
Fatigue	74%	11%	78%	7%
Nausea	64%	6%	57%	2%
Anemia	55%	17%	63%	4%
Diarrhea	32%	0	28%	9%
Neutropenia	28%	38%	17%	67%
Thrombocytopenia	17%	0	37%	2%
Febrile neutropenia	—	2%	—	6%

Pfeiffer P et al. *Lancet Oncol* 2020;21(3):412-20.

Regorafenib

Mechanism of action

- Oral multikinase inhibitor

Indication

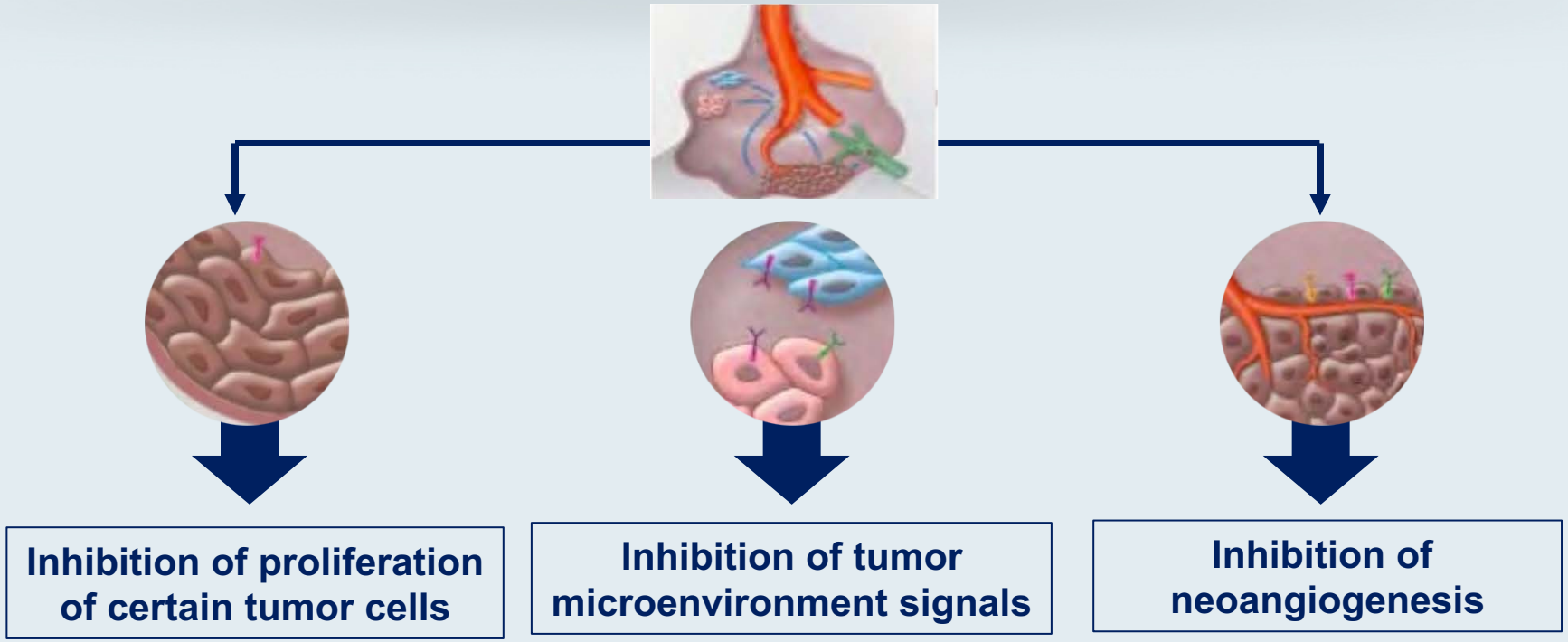
- For patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, with an anti-VEGF therapy and, if KRAS wild type, with an anti-EGFR therapy

Recommended dose

- 160 mg orally, once daily for the first 21 days of each 28-day cycle

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm321378.htm
Regorafenib package insert

Regorafenib: Mechanism of Action



- Regorafenib is an oral tumor deactivation agent that potently blocks multiple protein kinases, including kinases involved in:
  - Tumor angiogenesis (VEGFR1, -2, -3, TIE2)
  - Oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E)
  - Tumor microenvironment (PDGFR, FGBR)

https://www.slideshare.net/BayerAG/meet-management-20130319investorhandoutwebslideshare

Regorafenib Dose-Optimisation in Patients with Refractory Metastatic Colorectal Cancer (ReDOS): A Randomised, Multicentre, Open-Label, Phase 2 Study

Bekaii-Saab TS et al.
Lancet Oncol 2019;20(8):1070-82.

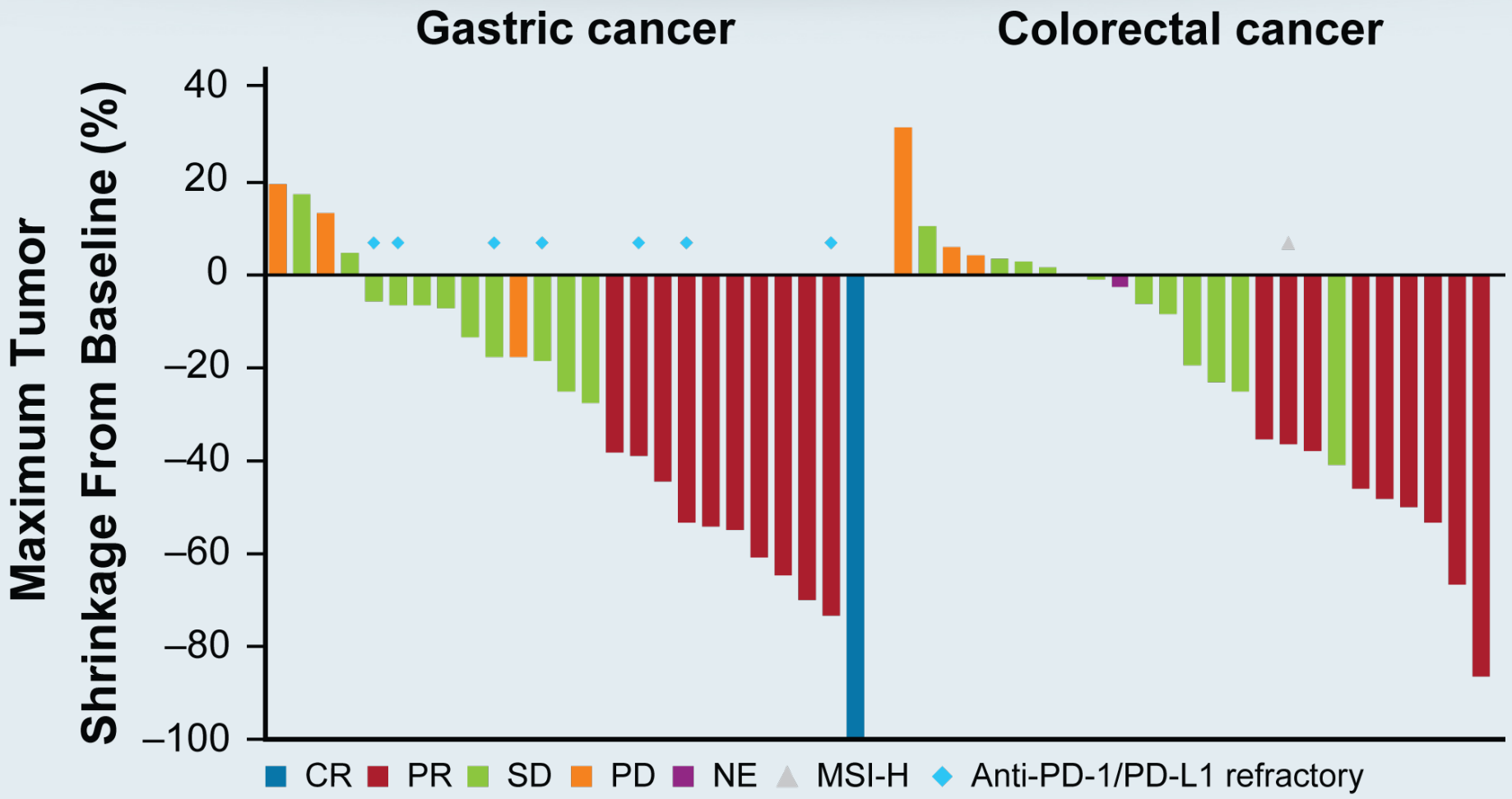
original reports

Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603)

Shota Fukuoka, MD, PhD[1,2]; Hiroki Hara, MD[3]; Naoki Takahashi, MD[3]; Takashi Kojima, MD[1]; Akihito Kawazoe, MD[1]; Masako Asayama, MD[3]; Takako Yoshii, MD, PhD[3]; Daisuke Kotani, MD[1]; Hitomi Tamura, RN[4]; Yuichi Mikamoto, BPharm[4]; Nami Hirano, MLT[4]; Masashi Wakabayashi, ME[4]; Shogo Nomura, PhD[4]; Akihiro Sato, MD[4]; Takeshi Kuwata, MD, PhD[5]; Yosuke Togashi, MD, PhD[2]; Hiroyoshi Nishikawa, MD, PhD[2]; and Kohei Shitara, MD[1]

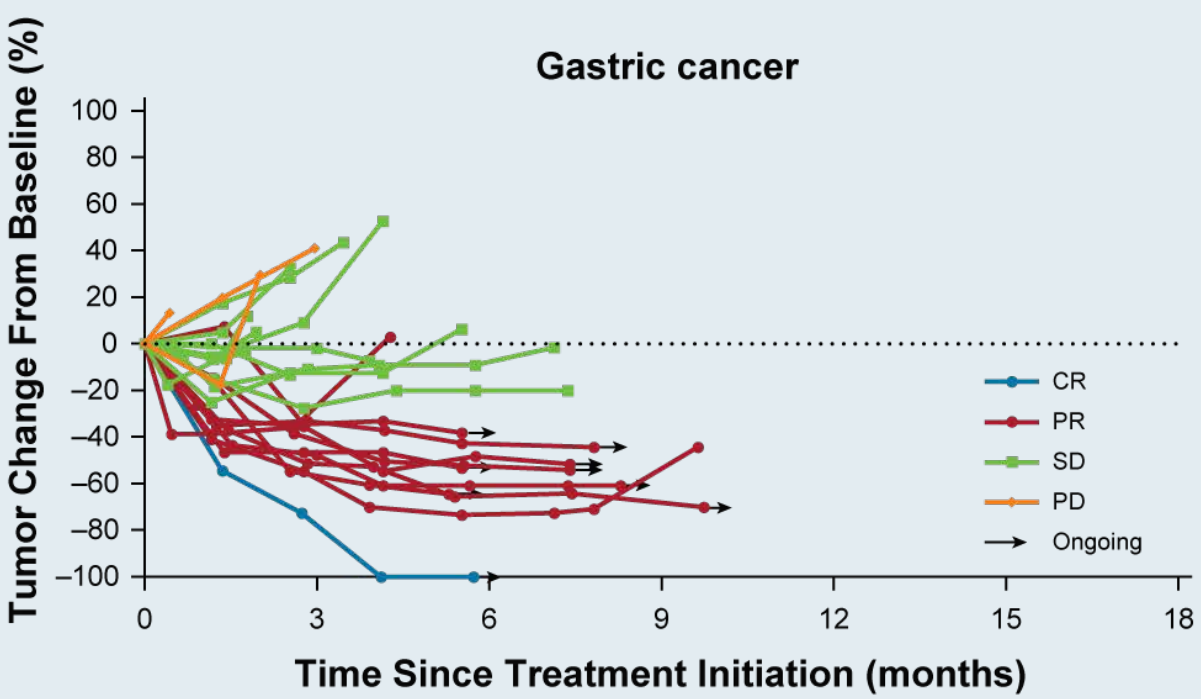
J Clin Oncol 2020;[Online ahead of print].

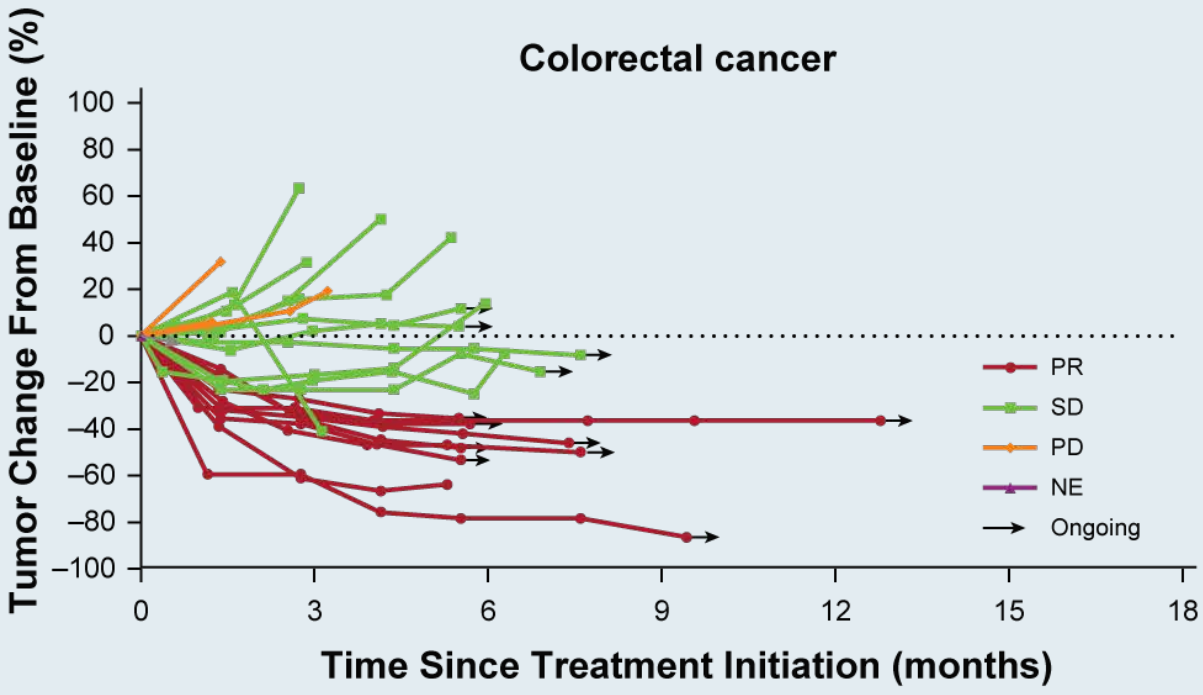
REGONIVO: Waterfall Plot of Maximum Percent Change in Tumor Size from Baseline



Fukuoka S et al. *J Clin Oncol* 2020;[Online ahead of print].

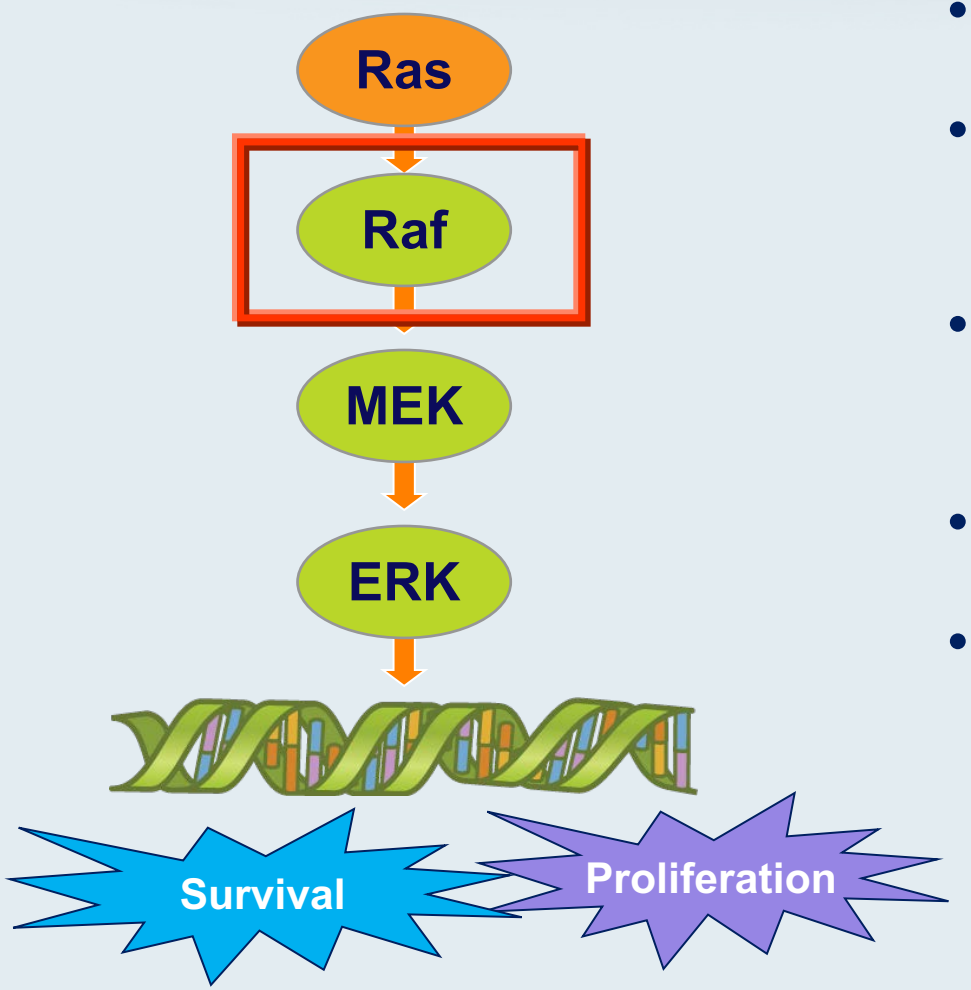
REGONIVO: Longitudinal Percent Tumor Change from Baseline





Fukuoka S et al. *J Clin Oncol* 2020;[Online ahead of print].

BRAF Mutations in Colorectal Cancer



- BRAF mutated in 10%-20% of CRC
- Leads to constitutive activation & cell proliferation
- Nonoverlapping pattern with KRAS mutation
- Confers inferior prognosis
- Poor response to single-agent BRAF inhibitors

Courtesy of Charles S Fuchs, MD.

Select Systemic Treatments for CRC with BRAF Tumor Mutations

BRAF V600E Mutation-Positive

- Dabrafenib + trametinib + (cetuximab or panitumumab)
- Encorafenib + binimetinib + (cetuximab or panitumumab)
- Vemurafenib + irinotecan + (cetuximab or panitumumab)
- Encorafenib + cetuximab

NCCN Guidelines Version 1.2019 – Colon Cancer.

Encorafenib and Cetuximab

Mechanism of action

- Encorafenib – oral Raf kinase inhibitor
- Cetuximab – anti-EGFR monoclonal antibody

Indication

- Encorafenib in combination with cetuximab: For patients with mCRC and a BRAF V600E mutation

Recommended dose

- 300 mg orally once daily in combination with cetuximab
- 400 mg/m^2 initial dose → 250 mg/m^2 weekly

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210496s006lbl.pdf

Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer

Kopetz S et al.
N Engl J Med 2019;381(17):1632-43.

BEACON CRC: Select AEs

Grade 3	Encora/cetux/bini (n = 222)	Encora/cetux (n = 216)	Control (n = 193)
Diarrhea	10%	2%	10%
Fatigue	2%	4%	4%
Nausea	5%	<1%	1%
Dermatitis acneiform	2%	1%	3%
Abdominal pain	6%	2%	5%
Decreased appetite	2%	1%	3%
Arthralgia	0	1%	0
Rash	<1%	0	2%

Kopetz S et al. *N Engl J Med* 2019;381(17)1632-43.

FDA Approval of Encorafenib in Combination with Cetuximab for mCRC — April 8, 2020

On April 8, 2020, the FDA 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.

Efficacy was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic CRC with disease progression after one or two prior regimens.

The most common adverse reactions (≥25%) for encorafenib with cetuximab were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation

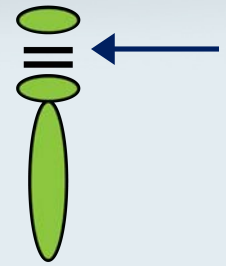
Encorafenib plus Cetuximab with or without Binimetinib for *BRAF* V600E Metastatic Colorectal Cancer: Updated Survival Results from a Randomized, Three-Arm, Phase III Study versus Choice of Either Irinotecan or FOLFIRI plus Cetuximab (BEACON CRC)

Kopetz S et al.
ASCO 2020;Abstract 4001.

What Is Microsatellite Instability (MSI)?

Microsatellites:

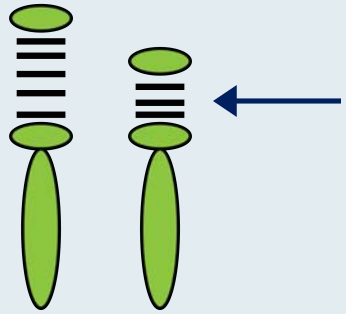
- Repetitive segments of DNA
- The same number of repeats are present in every cell



Normal microsatellite with 2 repeats

Microsatellite instability:

- The number of microsatellite repeats differs between normal cells/tissue and tumor cells/tissue



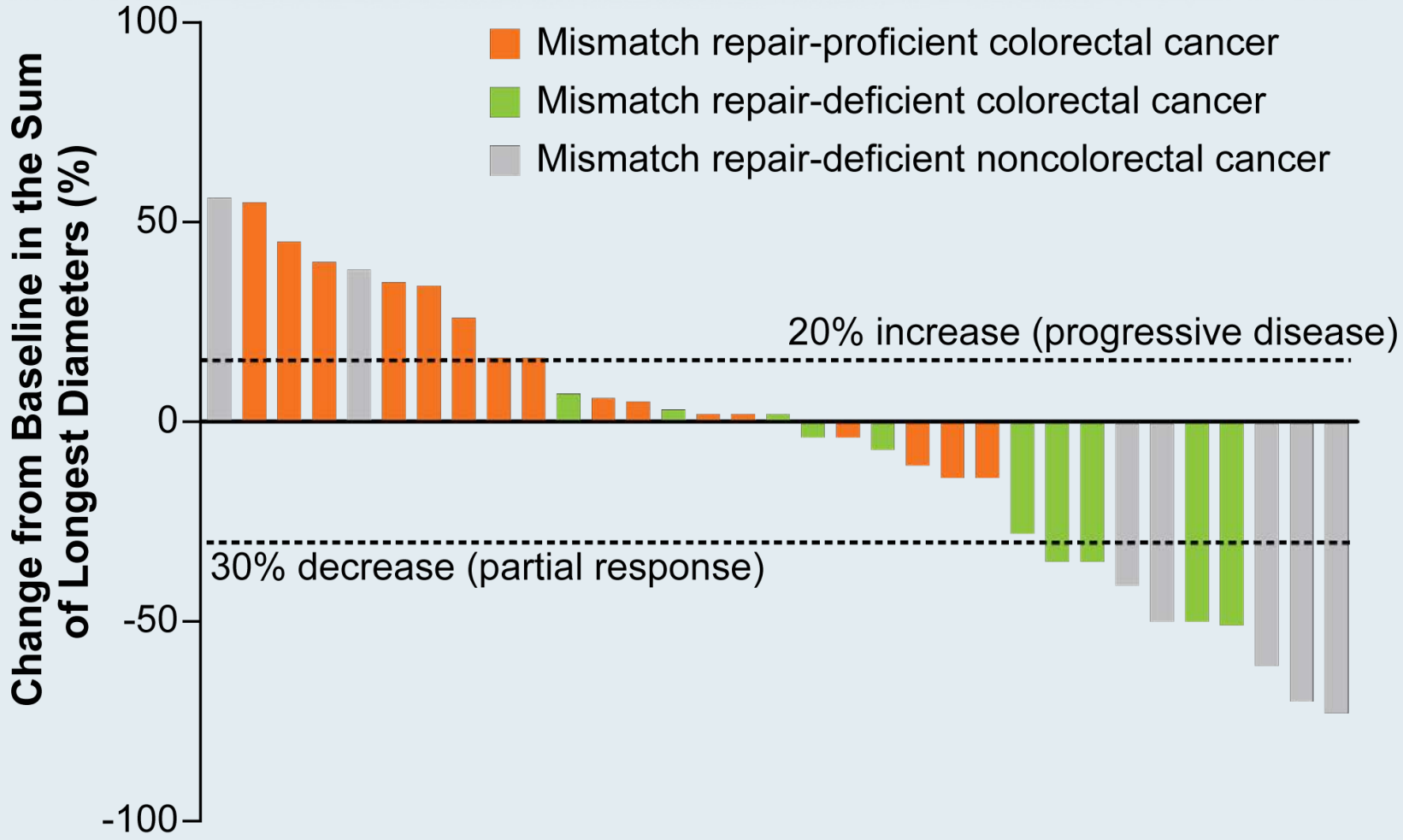
Tumor tissue with MSI variable repeat size 5 & 3

- *Most MSI tumors are sporadic*
- *Virtually all Lynch tumors are MSI high*

http://www.slideshare.net/Pammy98/hereditary-colorectal-cancer-powerpoint-educational-module

Immunotherapy in Cancers with Mismatch Repair Deficiency

Waterfall Plot: Radiographic Response to Pembrolizumab

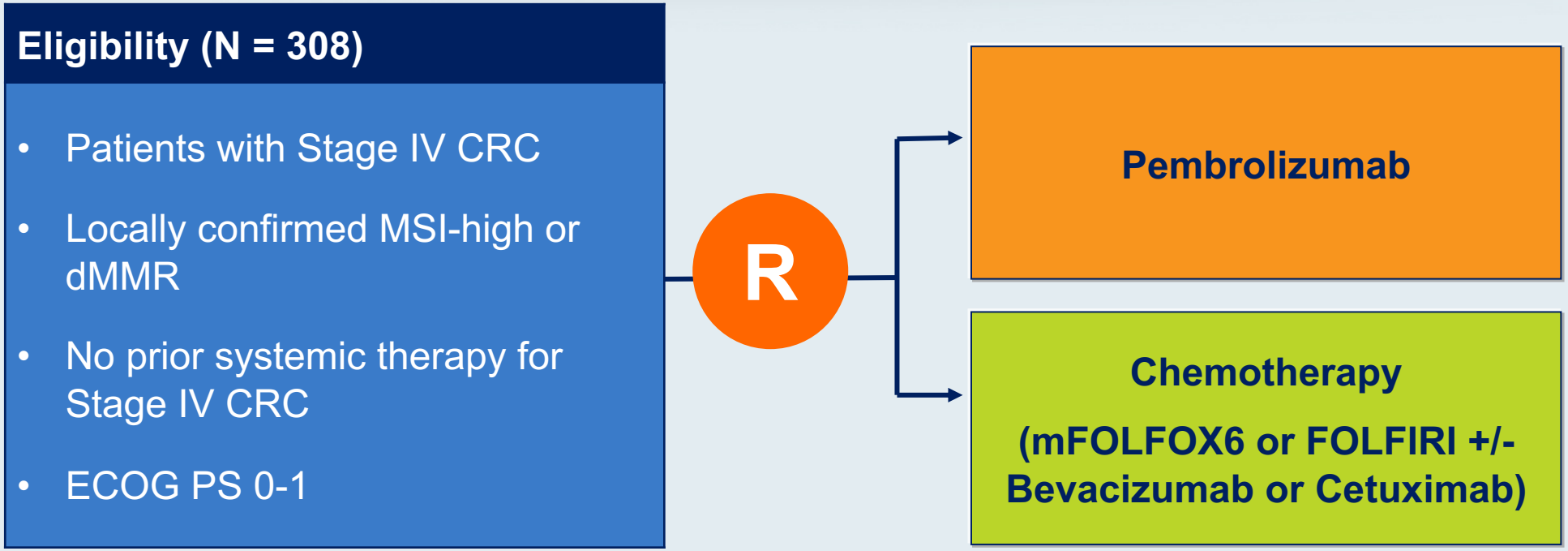


Le DT et al. *N Engl J Med* 2016;372(26):2509-20.

Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study

Andre T et al.
ASCO 2020;Abstract LBA4 (Plenary).

KEYNOTE-177: A Phase III Trial in MSI-High or dMMR mCRC



Primary endpoints: Progression-free survival and overall survival

Key secondary endpoints include: Overall response rate

Clinicaltrials.gov; Accessed May 2020.

A Phase II, Multicenter, Open-label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Expressing Metastatic Colorectal Cancer (mCRC): DESTINY-CRC01

Siena S et al.
ASCO 2020;Abstract 4000.

DESTINY-CRC01: Results from the Trial of Trastuzumab Deruxtecan

All patients	Cohort A (n = 53)
Confirmed ORR	24 (45.3%)
CR	1 (2%)
Disease control rate	44 (83%)
Median PFS	6.9 mo
Median OS	Not reached
Median duration of treatment	Not reached

- In Cohort A: ORR in pts with prior anti-HER2 treatment = 7/16 (43.8%)
- No responses were observed in Cohorts B or C.

Sienna S et al. ASCO 2020;Abstract 4000.

DESTINY-CRC01: Safety of Trastuzumab Deruxtecan

Treatment-emergent AEs	Cohort A/B/C (n = 78)
Grade ≥ 3	48 (61.5%)
Decreased neutrophil count	21.8%
Anemia	14.1%
Interstitial lung disease (ILD)*	3.8%
Leading to drug discontinuation	9.0%

* Grade 5 ILD (n = 2)

Sienna S et al. ASCO 2020;Abstract 4000.

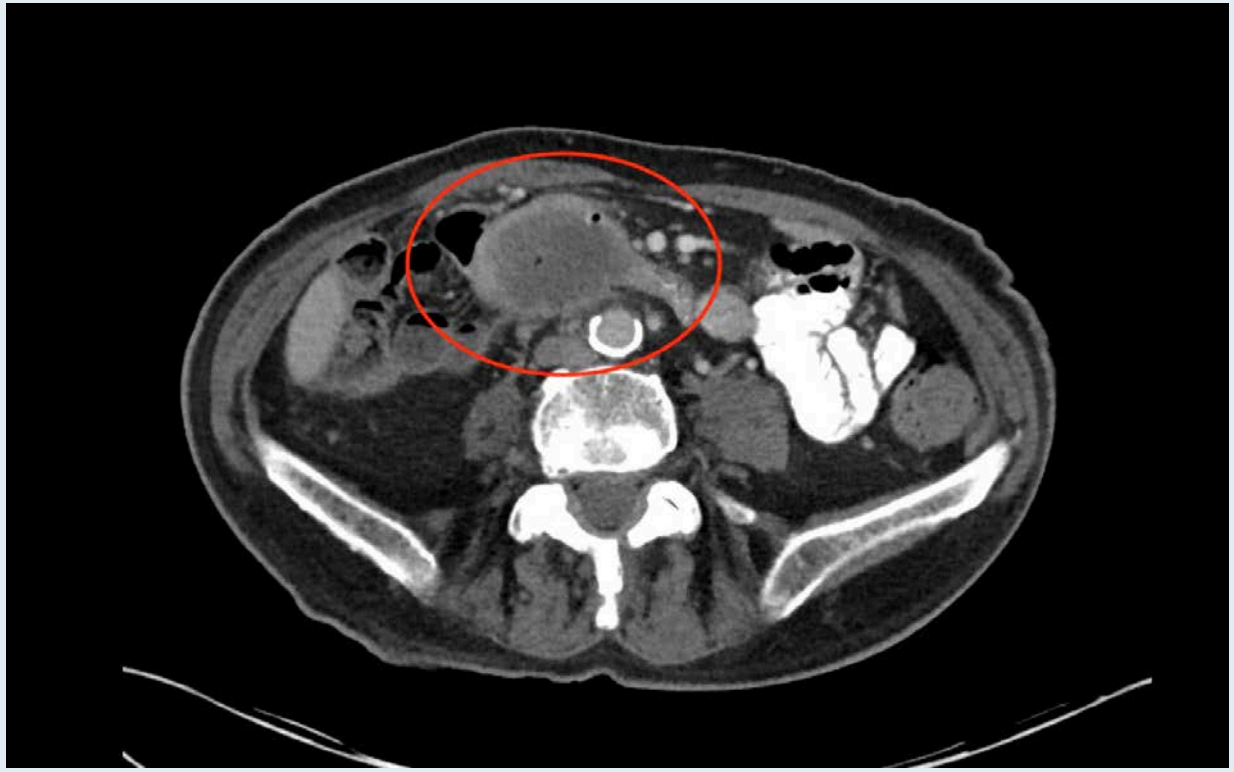
84-year-old man with PMH of DM, HTN, HLD and CAD s/p PCI and CABG (from the practice of Ms Triglianos)

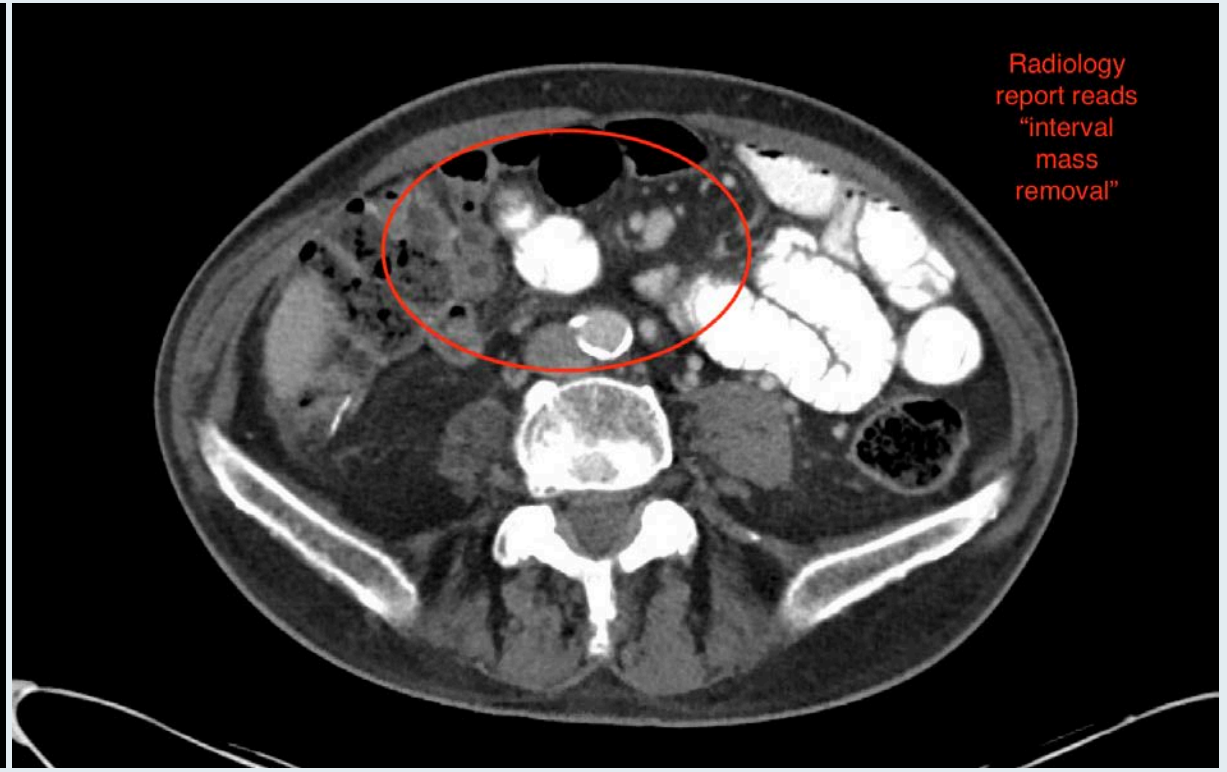
- Summer 2018: Decreased appetite, nausea, progressive weight loss
  - Partially obstructing 7-cm mass in cecum, non-obstructing 4-cm mass in the hepatic flexure
  - Biopsy: adenocarcinoma, CEA normal, no evidence of mets
- 7/2018: Right colectomy and omentectomy
  - 7.3-cm, Stage IIIB moderately differentiated cecal adenocarcinoma, 1/25 LN
  - 3.5-cm, Stage IIA hepatic flexure adenocarcinoma, 0/25 LN
  - Molecular profile: MSI-H
- Elected observation, due to good prognosis, pre-existing comorbidities
- 2/2019: Anorexia, new 7.3-cm duodenal mass, 2 retroperitoneal satellite lesions
  - Biopsy: Recurrent metastatic cecal adenocarcinoma, MSI-H
- 3/2019: Pembrolizumab
- 5/2019: “Interval resection” of duodenal mass and decrease in satellite lesions

84-year-old man (from the practice of Ms Triglianos)

Prior to pembrolizumab

After pembrolizumab treatment





84-year-old man (from the practice of Ms Triglianos)

Patient education for pembrolizumab

- Advise that when triggering the immune system, healthy organs can be adversely affected.
- Review of side effects:
  - diarrhea/intestinal issues (colitis)
  - skin reactions/rash or other skin changes/mouth sores
  - lung problems/SOB/cough (pneumonitis)
  - liver problems/yellowing of eyes, bleeding, abd pain (hepatitis)
  - hormone abnormalities (pituitary, thyroid, pancreas, adrenal glands)
  - headaches, nausea/vomiting, rapid heart rate, extreme fatigue, excessive thirst or urination, hair loss, changes in mood
  - brain (encephalitis) – headaches, vision changes, weakness, drooping of eyelids
- Other teaching points: Avoid systemic steroids for nonimmune-related side effects

52-year-old woman with 4 adult offspring and several grandchildren (from the practice of Ms Avella)

- 1/2015: Abdominal and pelvic pain, anorexia; emotionally distraught
  - Diagnosed with de novo mCRC, with large sigmoid colon primary, ovarian and pelvic mets
- 6/2015: Resection of primary
- CAPOX/bevacizumab → PD
- FOLFIRI/panitumumab x 2 years
  - Electrolyte insufficiencies (potassium and magnesium infusions)
- 7/2019: TAS-102 initiated at 35 mg/m^2 BID
  - Fatigue (primary complaint), mild nausea and diarrhea, neutropenia
  - Dose and schedule of TAS-102 modified due to tolerability issues

Module 3: Sequencing of Systemic Therapy in Patients with Metastatic Gastric Cancer

- Impact of MSI status, PD-L1 level and HER2 status on treatment choice

The usual second-line therapy for metastatic gastric cancer is…

a. Ramucirumab
b. Ramucirumab combined with paclitaxel
c. TAS-102
d. Regorafenib
e. I don’t know

Patients with MSS metastatic gastric adenocarcinoma should generally be offered an anti-PD-1 antibody…

a. As first-line therapy

b. As first-line therapy if PD-L1 expression level is high

c. As second-line therapy

d. As second-line therapy if PD-L1 expression level is high

e. I don’t know

Which of the following agents is approved for metastatic gastroesophageal adenocarcinoma previously treated with at least 2 lines of chemotherapy?

a. Regorafenib

b. TAS-102

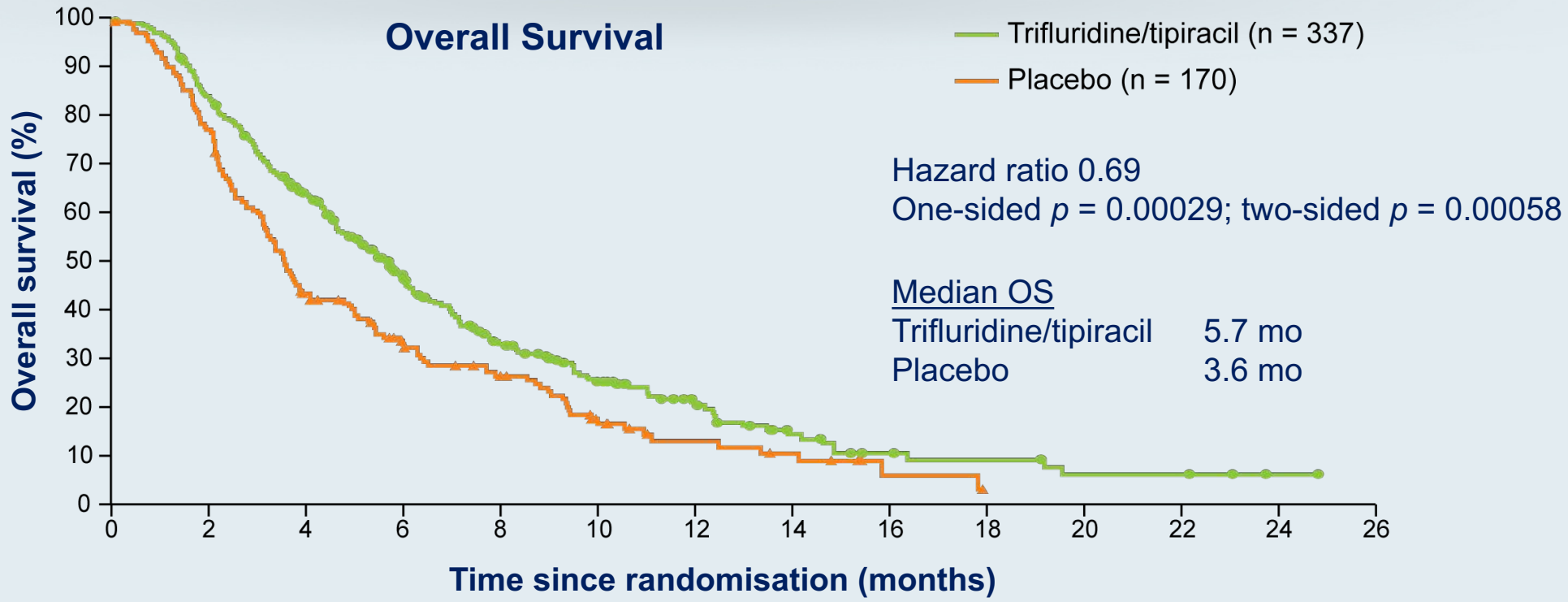
c. Ibrutinib

d. Ribociclib

e. Rucaparib

f. I don’t know

TAGS: Outcome Summary of Phase III Trial of Trifluridine/Tipiracil in Patients with Heavily Pretreated Metastatic Gastric Cancer



Clinical variable	Trifluridine/tipiracil	Placebo	HR	*p*-value
Median PFS	2.0 mo	1.8 mo	0.57	<0.0001
ORR	4.0%	2.0%	—	0.28

Shitara K et al. *Lancet Oncol* 2018;19(11):1437-48.

Press Release: FDA Approves Trifluridine/Tipiracil (TAS-102) for Previously Treated Advanced Gastric or GEJ Adenocarcinoma — February 25, 2019

The Food and Drug Administration approved trifluridine/tipiracil for the treatment of adult patients with metastatic gastric or GEJ adenocarcinoma previously treated with at least 2 prior lines of chemotherapy that included a fluoropyridimidine, a platinum, either a taxane or ininotecan, and if appropriate, HER2/neu-targeted therapy.

The approval follows an FDA Priority Review designation and is based on data from a global, randomized, Phase III TAGS trial that met its primary and secondary endpoints demonstrating prolonged overall survival (OS) with trifluridine/tipiracil versus placebo, and a safety profile consistent with prior experience with this drug.

https://www.taihooncology.com/us/newsroom/press-releases/2019-02-25-LON-PM-US-1213-FDA-Approves-Gastric

58-year-old man and non smoker with PMH of hyperlipidemia (from the practice of Ms Avella)

- Metastatic poorly differentiated adenocarcinoma of the gastroesophageal junction
  - HER2-negative, MSI-high, PD-L1 CPS score: 15, negative for Lynch Syndrome
- 2013: FOLFOX x 6, RT; 2014-2015: Paclitaxel + ramucirumab x 6
- PET/CT: Worsening mets (solitary liver met, acetabular and cerebellar met – stereotactic RT)
- 2016: FOLFOX x 12
- 2/2017 PET/CT: Bone mets with adjacent soft tissue extension
- 5/2017: Clinical trial of IDO inhibitor epacadostat + pembrolizumab
- 9/2018 CT: NED, with resolved lymph node, bone mets
- 11/2018: Dyspnea work up, including cardiac ECHO: LVEF 20-25% consistent with myocarditis
  - High-dose steroids x 6 weeks → LVEF > 50%
- 3/2020: Stable disease

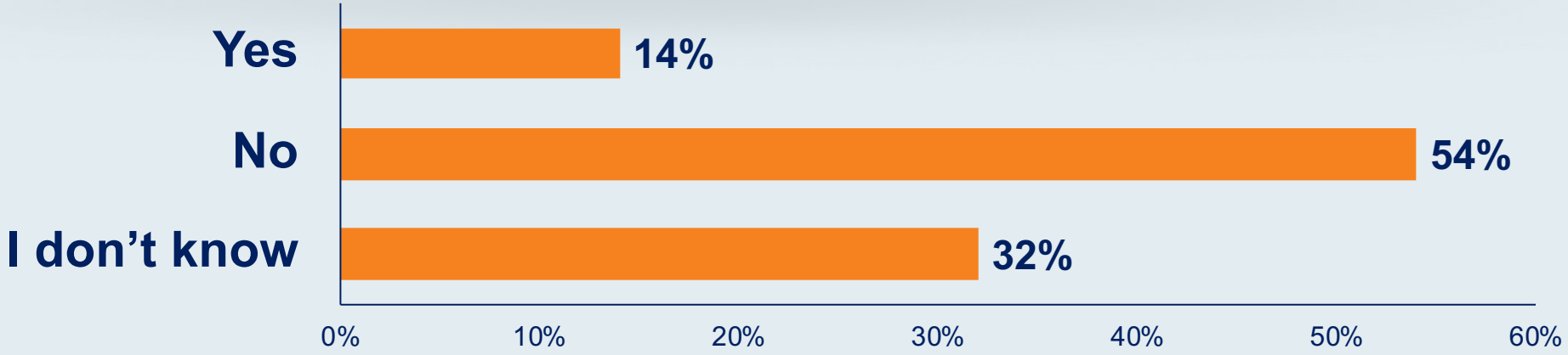
68-year-old woman with PMH of diabetes (from the practice of Dr Philip)

- Stage IV HER2-negative gastric cardia adenocarcinoma with liver mets (PS=1)
- FOLFOX x 9 (best response: PR) → PD
  - Grade 2 neuropathy, Grade 2 fatigue
- Ramucirumab monotherapy due to neuropathy (best response: SD) → PD after 4 months
  - Mild blood pressure elevation
- Tumoral Combined Positive Score (CPS): 0
- Overall PS of 2
- TAS-102 x 6 months (best response: SD)
  - Grade 3 neutropenia early in therapy, one level of TAS-102 dose reduction

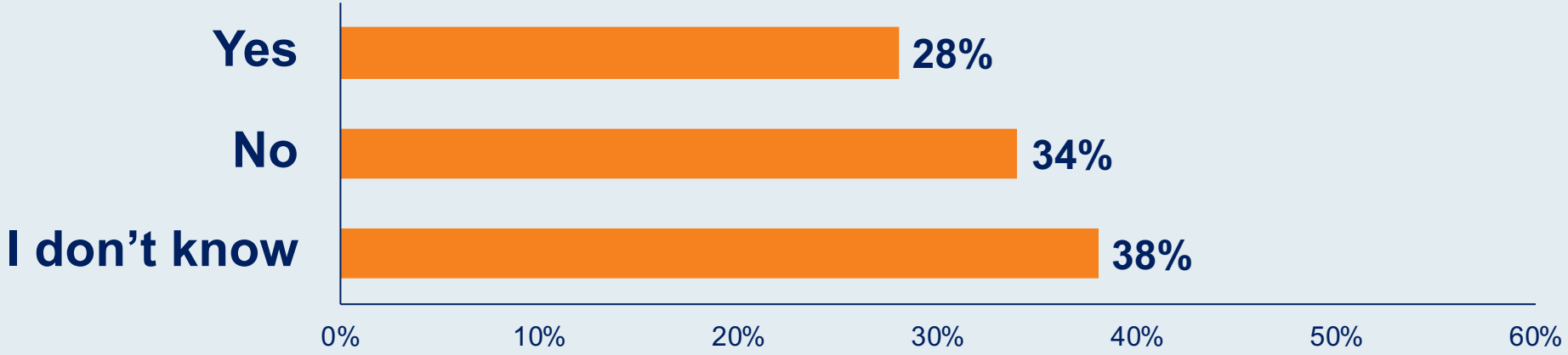
Module 4: Management of Gastrointestinal Cancers in the Era of COVID-19

- Telemedicine, minimization of surgeries, reduced infusions and clinic visits

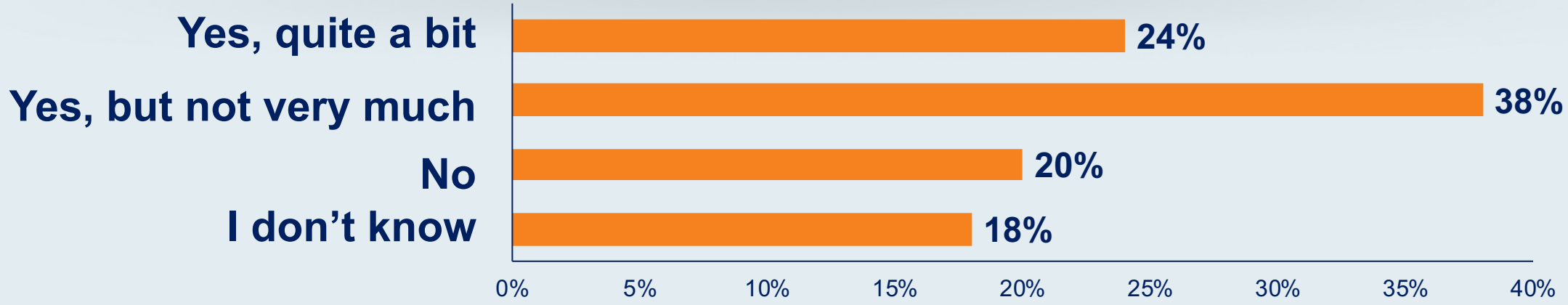
Do you believe that receiving an anti-PD-1/PD-L1 antibody makes a patient more susceptible to contracting COVID-19?



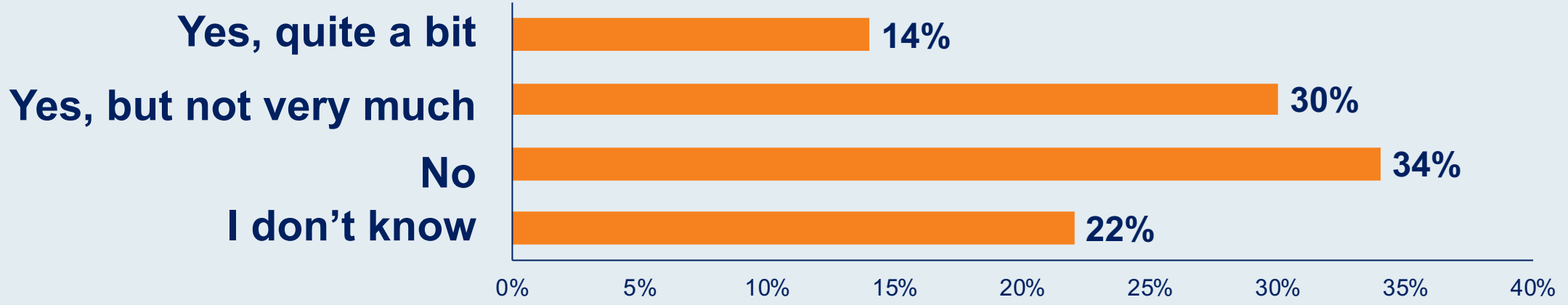
Do you believe that receiving an anti-PD-1/PD-L1 antibody increases a patient’s risk of developing complications associated with COVID-19?



Has the approach to primary surgery for patients with gastrointestinal cancers changed at your institution during the COVID-19 pandemic?

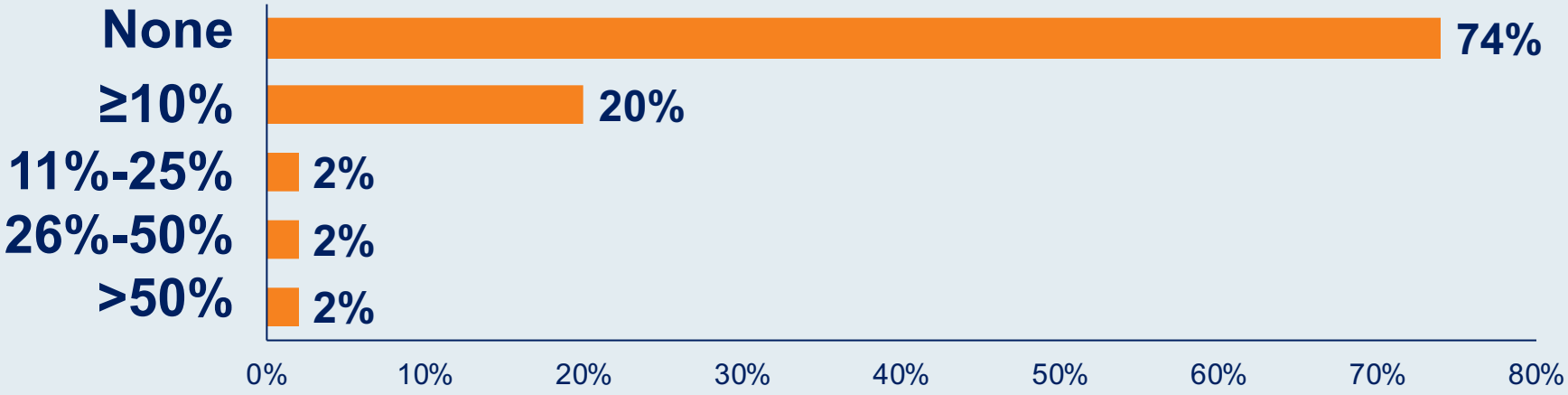


Has the approach to radiation therapy for patients with gastrointestinal cancers changed at your institution during the COVID-19 pandemic?

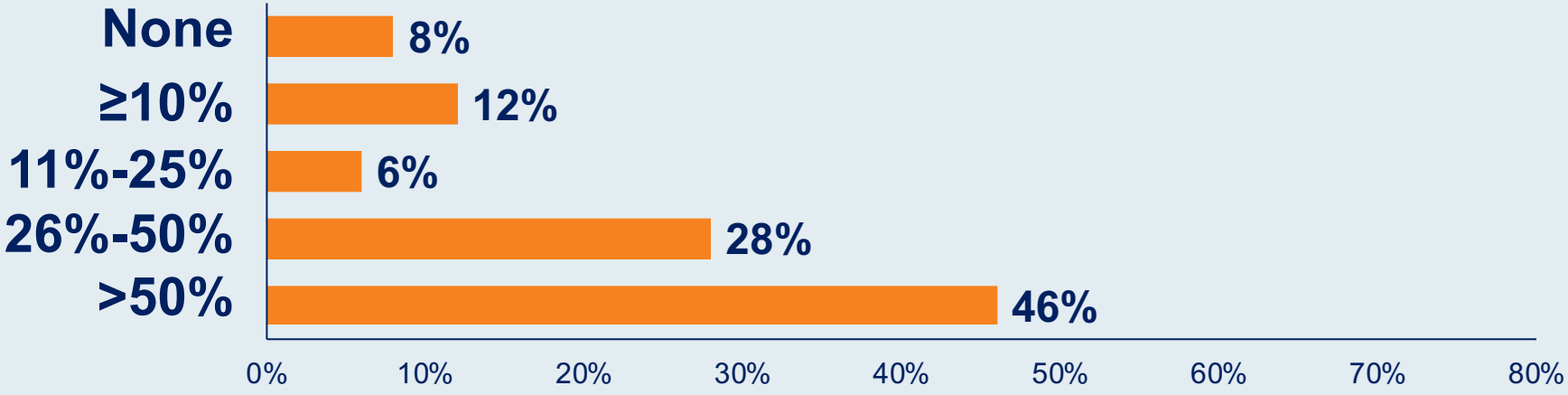


Approximately what proportion of your practice was/is telemedicine or virtual visits?

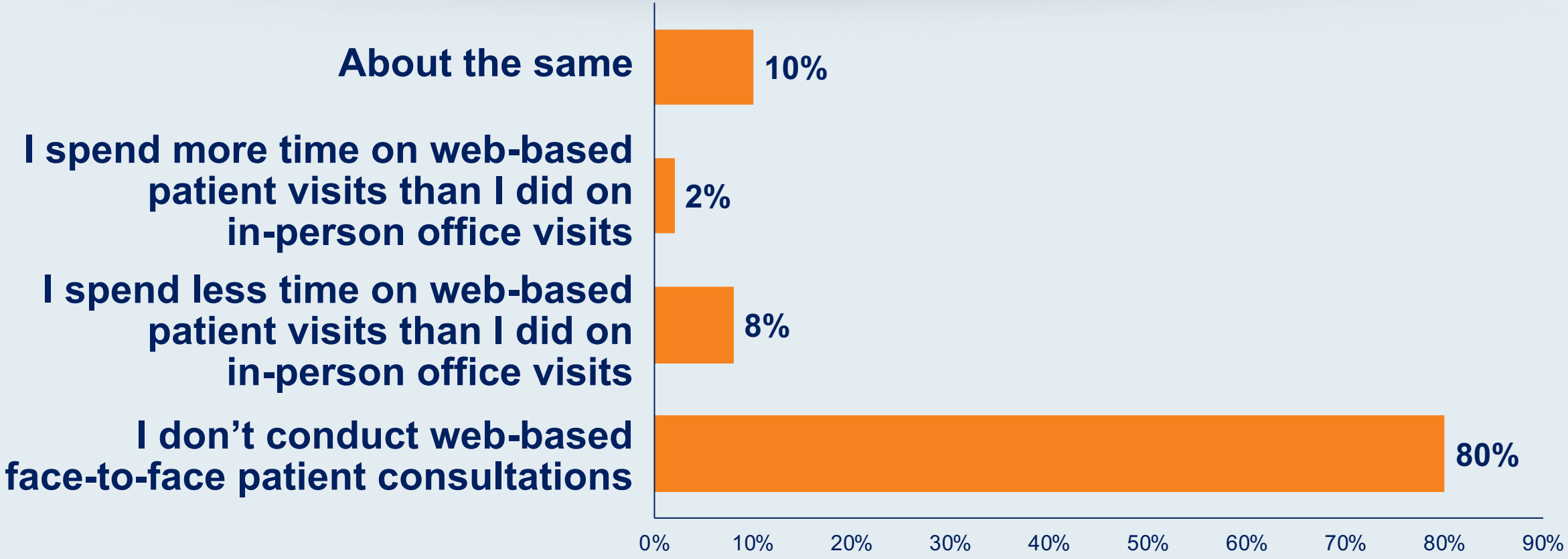
Before COVID-19



During COVID-19

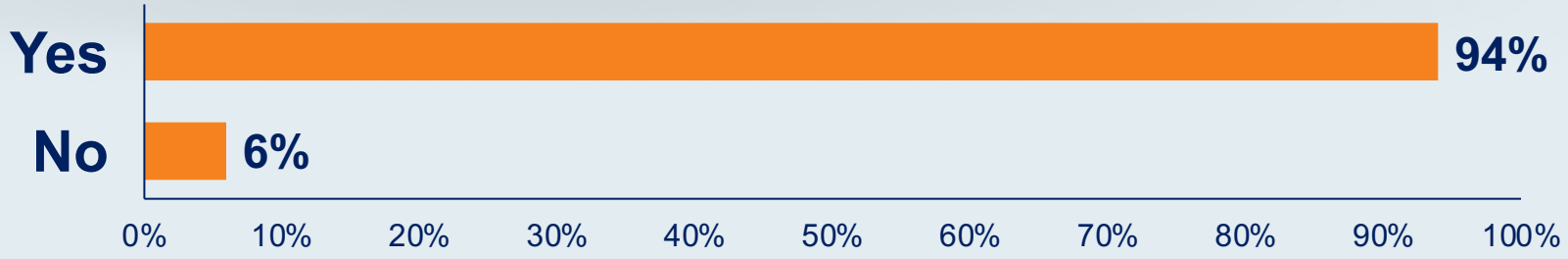


How does the amount of time you spend on web-based face-to-face patient consultations compare to the amount of time you would have spent conducting in-person office visits before the COVID-19 pandemic?

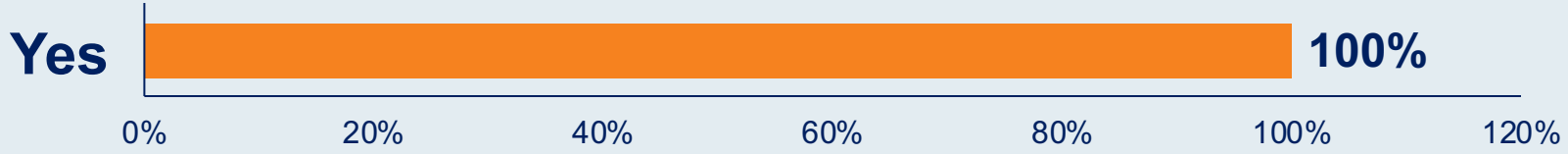


Duration of time spent for each web-based face-to-face patient consultation (Median): 20 minutes

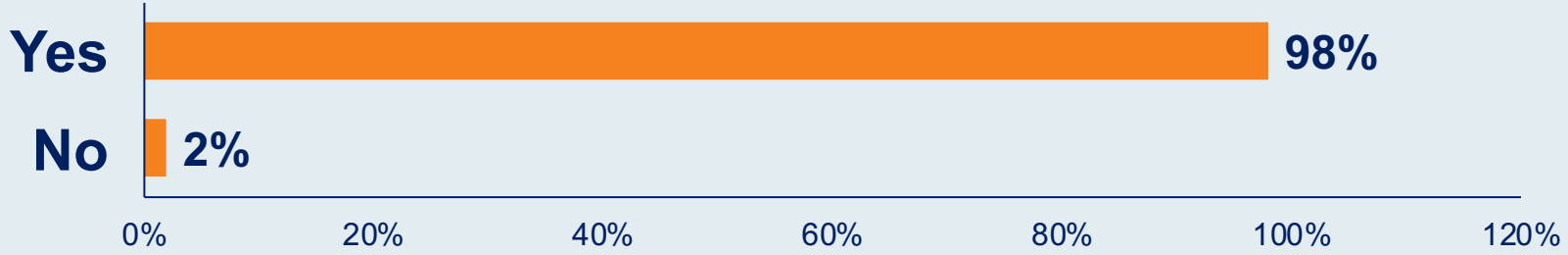
Are you restricting the number of visitors allowed in your clinic during the COVID-19 pandemic?



Are the healthcare workers in your clinic required to wear masks or other personal protective equipment (PPE) during the COVID-19 pandemic?



Are the patients who visit your clinic required to wear masks or other PPE during the COVID-19 pandemic?



Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.