

Yearⁱⁿ Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

**Saturday, February 8, 2020, 8:00 AM – 4:00 PM
Charlotte, North Carolina**

Faculty

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Mitchell R Smith, MD, PhD
Richard M Stone, MD
Zev Wainberg, MD, MSc

Moderator
Neil Love, MD

Research
To Practice®

Agenda

Module 1 — Lung Cancer: *Drs Langer and Riely*

Module 2 — Acute Leukemias: *Drs DiNardo and Stone*

Module 3 — Lymphomas and Chronic Lymphocytic Leukemia:
Drs Abramson, LaCasce and Smith

Module 4 — Gastrointestinal Cancers: *Drs Bendell, Marshall and Wainberg*

Module 5 — Genitourinary Cancers: *Drs Oh and Petrylak*

Module 6 — Gynecologic Cancers: *Drs Armstrong and Liu*

Module 7 — Breast Cancer: *Drs Geyer and Krop*



Johanna Bendell, MD

Chief Development Officer

Director, Drug Development Unit Nashville

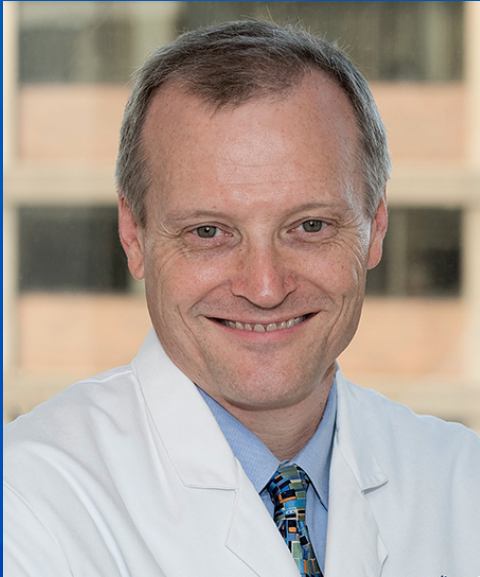
Sarah Cannon Research Institute

Tennessee Oncology

Nashville, Tennessee

Disclosures

Consulting Agreements	<p>Agios Pharmaceuticals Inc, Amgen Inc, Apexigen, Arch Oncology, ARMO BioSciences, Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Continuum Clinical, Cyteir Therapeutics, Daiichi Sankyo Inc, Five Prime Therapeutics Inc, FORMA Therapeutics, Genentech, Gilead Sciences Inc, GlaxoSmithKline, Incyte Corporation, Innate Pharma, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Leap Therapeutics Inc, Lilly, MacroGenics Inc, Merck, Merrimack Pharmaceuticals Inc, Moderna Inc, Molecular Partners, Novartis, OncoGenex Pharmaceuticals Inc, OncoMed Pharmaceuticals Inc, Pfizer Inc, PhoenixBio, Prelude Therapeutics, Roche Laboratories Inc, Sanofi Genzyme, Seattle Genetics, Taiho Oncology Inc, Tanabe Research Laboratories, TG Therapeutics Inc, Tizona Therapeutics Inc, Tolero Pharmaceuticals, Torque Therapeutics, Translational Drug Development</p>
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Data and Safety Monitoring Board	<p>Five Prime Therapeutics Inc</p>



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Disclosures

Advisory Committee, Consulting Agreements and Contracted Research	Amgen Inc, Bayer HealthCare Pharmaceuticals, Caris Life Sciences, Celgene Corporation, Indivumed GmbH, Roche Laboratories Inc, Taiho Oncology Inc
Speakers Bureau	Amgen Inc, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Merck, Roche Laboratories Inc, Taiho Oncology Inc



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Disclosures

Consulting Agreements	Bayer HealthCare Pharmaceuticals, EMD Serono Inc, Five Prime Therapeutics Inc, Lilly, Merck
Contracted Research	Bristol-Myers Squibb Company, Celgene Corporation, Merck
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Gastrointestinal Cancers – Drs Bendell, Marshall and Wainberg

Hepatocellular Carcinoma

Cholangiocarcinoma

Colorectal Cancer

Pancreatic Cancer

Gastroesophageal Cancer

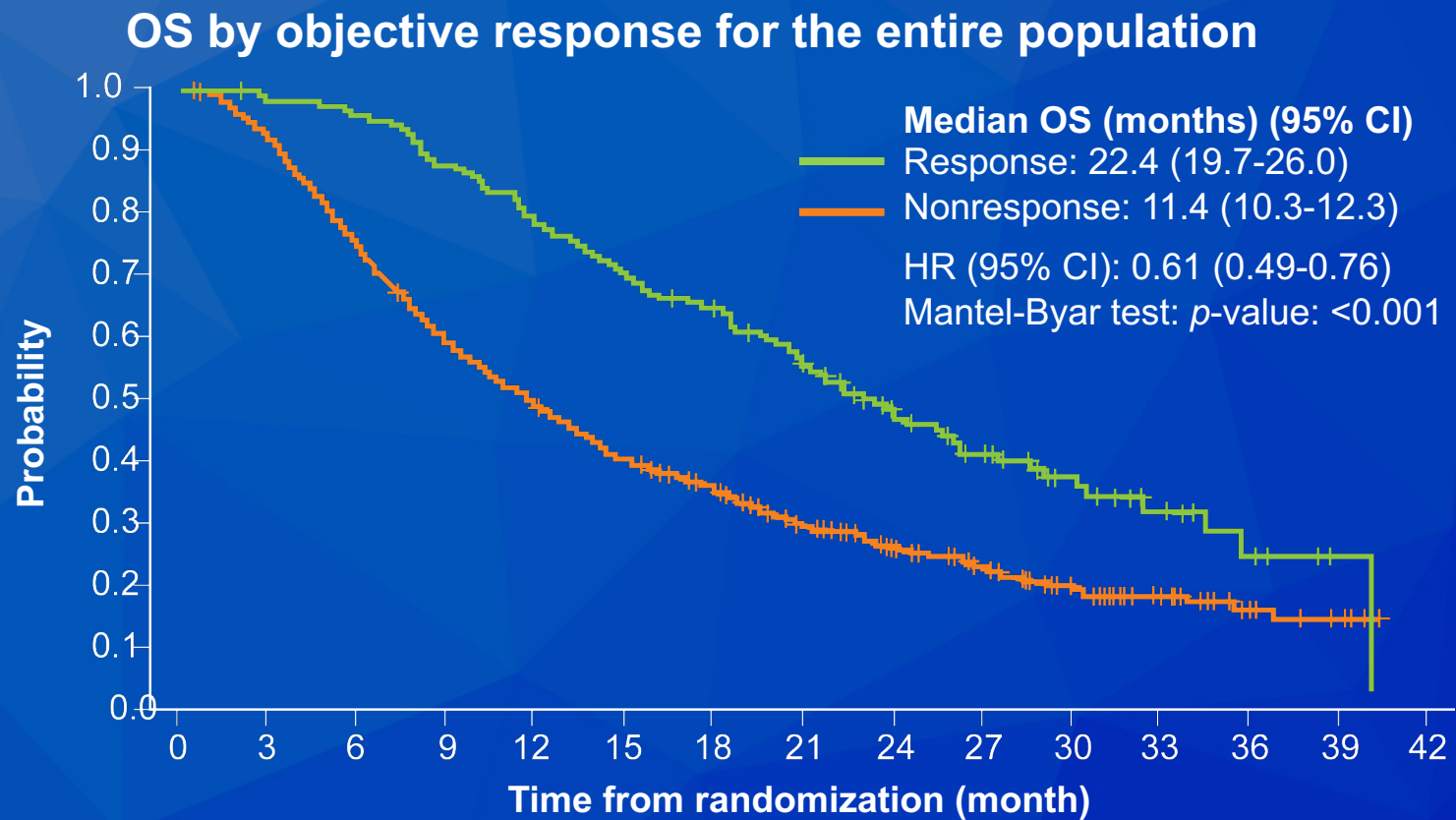
Analysis of Survival and Objective Response (OR) in Patients with Hepatocellular Carcinoma in a Phase III Study of Lenvatinib (REFLECT)

Kudo M et al.

Gastrointestinal Cancers Symposium 2019;Abstract 186.



REFLECT: Analysis of Overall Survival and Objective Response



Outcomes	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR* or OR†	p-value
Median OS	13.6 mo	12.3 mo	*0.92	—
Objective response rate	24.1%	9.2%	†3.13	<0.0001

* Hazard ratio; † Odds ratio

Editorial — Dr Bekaii-Saab

The landscape of systemic therapy for HCC has changed dramatically during the last few years with the approval of several novel agents. For first-line treatment, the tyrosine kinase inhibitors (TKIs) lenvatinib and sorafenib are now approved by the FDA. Sorafenib has been the standard of care for advanced HCC for a decade. Lenvatinib has been shown to be noninferior to sorafenib for OS. Although secondary endpoints such as ORR and PFS appear to be superior, results should be interpreted with extreme caution given the design of the study. Side-effect profiles differ with more hypertension with lenvatinib and more HFSR with sorafenib. Further exploratory data from REFLECT confirms the safety and efficacy of lenvatinib by starting dose (8 mg or 12 mg) based on body weight. Additionally, target-specific AEs have been linked to an improved OS, which is not unexpected. Finally, the presence of a response with lenvatinib may increase the likelihood of survival, although this will need to be further validated in prospective studies.

FDA Approves Cabozantinib for Hepatocellular Carcinoma

Press Release – January 14, 2019

“The Food and Drug Administration approved cabozantinib for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

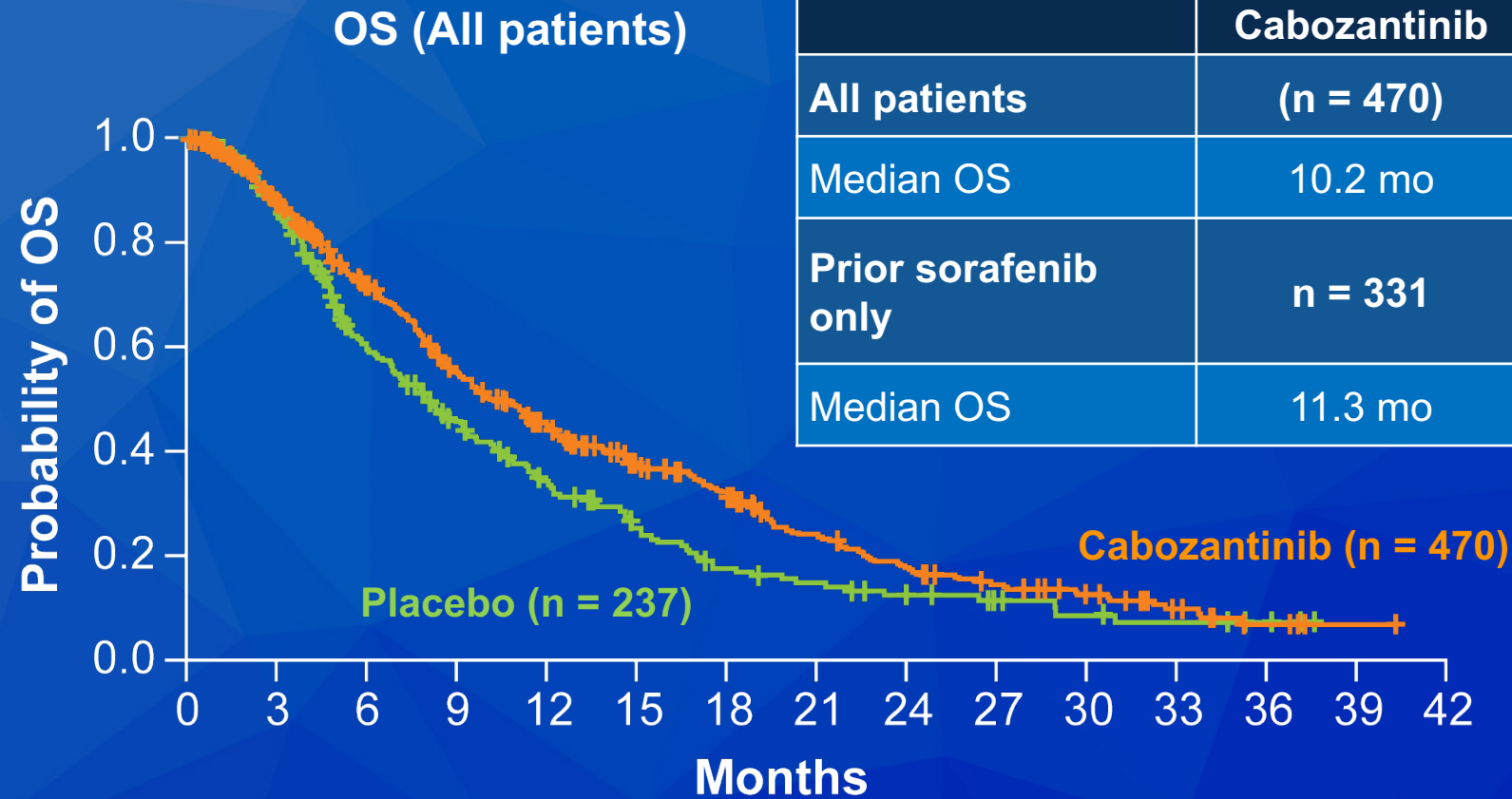
Approval was based on CELESTIAL (NCT01908426), a randomized (2:1), double-blind, placebo-controlled, multicenter trial in patients with HCC who had previously received sorafenib and had Child Pugh Class A liver impairment. Patients were randomized to receive cabozantinib 60 mg orally once daily (n = 470) or placebo (n = 237) until disease progression or unacceptable toxicity.”

Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma

Abou-Alfa GK et al.
N Engl J Med 2018;379(1):54-63.



CELESTIAL: A Phase III Trial of Cabozantinib versus Placebo for Advanced HCC



	Cabozantinib	Placebo	HR	p-value
All patients	(n = 470)	(n = 237)	0.76	0.005
Median OS	10.2 mo	8.0 mo		
Prior sorafenib only	n = 331	n = 164	0.70	NR
Median OS	11.3 mo	7.2 mo		

Nivolumab (NIVO) + Ipilimumab (IPI) + Cabozantinib (CABO) Combination Therapy in Patients (pts) with Advanced Hepatocellular Carcinoma (aHCC): Results from CheckMate 040

Yau T et al.

Gastrointestinal Cancers Symposium 2020;Abstract 478.

CheckMate 040: Response and Tolerability of Nivolumab + Ipilimumab + Cabozantinib for Advanced HCC

	Doublet arm NIVO 240 q2wk + CABO 40 qd (n = 36)	Triplet arm NIVO3 q2wk + IPI1 q6wk + CABO 40 qd (n = 35)
Overall response rate	19%	29%
Disease control rate	75%	83%
Median time to response	4.8 mo	3.5 mo
Median PFS	5.4 mo	6.8 mo
Median OS	21.5 mo	Not reached

- No new safety signals were observed during this study
 - The triplet combination resulted in a numerically higher rate of adverse events in comparison to the doublet combination (Grade 4 TRAEs: 20% vs 3%)

FDA Grants Approval to Ramucirumab for HCC

Press Release – May 10, 2019

“The Food and Drug Administration approved ramucirumab as a single agent for hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL and have been previously treated with sorafenib.

Approval was based on REACH-2 (NCT02435433), a multinational, randomized, double-blind, placebo-controlled, multicenter study in 292 patients with advanced HCC with AFP ≥ 400 ng/mL who had disease progression on or after sorafenib or who were intolerant.”

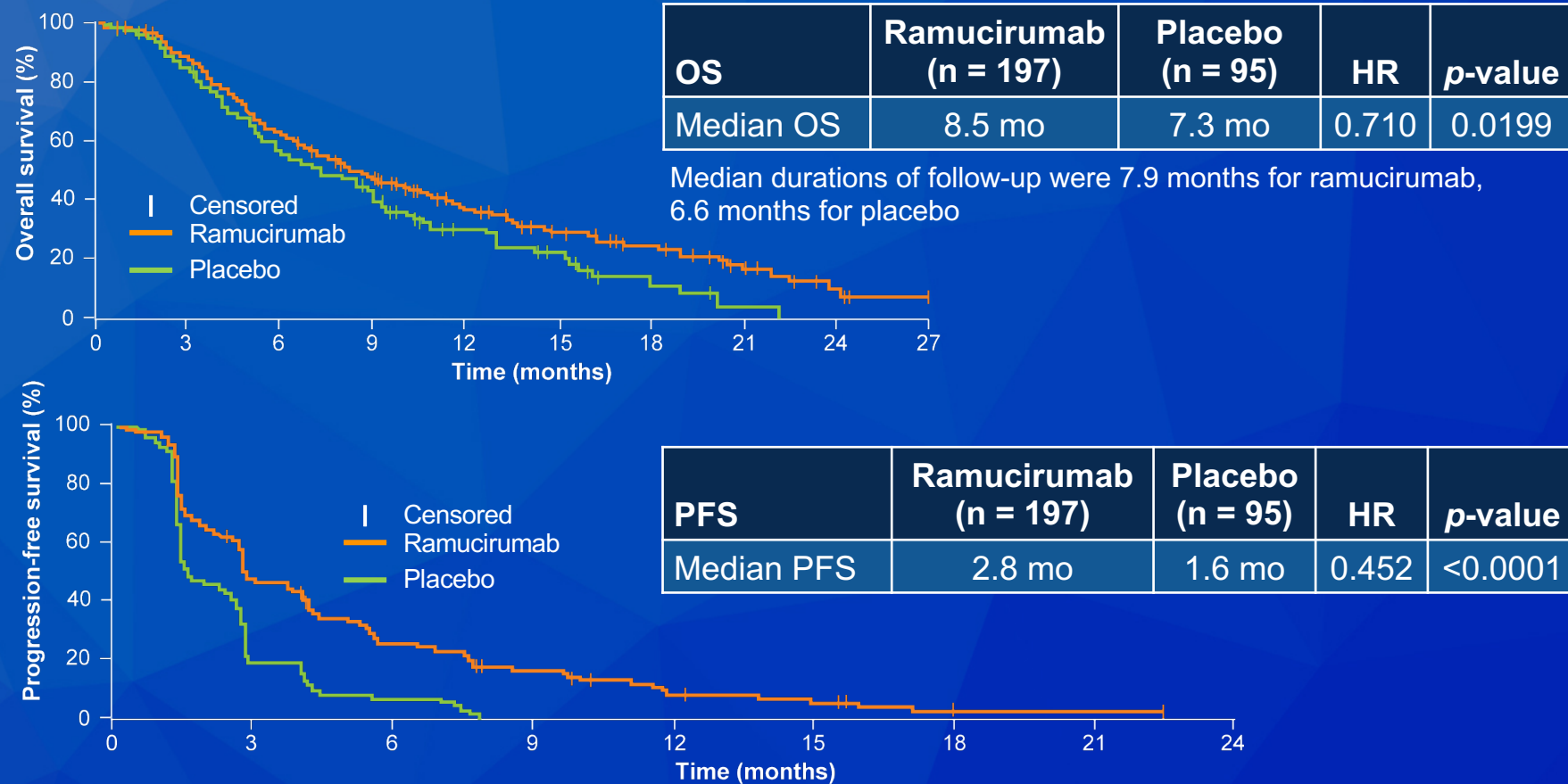
Ramucirumab After Sorafenib in Patients with Advanced Hepatocellular Carcinoma and Increased A-Fetoprotein Concentrations (REACH-2): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial

Zhu AX et al.

Lancet Oncol 2019;20(2):282-96.



REACH-2: A Phase III Trial of Ramucirumab After Sorafenib for Patients with Advanced HCC and Increased AFP



Grade ≥ 3 AEs associated with ramucirumab included hypertension and hyponatremia.

Pembrolizumab as Second-Line Therapy in Patients with Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial

Finn RS et al.

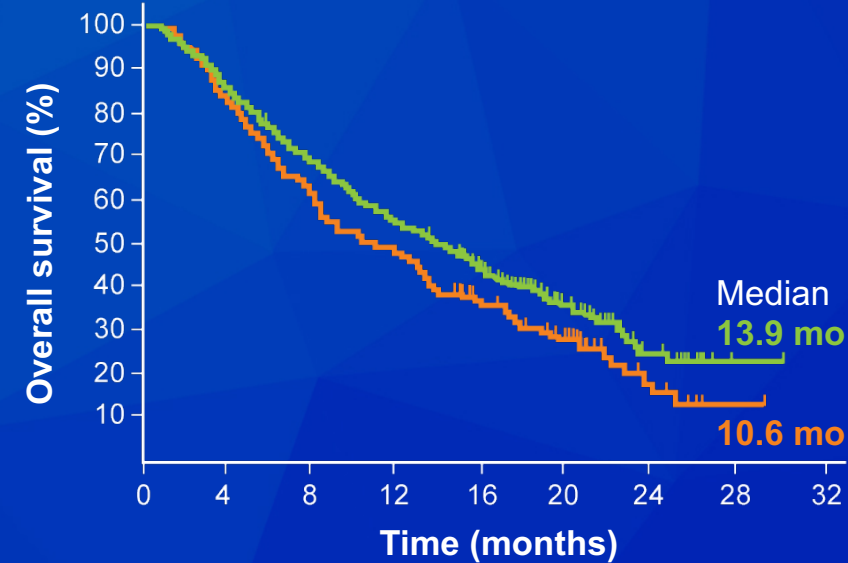
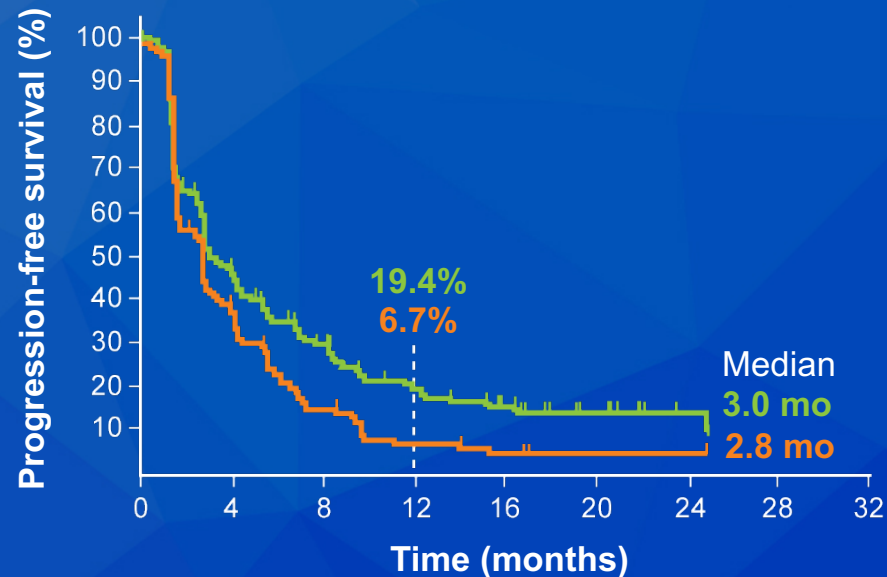
J Clin Oncol 2020;38(3):193-202.



Phase III KEYNOTE-240 Trial: Pembrolizumab versus Best Supportive Care as Second-Line Therapy for Advanced HCC

PFS final analysis			
	n	HR	p-value
Pembrolizumab	278	0.718	0.0022
Placebo	135		

Overall survival			
	n	HR	p-value
Pembrolizumab	278	0.781	0.0238
Placebo	135		



- Confirmatory KEYNOTE-240 trial: Numerical but no statistical advantage in PFS and OS

Editorial — Dr Bekaii-Saab

The landscape of systemic therapy for HCC has changed dramatically during the last few years with the approval of several novel agents. For second-line treatment in sorafenib-experienced patients, the TKIs regorafenib and cabozantinib and the VEGFR-2 antagonist ramucirumab (for patients with alpha-fetoprotein [AFP] levels ≥ 400 ng/mL) are now approved. The immune checkpoint inhibitors nivolumab and pembrolizumab have also been approved for patients with HCC who were previously treated with sorafenib; these 2 approvals were accelerated approvals based on single-arm phase II studies. The phase III KEYNOTE-240 trial was conducted to confirm efficacy and safety findings from the phase II KEYNOTE-224 trial, upon which pembrolizumab was approved for treating patients with HCC. The phase III study did not meet its co-primary endpoints of improved OS or PFS with second-line pembrolizumab vs placebo in patients with HCC. However, one finding from this study remains interesting.

Editorial — Dr Bekaii-Saab (continued)

The ORR was nearly 20% with pembrolizumab, and responses were durable, with a median duration of response of 13.8 months. Therefore, although pembrolizumab did not seem to confer much benefit to the total patient population, there did seem to be a clear benefit for approximately 10%-15% of patients. What remains unclear is how to select the patients who will benefit, especially given the fact that the control arm was placebo instead of one of the approved active agents. How will this affect practice? Based on current data and for second-line therapy, cabozantinib and regorafenib are both acceptable options. Ramucirumab should be considered if the patient has an AFP ≥ 400 ng/mL. Given the absence of level 1 evidence supporting their use in clinic, nivolumab or pembrolizumab can be considered only when first- and second-line level 1 evidence supported systemic therapy options for patients with HCC have failed.

FDA Grants Breakthrough Therapy Designation to Atezolizumab with Bevacizumab for First-Line HCC

Press Release – July 18, 2018

The Food and Drug Administration granted breakthrough therapy designation to atezolizumab in combination with bevacizumab as a first-line treatment for patients with the most common form of liver cancer, advanced or metastatic hepatocellular carcinoma (HCC). The designation was granted based on data from a phase Ib study that assessed the safety and clinical activity of the combination treatment.

Randomised Efficacy and Safety Results for Atezolizumab (Atezo) + Bevacizumab (Bev) in Patients (pts) with Previously Untreated, Unresectable Hepatocellular Carcinoma (HCC)

Lee M et al.

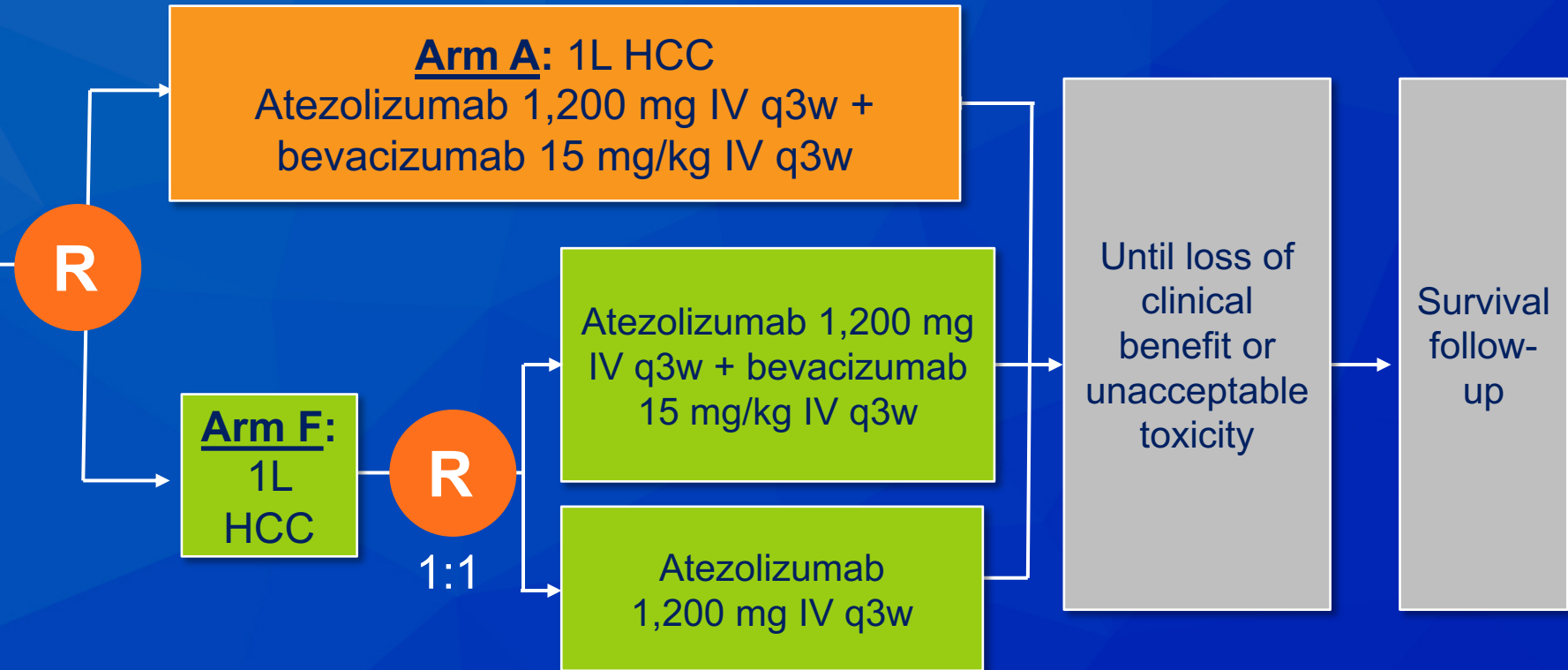
Proc ESMO 2019;Abstract LBA39.



GO30140: Phase IB Study Design

Eligibility

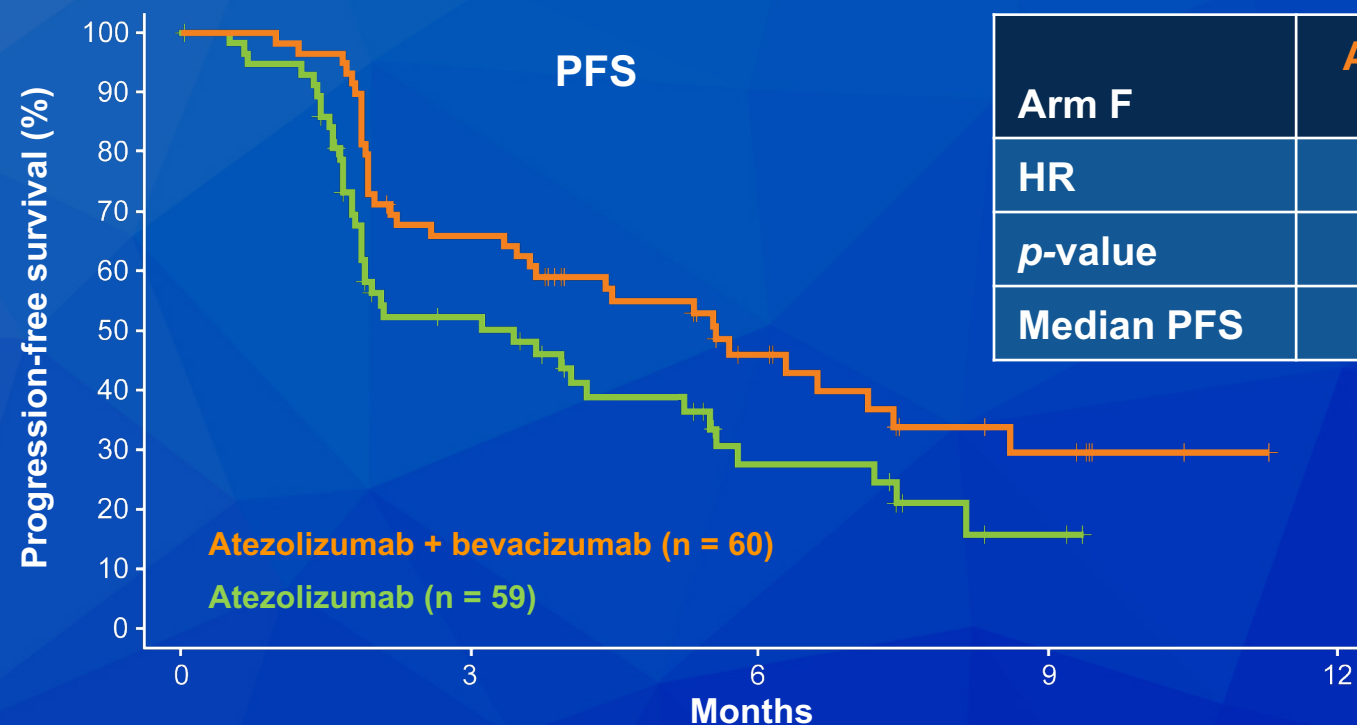
- Measurable disease per RECIST 1.1
- ECOG PS 0/1
- Adequate hematologic and organ function
- Child-Pugh score up to B7 for Arm A and Child-Pugh A for Arm F
- No prior systemic therapy
 - No prior treatment with anti-CTLA-4, anti-PD-1 or anti-PD-L1 antibodies



Primary Endpoints: Arm A (ORR, safety); Arm F (PFS, safety)

Results of the Phase Ib GO30140 Study

Arm A (N = 104)					
Confirmed ORR	CR	SD	DCR	mPFS	mOS
37 (36%)	12 (12%)	37 (36%)	74 (71%)	7.3 mo	17.1 mo



Arm F	Atezo + bev (n = 60)	Atezo (n = 59)
HR	0.55	
p-value	0.0108	
Median PFS	5.6 mo	3.4 mo

The combination of atezolizumab and bevacizumab was generally well tolerated, and toxicities were manageable.

Lee M et al. *Proc ESMO* 2019;Abstract LBA39.

FDA Grants Breakthrough Designation to Pembrolizumab with Lenvatinib as First-Line Therapy for Advanced Unresectable HCC

Press Release – July 23, 2019

The US Food and Drug Administration has granted breakthrough therapy designation for pembrolizumab in combination with lenvatinib for the potential first-line treatment of advanced unresectable HCC not amenable to locoregional treatment. This designation is based on updated interim results from the Phase Ib trial KEYNOTE-524/Study 116. An earlier interim analysis was presented at the American Association for Cancer Research Annual Meeting 2019.

A Phase Ib Trial of Lenvatinib (LEN) plus Pembrolizumab (PEMBRO) in Unresectable Hepatocellular Carcinoma (uHCC): Updated Results

Ikeda M et al.

Proc AACR 2019;Abstract CT061.



Updated Results of a Phase Ib Study of Pembrolizumab with Lenvatinib in Unresectable HCC

	PEMBRO + LEN (N = 30)		
	mRECIST per investigator	mRECIST per IIR	RECIST 1.1 per IIR
Objective response rate*	11 (36.7%)	15 (50.0%)	11 (36.7%)
Best overall response			
Complete response*	1 (3.3%)	3 (10.0%)	0
Partial response*	10 (33.3%)	12 (40.0%)	11 (36.7%)

IIR = independent imaging review. * Confirmed responses only

- The most common any-grade TEAEs were decreased appetite (63%) and hypertension (60%).
- No new safety signals were identified.

Editorial — Dr Bekaii-Saab

In addition to their anti-angiogenic activity, agents targeting angiogenesis, such as bevacizumab, lenvatinib and regorafenib, have immunomodulatory effects that alter the tumor micro-environment, which may augment PD-L1/PD-1 mediated anti-tumor immune responses. This scientific rationale, including preclinical and early clinical data results, supports the hypothesis that these combinations may be effective in advanced HCC. This has led to a number of studies that are ongoing and one that has completed with results pending (IMbrave150).

Atezolizumab + Bevacizumab vs Sorafenib in Patients with Unresectable Hepatocellular Carcinoma: Phase 3 Results from IMbrave150

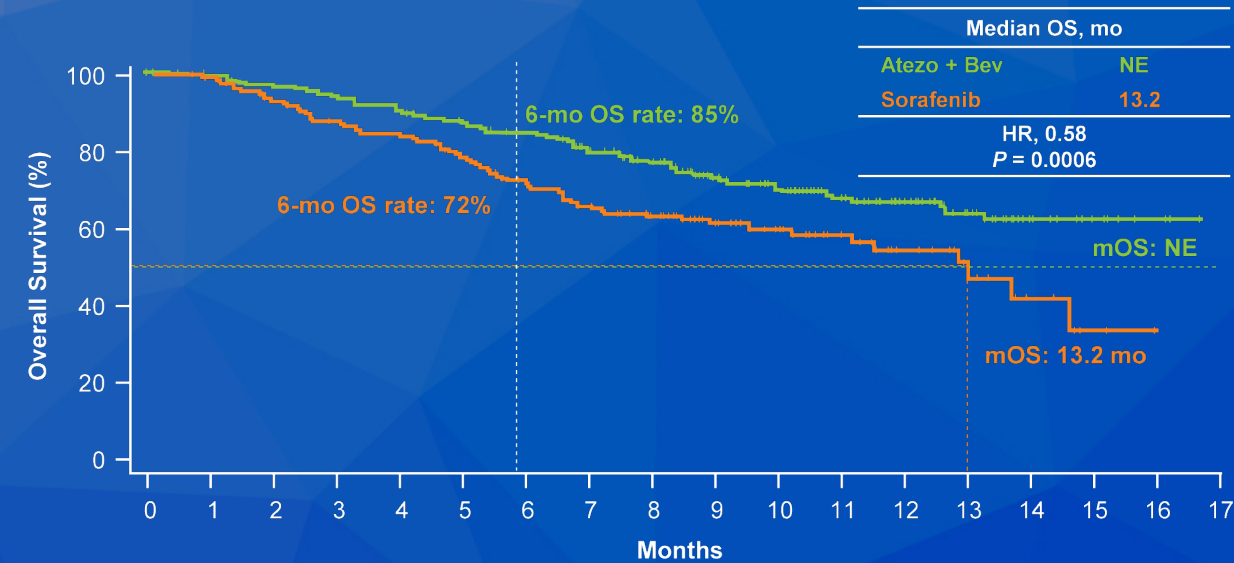
Cheng A-L et al.

Proc ESMO Asia 2019;Abstract LBA3.

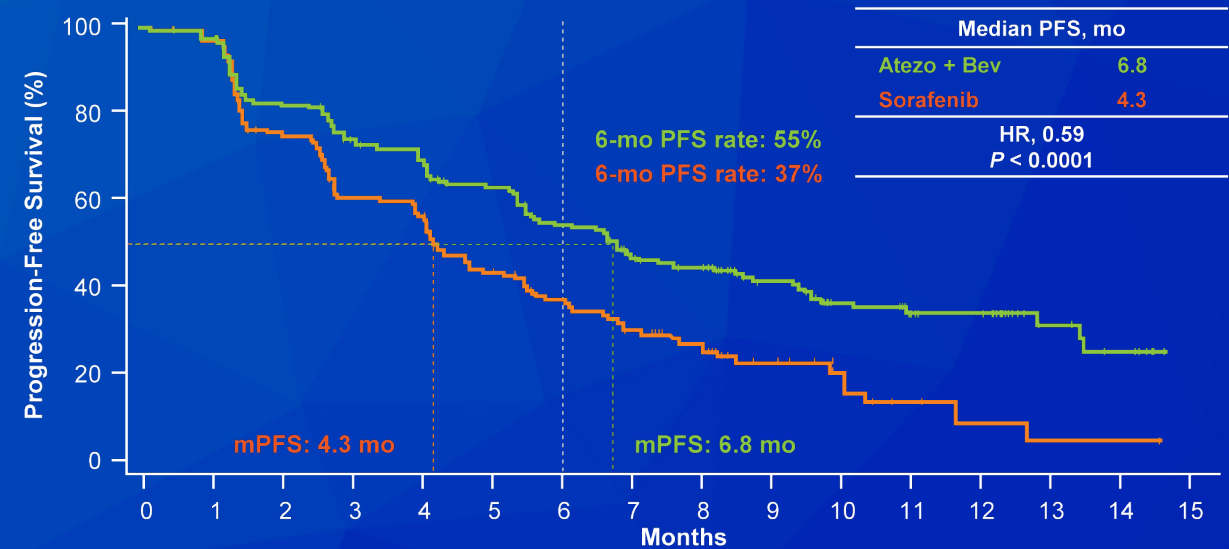


IMbrave150: Co-Primary OS and PFS Endpoints

OS



PFS



- OS and PFS benefits were generally consistent across subgroups
- The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known safety profiles of each agent

NE = not estimable

Editorial — Dr Philip

Sorafenib has been the mainstay of systemic therapy in patients with unresectable HCC for over a decade. IMbrave150 was a global phase III study testing atezolizumab plus bevacizumab versus sorafenib in patients with unresectable HCC who have not received prior systemic therapy. Standard doses and schedules were used. Patients had ECOG PS 0-1 and Child-Pugh A. The majority had HBV as the etiology of their HCC. Five hundred and one patients with a median age of 64-66 years were enrolled. Co-primary endpoints were OS and IRF-assessed PFS. Median OS was not reached on the experimental arm versus 13.2 months in the sorafenib arm (HR, 0.58, 95% CI: 0.42-0.79, $p = 0.0006$). Median PFS was 6.8 months and 4.3 months in the experimental and sorafenib arms, respectively (HR, 0.59, 95% CI: 0.47-0.76, $p < 0.0001$). Benefit was seen in all major subgroups. Median duration of response was not reached in the experimental arm.

Editorial — Dr Philip (continued)

Confirmed objective responses using IRF HCC mRECIST criteria were 33% and 13% in experimental and control arms, respectively ($p < 0.0001$). The toxicity profile of the combination revealed fewer all-grade adverse events (AEs) and treatment-related grade 3-4 AEs. Importantly, the combination significantly delayed the time to deterioration of patient-reported quality of life (HR, 0.63). IMbrave150 establishes the combination of atezolizumab and bevacizumab as a treatment standard in with systemically untreated unresectable Child-Pugh/PS favorable HCC. Superiority over sorafenib included to all efficacy endpoints including quality of life. No unexpected toxicities were seen using this combination.

CheckMate 459: A Randomized, Multi-Center Phase III Study of Nivolumab (NIVO) vs Sorafenib (SOR) as First-Line (1L) Treatment in Patients (pts) with Advanced Hepatocellular Carcinoma (aHCC)

Yau T et al.

Proc ESMO 2019;Abstract LBA38_PR.



CheckMate 459: A Phase III Trial of Nivolumab versus Sorafenib as First-Line Treatment for Advanced HCC

NCT02576509

Eligibility (n = 1,723)

- Child-Pugh Class A
- Advanced HCC not eligible for surgical and/or locoregional therapies; or progressive disease after surgical and/or locoregional therapies

R

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graph LR; A[Eligibility n=1,723] --> B((R)); B --> C[Nivolumab]; B --> D[Sorafenib];
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Nivolumab

Sorafenib

Primary Endpoint: Overall Survival

CheckMate 459: Efficacy and Tolerability of Nivolumab versus Sorafenib as First-Line Therapy for Advanced HCC

Primary endpoint	Nivolumab (n = 371)	Sorafenib (n = 372)	HR	p-value
Median OS	16.4 mo	14.7 mo	0.85	0.0752
12-mo OS rate	59.7%	55.1%		
24-mo OS rate	36.8%	33.1%		

Additional endpoints	Nivolumab	Sorafenib
Median PFS	3.7 mo	3.8 mo
ORR (CR, PR)	15% (4%, 12%)	7% (1%, 6%)
Patients with PD-L1 $\geq 1\%$	28%	9%
Patients with PD-L1 $< 1\%$	12%	7%

- Grade 3 or 4 treatment-related AEs: NIVO = 22%; SOR = 49%
- Treatment discontinuation: NIVO = 4%; SOR = 8%
- No new safety signals were observed with NIVO

Editorial — Dr Bekaii-Saab

CheckMate 459, a Randomized, Multi-Center Phase III Study of Nivolumab Versus Sorafenib as First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma, did not show an improvement in outcome vs. sorafenib. As such, single targeted strategies with PD-1 inhibitors do not appear to have a role in the first-line treatment of HCC. Fortunately, all is not lost for examining the role of these agents in advanced HCC. There are hints that certain disease-specific immune markers may select better patients most likely to respond to PD-1/PD-L1 inhibitors with prospective validation needed. In addition, based on promising early clinical observations and a number of preclinical supportive studies, clinical trials examining the role of CTLA4 inhibitors, VEGF blockade or multikinase inhibitors added to PD-1/PD-L1 inhibitors are ongoing.

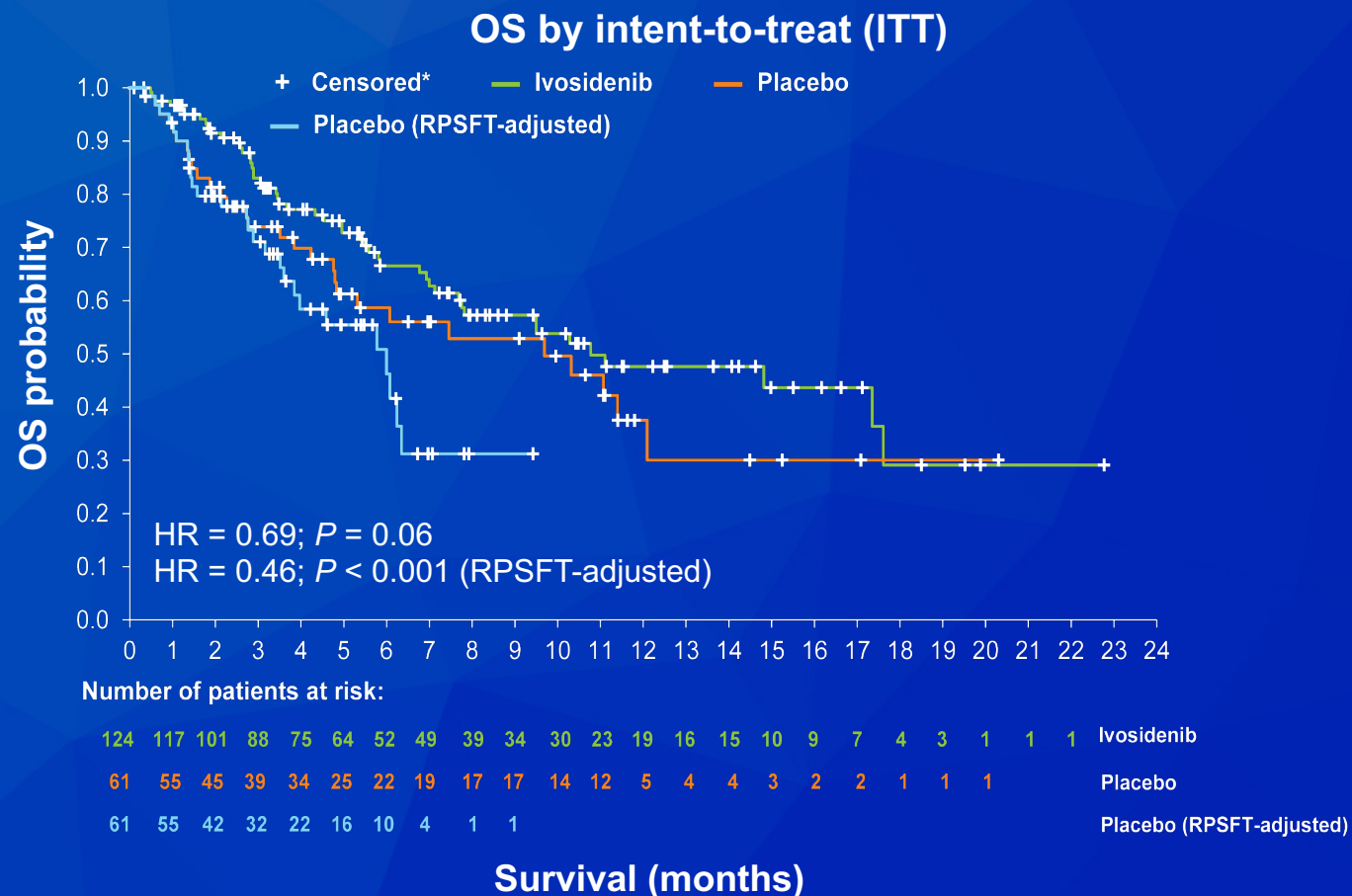
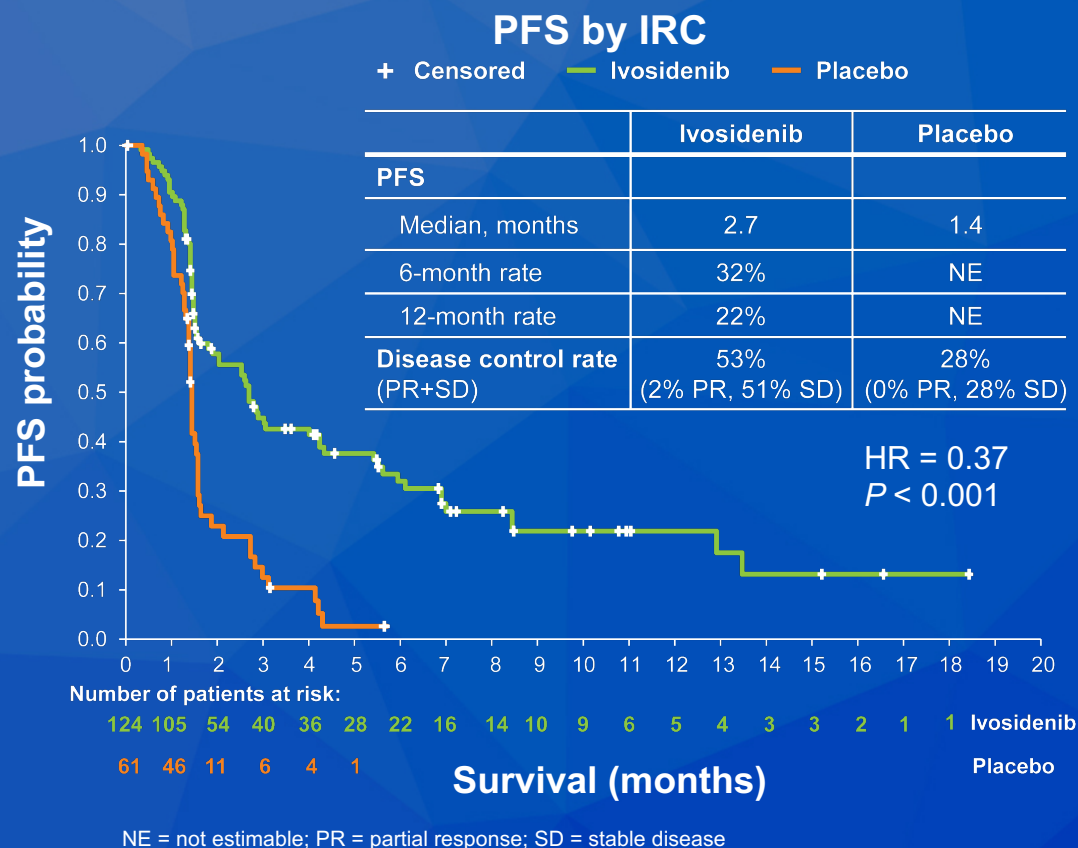
ClarIDHy: A Global, Phase 3, Randomized, Double-Blind Study of Ivosidenib vs Placebo in Patients with Advanced Cholangiocarcinoma with an Isocitrate Dehydrogenase 1 (IDH1) Mutation

Abou-Alfa GK et al.

Proc ESMO 2019;Abstract LBA10.



ClarIDHy: Survival Analysis



- Ivosidenib significantly improved PFS relative to placebo (HR = 0.37; $p < 0.001$) in patients with previously treated advanced cholangiocarcinoma with an IDH1 mutation
- Ivosidenib resulted in a numerical improvement in OS in comparison to placebo for the ITT population (HR = 0.46; $p < 0.001$)

Editorial — Dr O'Reilly

Cholangiocarcinoma is a rare malignancy with a number of actionable genomic alterations, including IDH1 mutations (18-20%), FGF fusions (15-20%), BRAF mutations, and others. IDH mutations do not appear to have prognostic value in cholangiocarcinoma. Ivosidenib (AG-120) is an IDH1 mutation inhibitor that induces differentiation and is FDA approved in AML. A phase I study of ivosidenib in cholangiocarcinoma demonstrated a PFS of 3.8 months and OS of 13.8 months (Lowery, *Lancet Gastroenterol Hepatol* 2019). The ClarIDHy trial was an international phase III trial in cholangiocarcinoma that evaluated ivosidenib 500 mg daily PO compared to placebo in a second- or third-line advanced disease setting. The primary endpoint was progression-free survival as adjudicated by blinded independent central review. Cross-over was permitted. The results were presented at ESMO 2019. Over 90% of patients had intrahepatic cholangiocarcinoma and metastatic disease.

Editorial — Dr O'Reilly (continued)

This was a positive phase III trial with the median PFS for ivosidenib vs placebo of 2.7 vs 1.4 months, HR 0.37 and p -value < 0.001 , and disease control was 53% vs 28%. Median OS was numerically longer (10.8 vs 9.7 months) for the ITT population, but when adjusted for cross-over (RPSFT), the OS was statistically significant: HR 0.46, $p < 0.001$. Ivosidenib was well-tolerated and quality of life analyses (physical and emotional functioning) favored ivosidenib over placebo. These data are under review with the FDA.

Gastrointestinal Cancers – Drs Bendell, Marshall and Wainberg

Hepatocellular Carcinoma

Cholangiocarcinoma

Colorectal Cancer

Pancreatic Cancer

Gastroesophageal Cancer

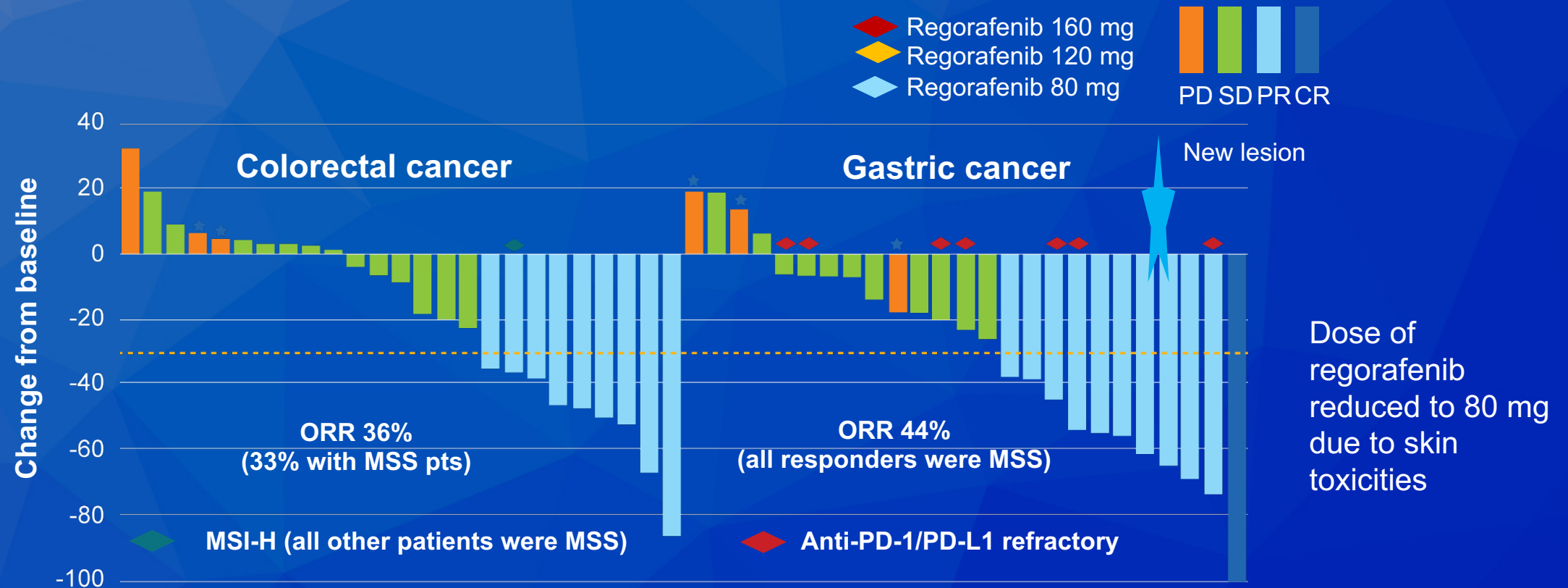
Regorafenib plus Nivolumab in Patients with Advanced Gastric (GC) or Colorectal Cancer (CRC): An Open-Label, Dose-Finding, and Dose-Expansion Phase 1b Trial (REGONIVO, EPOC1603)

Fukuoka S et al.

Proc ASCO 2019;Abstract 2522.



REGONIVO: A Phase Ib Study of Regorafenib with Nivolumab for CRC or Advanced Gastric Cancer (GC)



- Grade ≥ 3 treatment-related AEs (TRAEs) in all patients: 40%
- Grade ≥ 3 TRAEs in patients receiving regorafenib 80 mg: 27%
 - Proteinuria (9%), liver dysfunction (9%)
- One treatment-related death due to diabetic ketoacidosis

Editorial — Dr Hecht

Up to 97% of metastatic colorectal cancers are MSS and are resistant to single agent checkpoint inhibitors, making MSS CRC one of the largest unmet needs in immunotherapy. Preclinical models, however, have shown synergy between antiangiogenic agents and checkpoint inhibitors. Tumor angiogenesis has multiple potential immunosuppressive effects, including increasing intratumoral pressure, creating a hostile tumor microenvironment for infiltrating cytotoxic T cells, inhibiting dendritic cell maturation and increasing immunosuppressive Tregs and M2 tumor-associated macrophages. Small molecule anti-VEGFR TKIs inhibit several other potential nonangiogenic immunosuppressive pathways, including CSF1R, as well. There are multiple trials ongoing combining anti-VEGF agents and CPIs, and two phase III trials in renal cell carcinoma showed improved outcomes with axitinib plus a PD-L1 compared to single-agent sunitinib, though both VEGFR TKIs and CPIs have single-agent activity in RCC.

Editorial — Dr Hecht (continued)

Building on this, Hara and Fukuoka recently presented the exciting REGONIVO trial, a dose-escalation phase IB with expansion cohorts in patients with colon and gastric cancers. The combination was relatively well tolerated with MTD regorafenib 120mg and nivolumab 3mg/kg q2w. Focusing on the MSS colorectal cancer patients, they showed an impressive 33% response rate. In contrast, nivolumab has an expected 0% RR in MSS CRC while regorafenib single agent has a 1% RR. There was no correlation of response with PD-L1 expression, and many responses were durable and ongoing. If this can be replicated in the larger trials, it would truly be the immunotherapy breakthrough MSS CRC patients have been waiting for.

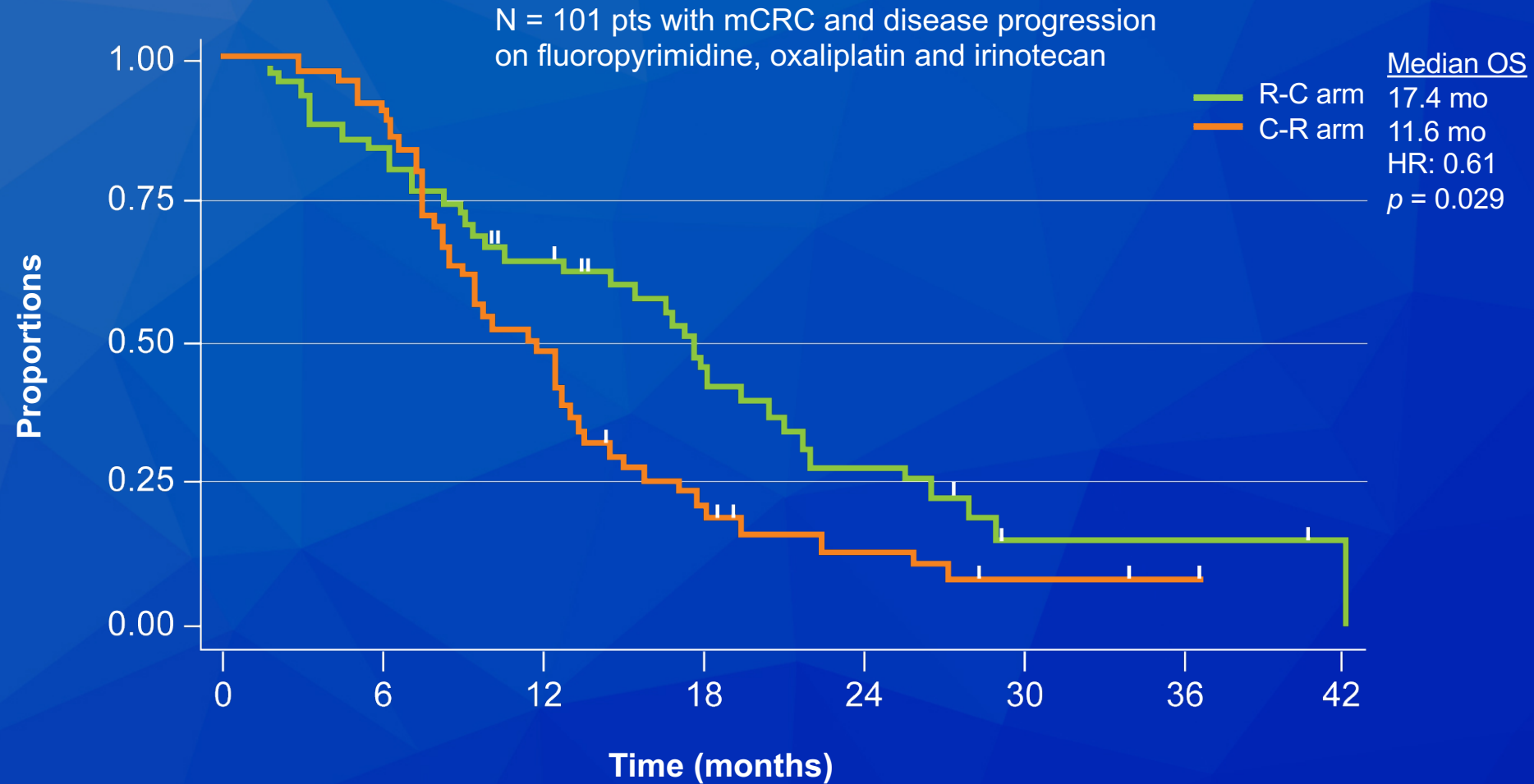
REVERCE: A Randomized Phase II Study of Regorafenib Followed by Cetuximab versus the Reverse Sequence for Previously Treated mCRC Patients

Shitara K et al.

Ann Oncol 2019;30(2):259-65.



REVERCE: Overall Survival with Regorafenib Followed by Cetuximab versus the Reverse Sequence



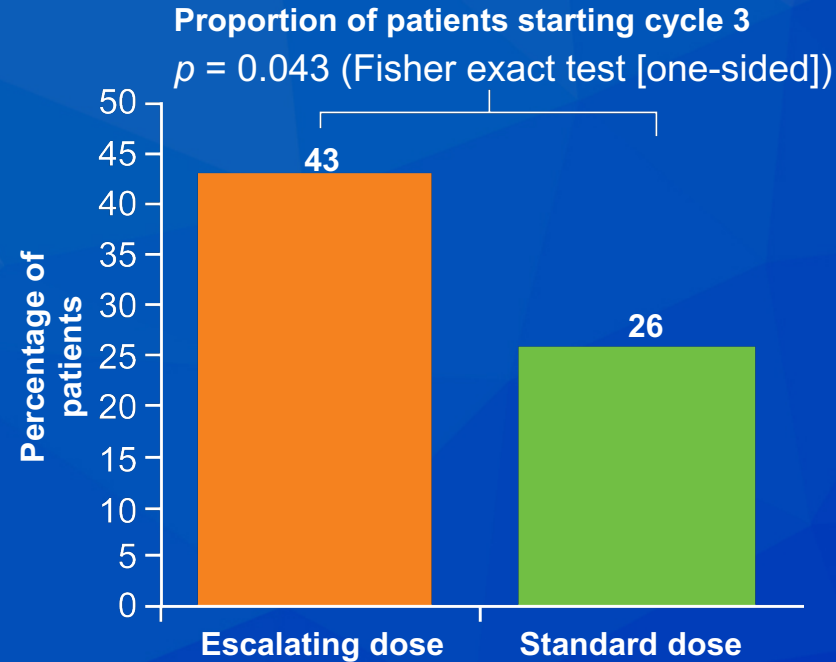
Regorafenib Dose-Optimisation in Patients with Refractory Metastatic Colorectal Cancer (ReDOS): A Randomised, Multicentre, Open-Label, Phase 2 Study

Bekaii-Saab TS et al.

Lancet Oncol 2019;20(8):1070-82.



Regorafenib Dose Optimization Study (ReDOS): A Phase II Trial to Evaluate Dosing of Regorafenib for Refractory mCRC



Survival	Esc dose (n = 54)	Std dose (n = 62)	HR	p-value
Median OS	9.8 mo	6.0 mo	0.72	0.12
Median PFS	2.8 mo	2.0 mo	0.84	0.38

- Multiple QoL parameters were favorable with the escalating dose versus standard dose strategy primarily at week 2 of cycle 1

Editorial — Dr Hecht

Regorafenib has modest, but definite, activity in salvage CRC, but toxicity has made dosing with the registrational dose of 160mg/day challenging, with many patients coming off treatment early. Several alternative dosing strategies are being examined in relatively small trials. Bekaii-Saab's ReDOS trial changed practice after being presented in 2018 and has now been published. This phase II trial compared a dose-escalation scheme starting with 80mg/day to standard dosing, showing at least comparable PFS (HR 0.72; 0.47-1.10) and an increased fraction of patients starting cycle 3, the primary endpoint. This strategy is now part of the NCCN guidelines. In the phase II REARRANGE trial, Argilés compared standard dosing with either starting at 120mg or 160mg alternating weeks and had similar outcomes, but less fatigue. Both trials show that alternative dosing regimens are reasonable and probably preferred.

Editorial — Dr Hecht (continued)

The Japanese REVERSE sequencing trial is a provocative regorafenib phase II which looked at the strategy of regorafenib followed by cetuximab vs cetuximab followed by regorafenib in the earlier treatment of KRAS exon 2 wild-type patients. While PFS was the same in both arms, overall survival was surprisingly higher in the regorafenib/cetuximab arm (HR 0.61; 0.39-0.96) with better second PFS. Potential reasons for this include upregulation of pro-angiogenic factors by earlier bevacizumab treatment now inhibited by regorafenib, upregulation of downstream resistance factors when cetuximab is used first, or random chance in a small study. This hypothesis-generating study requires confirmation in a larger trial before changing practice.

Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164.

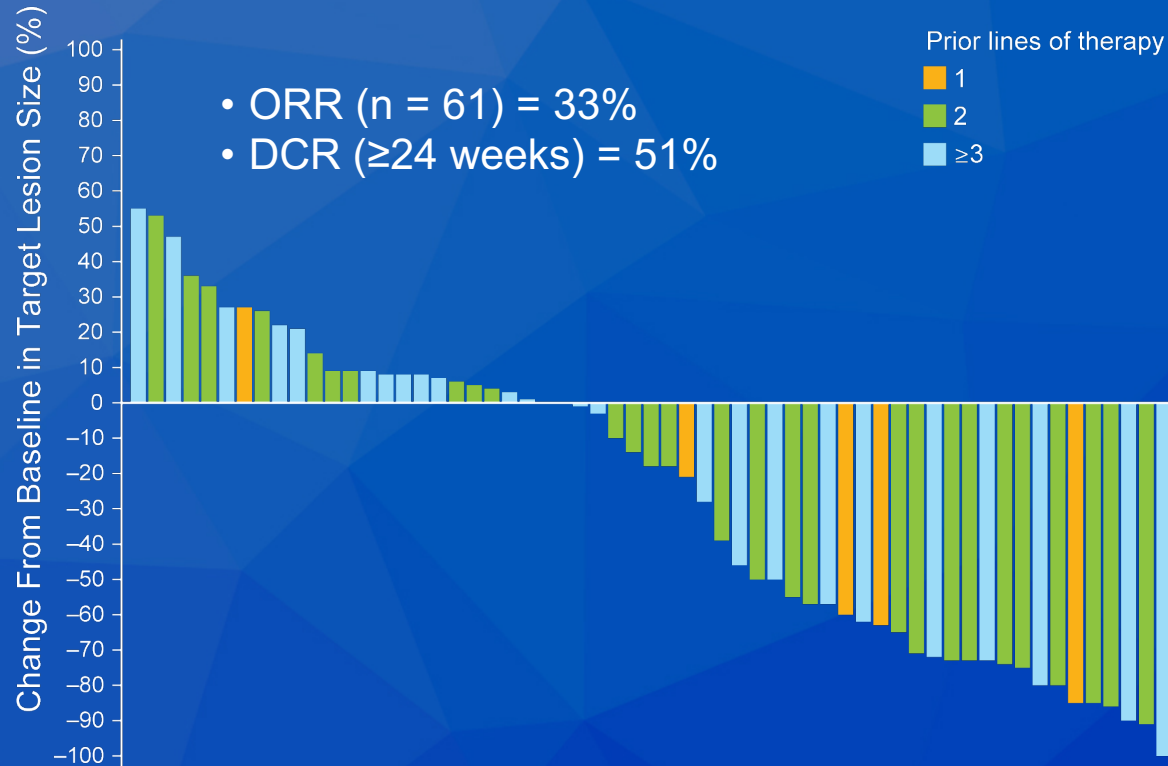
Le DT et al.

J Clin Oncol 2020;38(1):11-19.

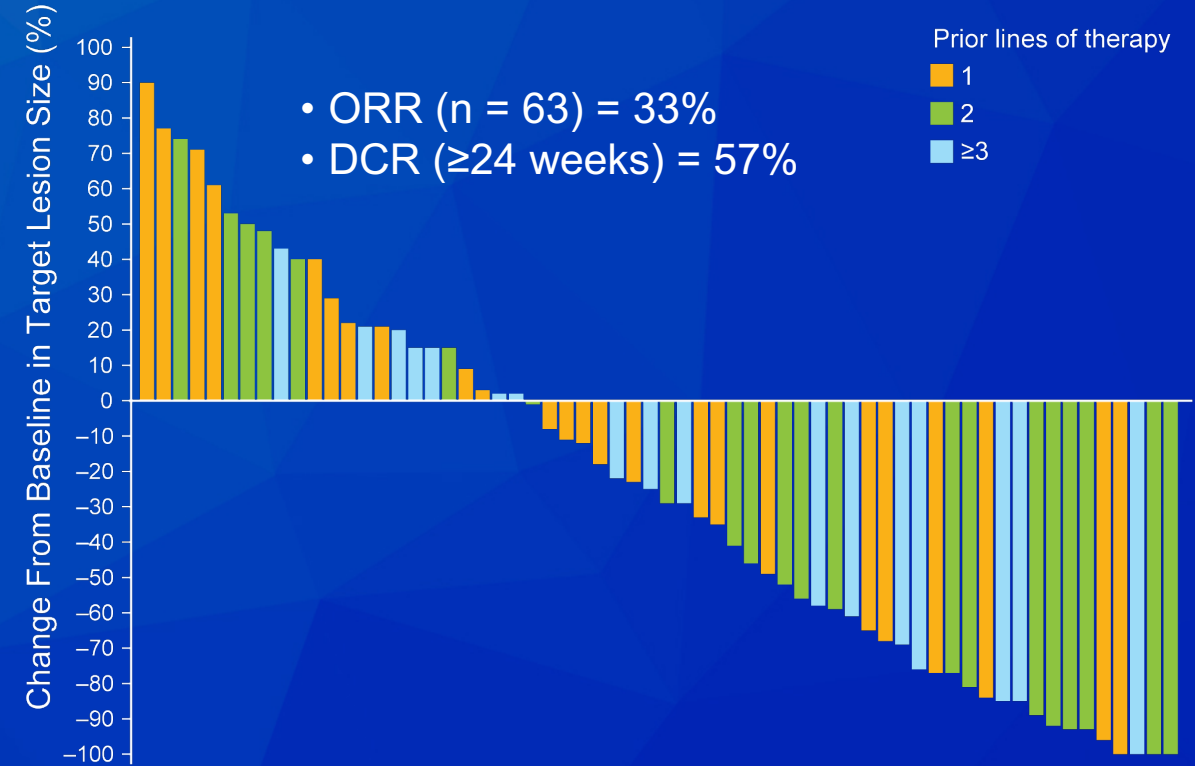


KEYNOTE-164: Pembrolizumab in Previously Treated dMMR/MSI-H mCRC

Cohort A: ≥ 2 prior lines of standard therapy



Cohort B: ≥ 1 prior line of systematic therapy



Select Grade 3/4 immune-mediated AEs:

- Cohort A: Pancreatitis (3%), hepatitis (2%), pneumonitis (2%), severe skin toxicity (2%)
- Cohort B: Colitis (2%), pneumonitis (2%)

Editorial — Dr Philip

mCRC patients with mismatch repair deficient (MMRd)/microsatellite instability-high (MSI-H) disease represent a subgroup known to benefit from immune checkpoint inhibitors. KEYNOTE-164 tested pembrolizumab in an open-label phase II study. Eligible patients had mCRC that progressed on 1 or more prior standard lines of therapy. One hundred and twenty-four patients were treated with pembrolizumab 200 mg Q3 weeks. Objective response (primary endpoint) was similar in patients who failed ≥ 1 or ≥ 2 lines of therapy, both at 33%, including a total of 7 CRs. Median duration of response was not reached. Median OS was not reached and 31.4 months in ≥ 1 and ≥ 2 line failure cohorts, respectively. The side-effect profile was what would be expected with this class of agents. Collectively data from KEYNOTE-164 firmly establishes the role of pembrolizumab's durable benefit in patients with mCRC who have progressed on 1 or more lines of therapy.

Editorial — Dr Philip (continued)

It is also noteworthy that results suggested a benefit from pembrolizumab irrespective of BRAF/RAS mutational status. KEYNOTE-164 supports the use of pembrolizumab earlier in the treatment sequence (e.g., second line) of mCRC, providing an alternative to cytotoxic-based therapy. The ongoing KEYNOTE-177 trial is addressing pembrolizumab's benefit in the frontline setting. In conclusion, KEYNOTE-164 supports the efficacy of pembrolizumab in this subgroup of molecularly defined patients with previously treated mCRC. It also demonstrates the value of routine testing for MMR/MSI in mCRC, to be performed earlier in the course of managing patients with mCRC.

Nivolumab (NIVO) + Low-Dose Ipilimumab (IPI) in Previously Treated Patients (pts) with Microsatellite Instability-High/Mismatch Repair-Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC): Long-Term Follow-Up

Overman MJ al.

Gastrointestinal Cancers Symposium 2019;Abstract 635.

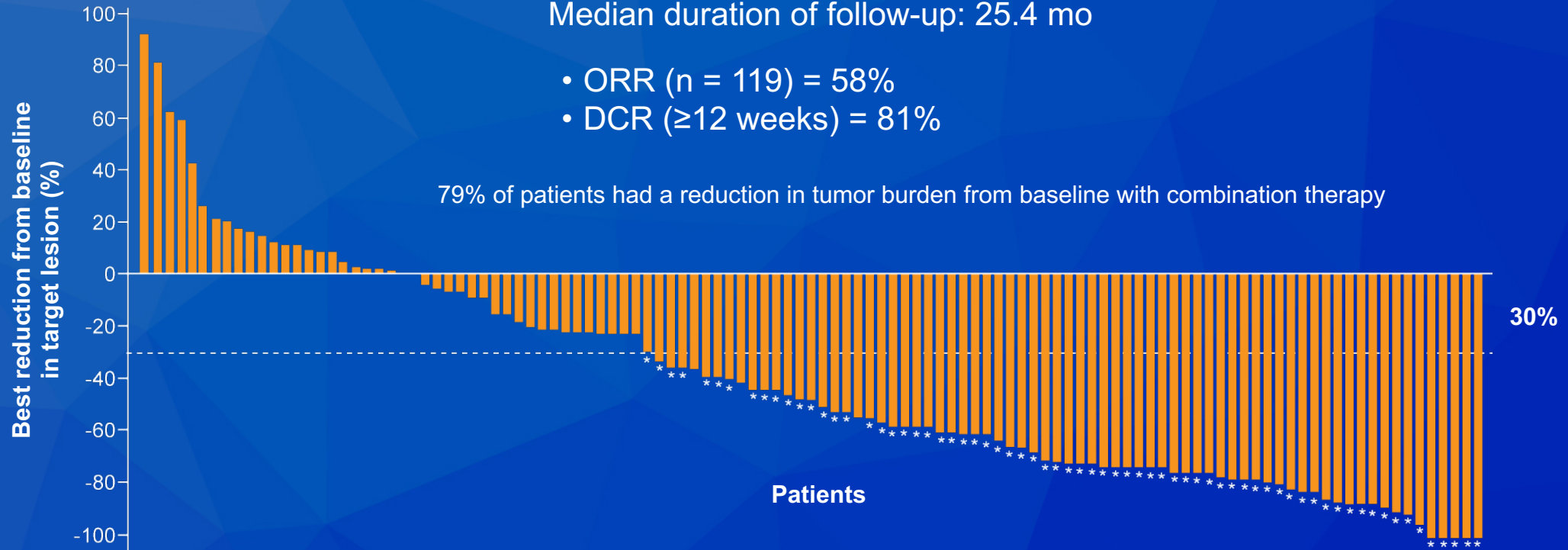


CheckMate 142: Long-Term Follow-Up of Nivolumab + Low-Dose Ipilimumab in Previously Treated dMMR/MSI-H mCRC

Nivo (3 mg/kg) + ipi (1 mg/kg) q3wk x 4, then nivo (3 mg/kg) q2wk until disease progression
Median duration of follow-up: 25.4 mo

- ORR (n = 119) = 58%
- DCR (≥12 weeks) = 81%

79% of patients had a reduction in tumor burden from baseline with combination therapy



Patients had target lesion at baseline and at least 1 on-treatment tumor assessment.

* Confirmed response per investigator assessment

- Select Grade 3/4 treatment-related AEs:
 - Elevated AST (8%), diarrhea (3%), pruritus (2%), fatigue (2%)

Editorial — Dr Bendell

Testing of microsatellite instability status has become standard of care in the management of patients with colorectal cancer. We have seen that checkpoint inhibitors are effective treatment options for patients with microsatellite instable colorectal cancer, likely secondary to increased tumor mutational burden. Pembrolizumab and nivolumab are both FDA approved for the treatment of patients with metastatic microsatellite instable colorectal cancer after progression on fluorouracil, oxaliplatin, and irinotecan chemotherapies. We have more recently seen the FDA approval of the combination of nivolumab plus ipilimumab for these patients. This approval was based on data from the phase II CheckMate 142 trial where patients were dosed with nivolumab at 3 mg/kg plus low-dose ipilimumab at 1 mg/kg for a total of 4 doses, continuing the nivolumab every 2 weeks until disease progression. In 119 patients treated, the overall response rate was 55%.

Editorial — Dr Bendell (continued)

The phase II data of nivolumab alone showed an overall response rate of 31%. Even more impressive for the combination was a 24-month progression free survival rate of 60% and a 24-month overall survival rate of 74%. At this point for patients who can tolerate nivolumab plus ipilimumab, there should be consideration of the combination rather than single agent checkpoint inhibitors based on this published data.

Currently the FDA approvals for checkpoint inhibitors either alone or in combination are in the post-chemotherapy setting. There are two major randomized trials currently evaluating the possible benefit of a checkpoint inhibitor and chemotherapy in the first-line setting. One is the KEYNOTE-177 trial, which compares pembrolizumab alone to standard first-line chemotherapy with FOLFOX or FOLFIRI and bevacizumab or cetuximab. This study has completed accrual and we look forward to the results.

Editorial — Dr Bendell (continued)

The next study (COMMIT) is FOLFOX plus bevacizumab with or without the PD-L1 inhibitor atezolizumab for patients with microsatellite instable colorectal cancer. This study is currently open and recruiting.

With the significant data seen using checkpoint inhibitors in the treatment of microsatellite instable colorectal cancer in the metastatic setting, trials are now addressing whether these agents would be effective in the adjuvant setting.

Two randomized studies are open and recruiting for this patient population. The first is the ATOMIC study, which randomizes patients with microsatellite instable stage III colon cancer to FOLFOX plus atezolizumab for 6 months followed by single agent atezolizumab for 6 months versus FOLFOX alone. The next study is the POLEM study, which randomizes patients to FOLFOX plus avelumab followed by single agent avelumab versus FOLFOX alone.

Editorial — Dr Bendell (continued)

The POLEM study will not only include patients with microsatellite instable colon cancer but also include patients with POLE mutated colon cancers. Patients with POLE mutations have a high frequency of mutations, which makes them more likely to respond to a checkpoint inhibitor.

Commonly the determination of mismatch repair deficiency is done via IHC testing. Some will also test for microsatellite instability using PCR or NGS assays. There is a new blood-based test that evaluates microsatellite instability using cell-free DNA. This test would be part of a larger blood-based profiling panel. A study looking at over 1000 samples and comparing the cell-free DNA results with standard of care tissue testing results showed an accuracy of 98.4% for the blood-based analysis with a positive predictive value of 95%. This suggests that one may be able to use blood-based testing to assess microsatellite instability.

Editorial — Dr Wainberg

It has been well established that deficiencies in mismatch proteins (dMMR) confer MSI and that simple IHC testing can identify 95% of those patients. Both single-agent nivolumab and pembrolizumab have demonstrated response rates of approximately 30%-40% as single agents in patients who have progressed on prior chemotherapy. Because many of the responses have been so durable, both drugs have received FDA breakthrough designations. In CheckMate 142, Overman et al have demonstrated that in a previously treated cohort there was an increase in RR to 26% with nivo + ipi (1 mg/kg). Most recently with much longer median follow-up reported, Overman et al have reported that the RR is even higher (58%) with a manageable safety profile. While there is an increase in RR, differences in PFS and OS have not clearly been demonstrated. In addition, while there is an increase in toxicity, primarily in regard to increases in grade 3 GI toxicity, it is much less than previously reported because only 4 doses of low-dose ipilimumab were received.

Editorial — Dr Wainberg (continued)

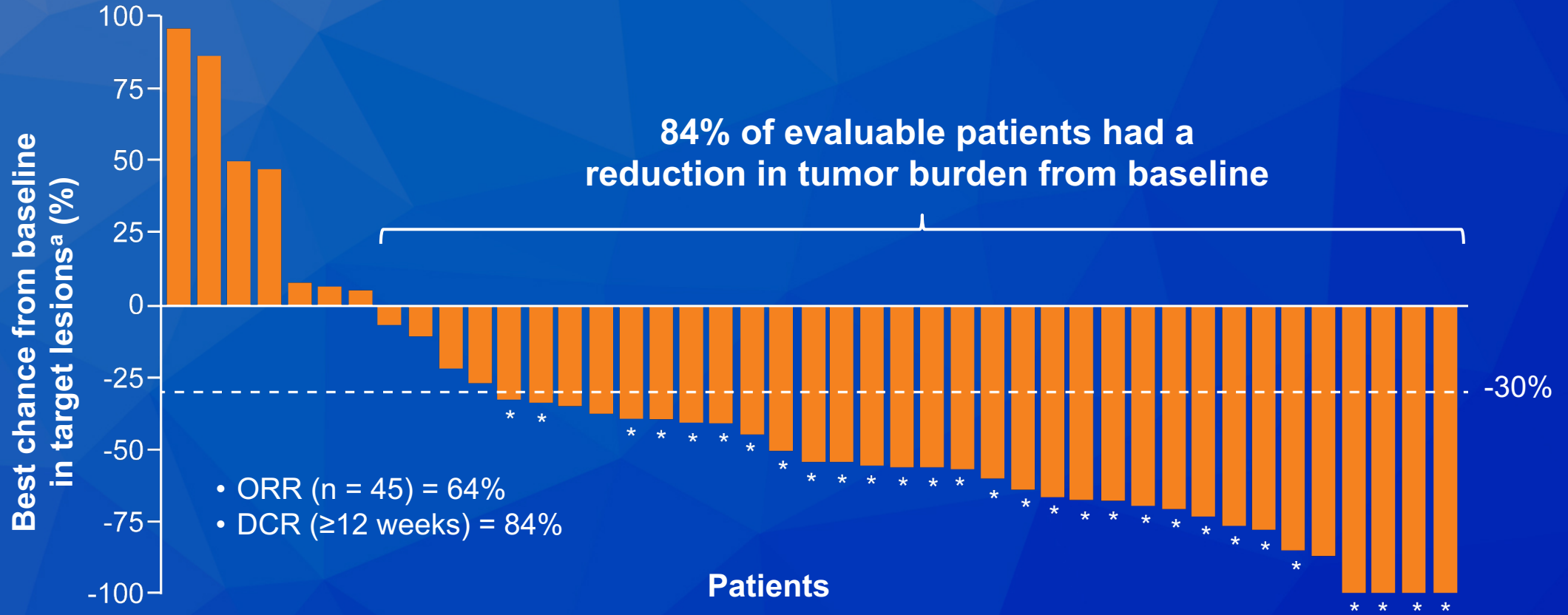
Ultimately, all practitioners now have 3 choices: single-agent nivo, single-agent pembro or nivo/ipi. A front-line study (KEYNOTE-177) has completed enrollment comparing single-agent pembro vs investigator's choice of chemotherapy. This study will provide much more clarity about the role of checkpoint inhibitors in MSI CRC and whether first-line therapy use will affect survival.

Nivolumab plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/DNA Mismatch Repair Deficient Metastatic Colorectal Cancer: Clinical Update

Lenz HJ al.

Gastrointestinal Cancers Symposium 2020;Abstract 11.

CheckMate 142: Nivolumab with Low-Dose Ipilimumab as First-Line Therapy for dMMR/MSI-H mCRC



* Confirmed response from investigator assessment

^a Evaluable patients per investigator assessment

Bevacizumab Improves Efficacy of Trifluridine/Tipiracil (TAS-102) in Patients with Chemorefractory Metastatic Colorectal Cancer: A Danish Randomized Trial

Pfeiffer P et al.

Proc ESMO World Congress GI 2019;Abstract O-014.



TAS-102 with Bevacizumab for Chemorefractory mCRC

- Randomized study with N = 93 patients with chemorefractory mCRC

	TAS-102/ bevacizumab	TAS-102	HR	<i>p</i>-value
Median PFS	4.6 mo	2.6 mo	0.45	0.001
Median OS	9.4 mo	6.7 mo	0.55	0.03

- Adverse events were as expected
- Grade 3 or 4 neutropenia (TAS-102/bev vs TAS-102): 67% vs 38% ($p < 0.05$)
- Serious adverse events (TAS-102/bev vs TAS-102): 19 patients vs 21 patients

Editorial — Dr Hecht

As noted above, anti-angiogenic agents are stopped when patients get treatment with anti-EGFR MAb or with salvage trifluridine/tipiracil (TAS-102). Prior anti-VEGF treatment such as bevacizumab can cause compensatory upregulation of multiple pro-angiogenic factors. There may be other synergies as well between anti-VEGF and cytotoxic therapies, and large randomized trials have shown benefits in continuing anti-VEGF therapy beyond progression. Single-agent TAS-102 has modest activity but improves PFS and overall survival in salvage CRC. Several trials have examined combining TAS-102 with bevacizumab. The C-TASK FORCE trial was a single-arm trial with better than expected outcomes with the combination. The recent TAS-CC3 study repeated this in a pure third-line setting with similar results. Pfeiffer now presents an 93-patient randomized phase II trial of TAS-102 +/- bevacizumab in the salvage setting with significantly improved PFS and OS (9.4 vs 6.7 months [HR 0.55, 0.32 to 0.94; $P = 0.03$]).

Editorial — Dr Hecht (continued)

The combination was well tolerated, though increased neutropenia was noted. If confirmed in a larger trial, this could lead to the use of bevacizumab with cytotoxics across even more lines of therapy.

Cytotoxic therapies also have preclinical synergy with CPIs and may upregulate PD-L1, cause immunogenic cell death, and reduce myeloid-derived suppressor cells. Patel, however, reported a single-arm phase II study of nivolumab with TAS-102 with no responders and PFS as expected with single-agent TAS-102. This does not encourage further exploration of the combination in unselected patients.

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: Encorafenib and Cetuximab with or without Binimetinib for mCRC with BRAF V600E Mutation

	ENCO/CETUX/BINI (n = 224)	ENCO/CETUX (n = 220)	Control – Irinotecan or FOLFIRI + cetuximab (n = 221)
Confirmed ORR	26%*	20%*	2%
Median OS	9.0 mo	8.4 mo	5.4 mo
Hazard ratio (<i>p</i> -value)	0.52 (<0.001)	0.60 (<0.001)	Ref

* *p*-value versus control < 0.001

Adverse events were as anticipated based on prior trials with each combination.

Editorial — Dr Hecht

Metastatic BRAF V600E mutant CRCs have a very poor outcome with low response rates to therapy and short overall survival. Unlike in melanoma, single-agent BRAF inhibition has little activity, and preclinical studies showed CRC-specific feedback loops involving EGFR. Building on this, several small trials of combinations of BRAF inhibitors with chemotherapy, anti-EGFR MAb and downstream MEK inhibitors have had promising results. BEACON is a randomized phase III trial comparing standard irinotecan-based therapy and cetuximab with a doublet of the BRAF inhibitor encorafenib with cetuximab and a triplet adding the MEK inhibitor binimetinib. There was a 30-patient run-in showing tolerable toxicity and a very promising 48% RR. Kopetz presented the randomized outcome data at ESMO World Congress on GI. The triplet had 26% RR compared to 22% for the doublet and 2% for standard therapy. Triplet OS was also increased compared to control (9.0 vs 5.4 m, HR 0.52, 0.39-0.70, $P < 0.0001$), while the doublet had similar results (HR 0.60).

Editorial — Dr Hecht (continued)

Toxicity was similar to the control despite longer time on treatment, though less with the doublet. These are exciting results for this poor-prognosis subgroup of patients and is a new standard of therapy. Nevertheless, the results are still not stellar compared to targeted therapies for driver mutations in other cancers, and several questions remain. The triplet was more toxic than the doublet with little further improvement in outcome. Which is the new standard? Finally, would adding chemotherapy further improve outcomes or just add toxicity?

Only the Doublet of Encorafenib and Cetuximab will Undergo Regulatory Review by the FDA for CRC with BRAF Mutation

Press Release – January 27, 2020

“The decision follows updated results from the three-arm BEACON CRC trial, a Phase III study showing that the BRAF/EGFR-inhibiting doublet reached a median OS of 9.3 months, identical to the arm that also included the MEK inhibitor binimetinib...compared with the study’s control arm (5.9 months) at a median follow-up of 12.8 months.

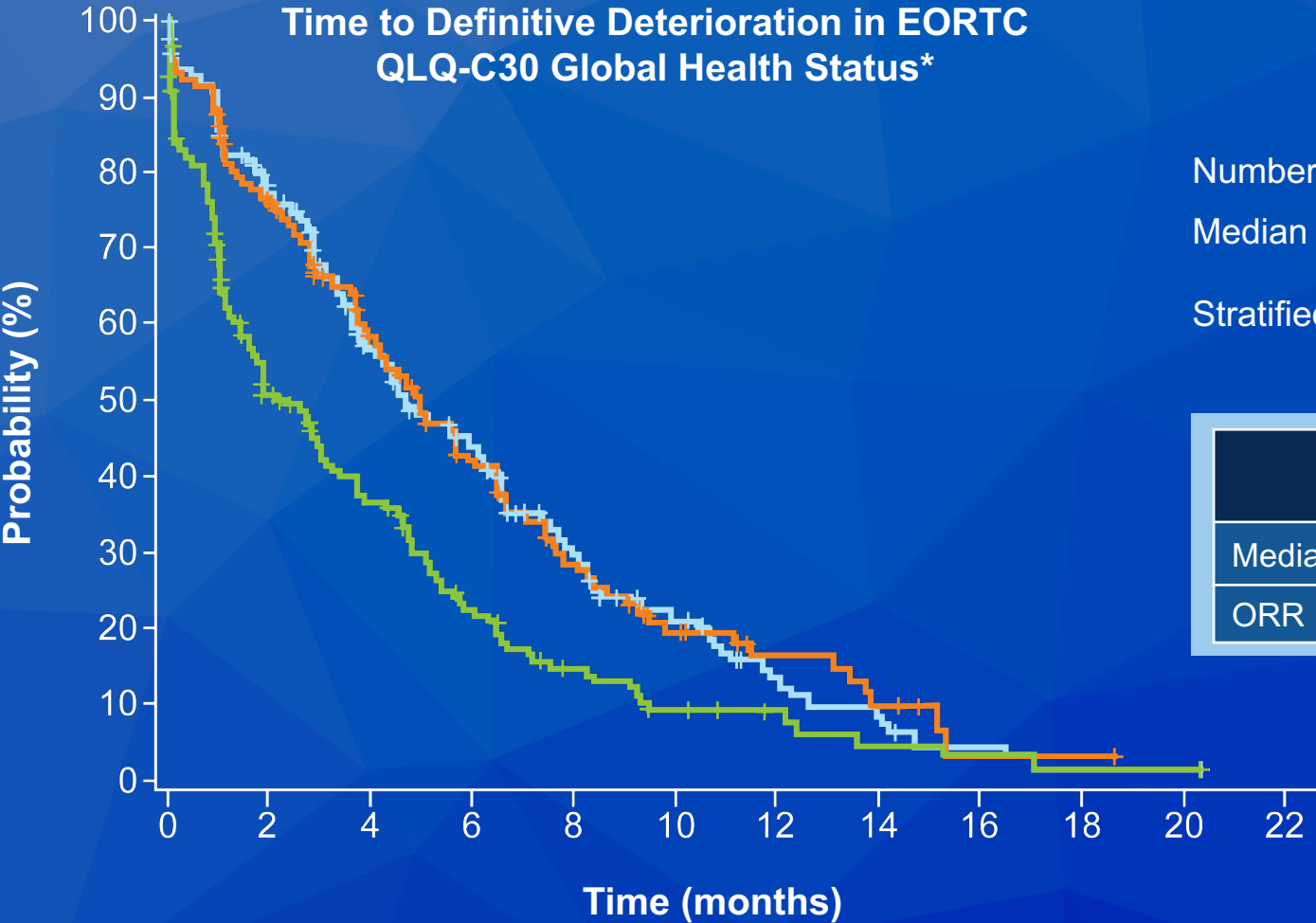
There’s really no discernable difference in the survival curves, Dr Scott Kopetz said during a Q&A following his presentation [at the 2020 Gastrointestinal Cancers Symposium]: So in my practice right now, I’m using the doublet.”

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

Kopetz S et al.

Gastrointestinal Cancers Symposium 2020;Abstract 8.

BEACON CRC: Maintenance of Quality of Life and Updated OS Analysis



	Triplet	Doublet	Control
Number of events (%)	138 (61.6)	146 (66.4)	151 (68.3)
Median (months)	4.96	4.60	2.20
Stratified HR	0.55 1.00	0.54 REF	REF

	Triplet (n = 224)	Doublet (n = 220)	Control (n = 221)
Median OS (f/u 12.8 mo)	9.3 mo	9.3 mo	5.9 mo
ORR	27%	20%	2%

* The time to definitive deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% worsening relative to baseline of the corresponding scale score with no later improvement above this threshold observed during the course of the study or death due to any cause.

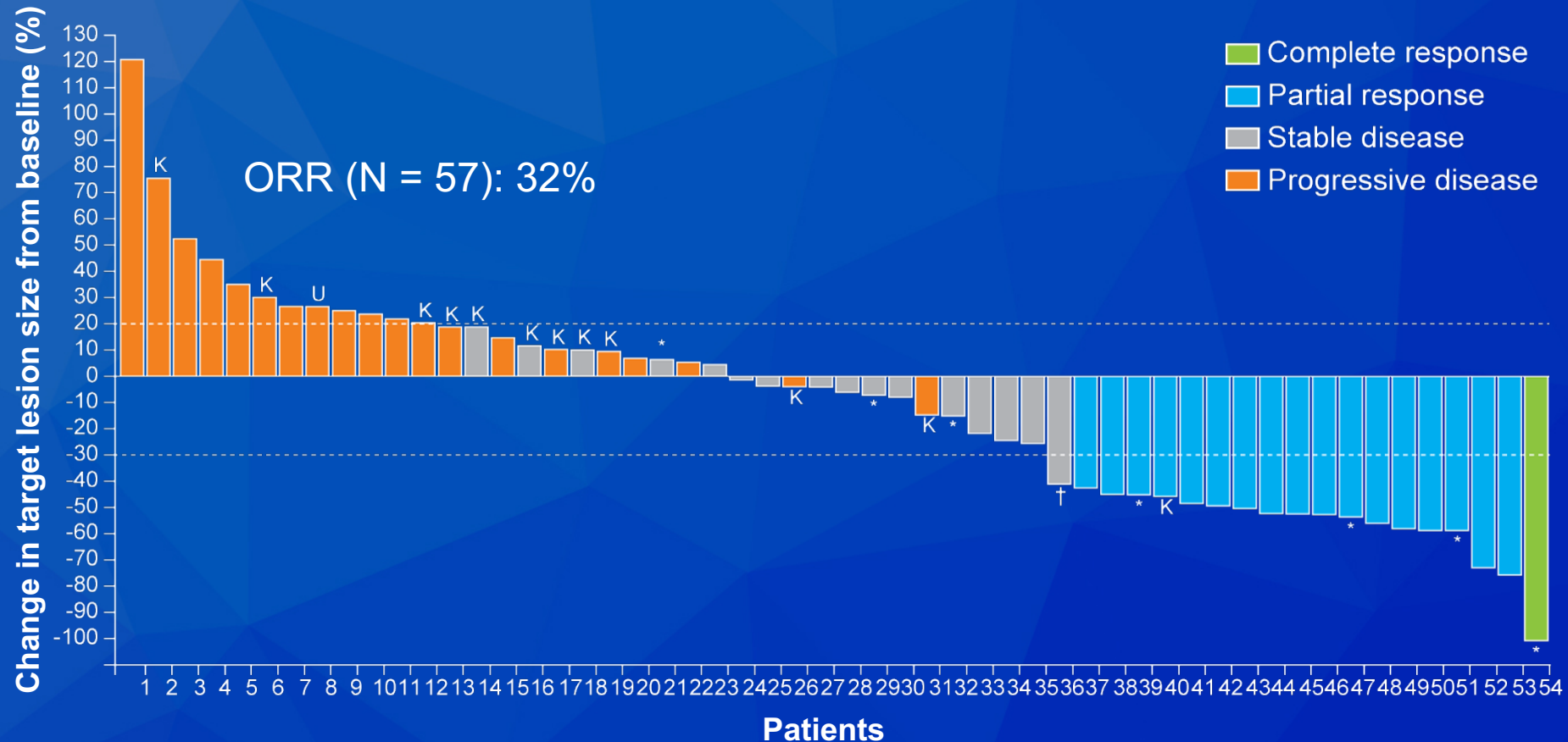
Pertuzumab plus Trastuzumab for HER2-Amplified Metastatic Colorectal Cancer (MyPathway): An Updated Report from a Multicentre, Open-Label, Phase 2a, Multiple Basket Study

Meric-Bernstam F et al.

Lancet Oncol 2019;20(4):518-30.



MyPathway Phase IIa Basket Study: Interim Analysis of Trastuzumab and Pertuzumab in HER2-Amplified mCRC Patient Cohort



K = KRAS-mutated; U = KRAS status unknown

* Treatment ongoing. † Patient with stable disease who had a 41% reduction in target lesion size at their final assessment on study but whose treatment was discontinued because of symptomatic deterioration.

Editorial — Dr Hecht

HER2 amplification/overexpression is found in a small fraction of patients with metastatic CRC. It may be a marker of poor prognosis and resistance to anti-EGFR therapy. Multiple anti-HER2 agents have been approved, leading to efforts to bring them to CRC patients. The first large trial was the Italian HERACLES trial which screened 914 KRAS exon 2 wild-type patients to treat 27 patients with trastuzumab and lapatinib yielding a 30% RR. Now Meric-Bernstam recently published the results of trastuzumab/pertuzumab in the HER2-amplified cohort of the MyPathway basket trial. 57 HER2-amplified patients received trastuzumab/pertuzumab, resulting in a 32% RR and 44% disease control. Median PFS was 2.9 months, but a few patients have had long-lasting responses. Correlative studies found that surprisingly 13 (23%) also had KRAS mutations, and only 1 of those responded. The results of these two trials have made these regimens options in the NCCN guidelines for HER2+ KRAS wild-type CRC.

Trastuzumab and Tucatinib for the Treatment of HER2 Amplified Metastatic Colorectal Cancer (mCRC): Initial Results from the MOUNTAINEER Trial

Strickler JH et al.
Proc ESMO 2019;Abstract 527PD.



MOUNTAINEER: Trastuzumab with Tucatinib for HER2-Amplified mCRC

- Single-arm Phase II for patients with RAS wt, HER2-amplified mCRC (n = 26)
 - Primary tumor site of origin: Right colon (n = 4), left colon/rectum (n = 17), transverse colon (n = 3) and overlapping (n = 2)

	Evaluable patients (n = 22)
Overall response rate	55%
Clinical benefit rate	64%
Median PFS	6.2 months
Median OS	17.3 months
Median DoR	Not reached

- Median follow-up = 10.6 months
- Grade 3 treatment-related AEs (TRAEs) = 9% (no grade 4/5 TRAEs)
- Most common TRAEs: AST elevation (48%; all G1), ALT elevation (30%; all G1) and diarrhea (26%)

Editorial — Dr Philip

Targeting HER2 is an emerging therapeutic strategy in patients with RAS wild-type metastatic colorectal cancer (mCRC). In fact, HER2 amplification/overexpression may contribute to suboptimal response to anti-EGFR drugs. Currently there are several approaches being developed in targeting HER2 in patients with mCRC, testing several anti-HER2 combinations. The MOUNTAINEER trial was a single-arm phase II study in patients with mCRC with overexpressed HER2 tumors who failed standard upfront therapy including an anti-VEGF antibody. Twenty-six patients received tucatinib (oral TKI targeting HER2, 300 mg BID) and standard-dose trastuzumab. Most patients had left-sided colon/rectal primaries. Overall response rate (primary endpoint) and median PFS were 55% and 6.2 months, respectively. Median OS was 17.3 months, and median duration of response was not reached. Nine percent of patients experienced grade 3 toxicities, mostly liver enzyme elevations and diarrhea.

Editorial — Dr Philip (continued)

The conclusion from this study at this time is that a “non-cytotoxic” based anti-HER2 regimen is active in patients with HER2-positive mCRC with manageable toxicities but needs further evaluation given the relatively small size of the current trial. Tucatinib plus trastuzumab would be a valid treatment option in mCRC after failure of first-line therapy and underscores the need to look for HER2 overexpression/amplification in patients with RAS wild-type tumor profile to extend treatment options. Testing early in the course of therapy for mCRC would be appropriate.

Napabucasin versus Placebo in Refractory Advanced Colorectal Cancer: A Randomised Phase 3 Trial

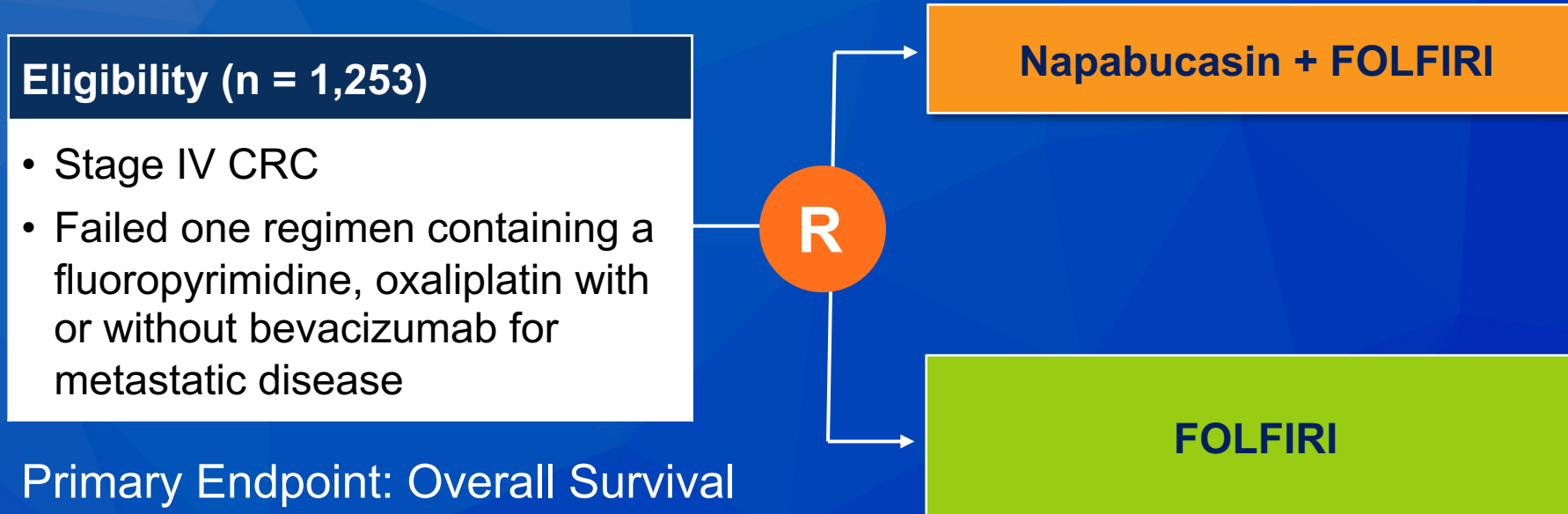
Jonker DJ et al.

Lancet Gastroenterol Hepatol 2018;3(4):263-70.

Phase III Trial of Napabucasin versus Placebo in Refractory Advanced CRC

- Patients with refractory, advanced CRC (n = 282) were randomized to napabucasin or placebo
- Median OS: napabucasin (n = 138) 4.4 mo, placebo (n = 144) 4.8 mo (HR 1.13, $p = 0.34$)
- A prespecified biomarker analysis of patients who were pSTAT3 positive: median OS: napabucasin 5.1 mo, placebo 3.0 mo (HR 0.41, $p = 0.0025$)
- Grade >3 AEs associated with napabucasin included diarrhea, fatigue, abdominal pain

CanStem303C: Ongoing Phase III Trial of Napabucasin in Combination with FOLFIRI for Previously Treated mCRC



Gastrointestinal Cancers – Drs Bendell, Marshall and Wainberg

Hepatocellular Carcinoma

Cholangiocarcinoma

Colorectal Cancer

Pancreatic Cancer

Gastroesophageal Cancer

FDA Approves Olaparib as First-Line Maintenance for Metastatic Pancreatic Cancer with a Germline BRCA Mutation

Press Release – December 27, 2019

“The Food and Drug Administration approved olaparib for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

The FDA also approved the BRACAnalysis CDx test as a companion diagnostic for the selection of patients with pancreatic cancer for treatment with olaparib based upon the identification of deleterious or suspected deleterious germline mutations in BRCA1 or BRCA2 genes.”

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer¹

Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial²

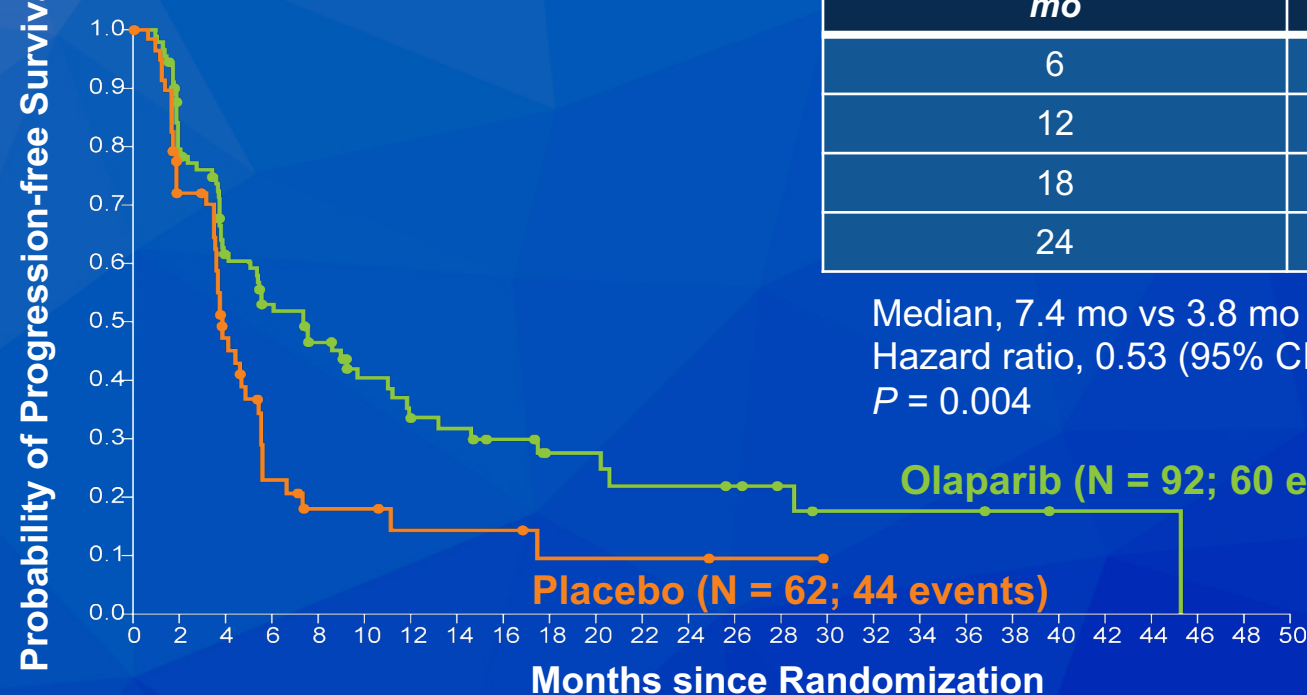
¹ Golan T et al.
N Engl J Med 2019;381(4):317-27.

² Kindler HL et al.
Proc ASCO 2019;Abstract LBA4.



POLO: A Phase III Trial of Maintenance Olaparib for Metastatic Pancreatic Cancer with BRCA Mutation

Progression-free Survival



Progression-free survival mo	Olaparib group	Placebo group
6	53.0%	23%
12	33.7%	14.5%
18	27.6%	9.6%
24	22.1%	9.6%

Median, 7.4 mo vs 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35-0.82)
 $P = 0.004$

Olaparib (N = 92; 60 events)

Placebo (N = 62; 44 events)

- An interim analysis of overall survival showed no difference between olaparib and placebo (median 18.9 mo vs 18.1 mo, HR 0.91, $p = 0.68$)
- The adverse-effect profile of maintenance olaparib was similar to that observed in other tumor types

Editorial — Dr Bekaii-Saab

The POLO study establishes a proof of concept that biomarker-driven therapies can be effective in pancreatic cancer as it has been very challenging to find targeted agents that have meaningful activity in this disease. Early data suggest that treatment with rucaparib is associated with historically similar outcomes to those observed with olaparib including in patients with somatic BRCA mutations and PALB2 mutations to be included. It is unclear how olaparib (or rucaparib) will fit into real-world practice. The maintenance setting assessed in the POLO study is not representative of how patients with pancreatic cancer are currently treated where typically we do not allow for treatment interruption. Typically, patients may switch to FOLFIRI following FOLFIRINOX. Data from the PRODIGE 35-PANOPTIMOX study also suggest that maintenance with 5-FU/leucovorin following FOLFIRINOX treatment of metastatic pancreatic cancer could provide similar PFS rates to continuation of FOLFIRINOX. Such a control arm was not tested in POLO, which makes the latter difficult to put into clinical context.

Editorial — Dr Bekaii-Saab (continued)

In addition to cost, the toxicity of olaparib is relatively manageable, but considerable adverse events have been associated with single agent. I do not see the benefit of switching to olaparib maintenance compared with continuing FOLFIRINOX, switching to FOLFIRI or even continuing 5-FU maintenance. Therefore, at this point in time, it is unclear how POLO would change current practice. I think the preferred pathway with PARP inhibitors remains with clinical trials that attempt to further improve the activity of these agents in patients with germline or somatic BRCA mutations and other alterations that represent BRCAness, such as homologous recombination deficiency. Patients may also benefit from trials assessing combinations of PARP inhibitors and immune therapy agents such as PD-1 inhibitors or rational topoisomerase inhibitors (such as nal-IRI).

APACT: Phase III, Multicenter, International, Open-Label, Randomized Trial of Adjuvant *Nab*-Paclitaxel plus Gemcitabine (*Nab*/Gem) vs Gemcitabine (G) for Surgically Resected Pancreatic Adenocarcinoma¹

An International, Randomized, Open-Label, Phase III Trial of Adjuvant *Nab*-Paclitaxel plus Gemcitabine vs Gemcitabine Alone for Surgically Resected Pancreatic Adenocarcinoma (APACT): Primary Analysis and Quality of Life Outcomes²

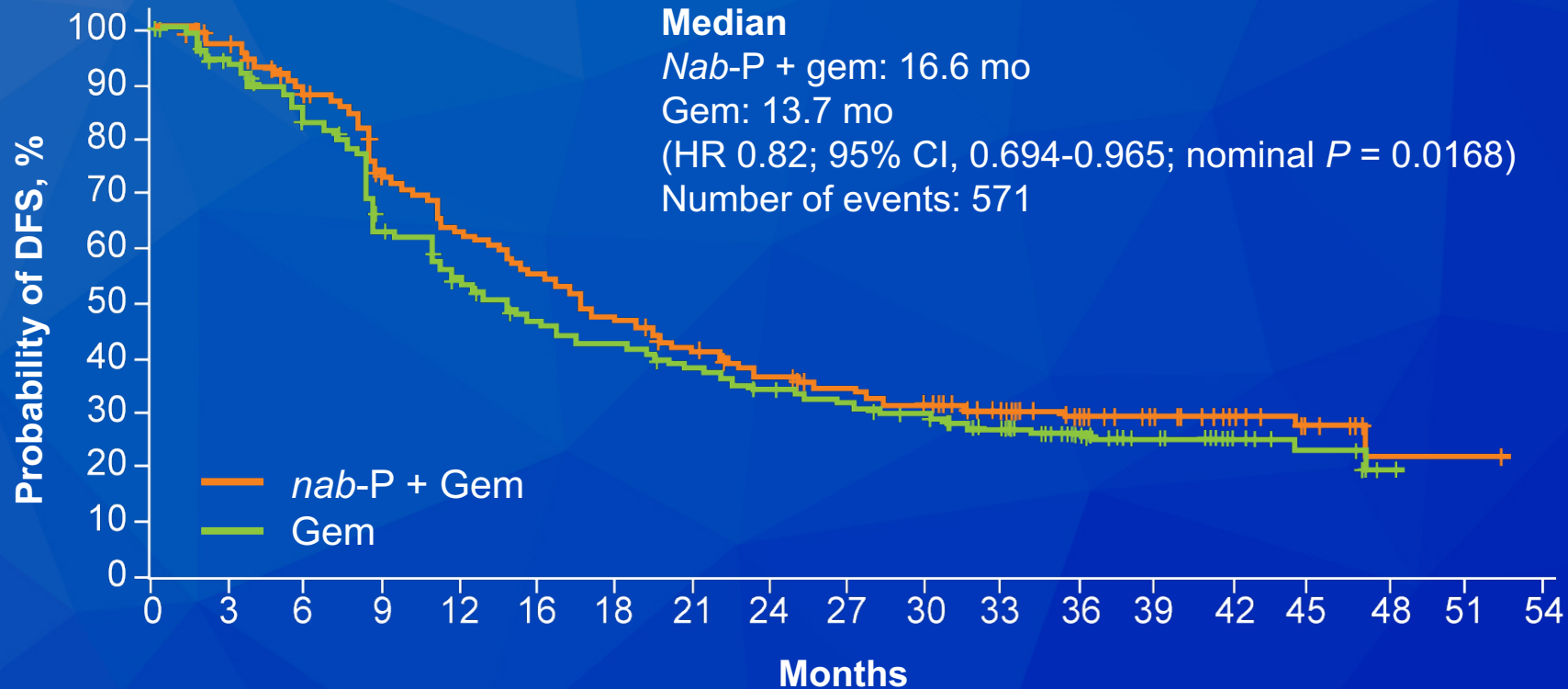
¹ Tempero MA et al. *Proc ASCO* 2019;Abstract 4000.

² Reni M et al. *Proc ESMO World Congress GI* 2019;Abstract O-001.



Phase III APACT Trial of Adjuvant Gemcitabine/*Nab* Paclitaxel for Surgically Resected Pancreatic Adenocarcinoma

Primary Endpoint: Investigator assessed DFS



- The primary endpoint was not met.
- Interim-analysis OS was improved for *nab*-P + gem compared to gem (40.5 mo vs 36.2 mo; HR 0.82, nominal $p = 0.045$).

Editorial — Dr Bekaii-Saab

The role of adjuvant chemotherapy in pancreas cancer has been established for 2 decades now. ESPAC-4 established the superiority of the combination of gemcitabine and capecitabine over single-agent gemcitabine. The challenge with this regimen had been with the continuous dosing of capecitabine over 21 days which limited its applicability in the US patient population. Different dosing strategies including intermittent breaks (weekends or week on/off) allowed for better tolerability. A secondary analysis from ESPAC-4 suggests no significant differences between the time to recurrence and subsequent and overall survival between local and distant recurrence. These results strongly suggest that pancreatic cancer behaves as a systemic disease requiring effective systemic therapy following resection. The PRODIGE trial results showed a significant and meaningful improvement in all outcomes with FOLFIRINOX vs. gemcitabine. Unfortunately, most of patients with pancreas cancer are unable to tolerate FOLFIRINOX following resection.

Editorial — Dr Bekaii-Saab (continued)

The disappointing results of APACT comparing gemcitabine and *nab*-paclitaxel to gemcitabine have closed the door on additional options for this group of patients. The collective interpretation of these results suggests that mFOLFIRINOX is the preferred option for patients who are eligible for the treatment (younger, great PS, great recovery from surgery, etc). For most others, gemcitabine and capecitabine should be considered while acknowledging the limitations of the capecitabine dosing schedule. My preference is for every other week, which seems to have the best tolerability while maintaining dose. The role of radiation remains undefined, with data strongly suggesting the lack of benefit regardless of margin status in the adjuvant setting.

Since close to 30% of patients with resected pancreas cancer will never receive adjuvant therapy for various reasons, total neoadjuvant therapy has become a standard at our institution and many other centers with emerging supportive data and more on the way.

NAPOLI-1 Phase 3 Study of Liposomal Irinotecan in Metastatic Pancreatic Cancer: Final Overall Survival Analysis and Characteristics of Long-Term Survivors¹

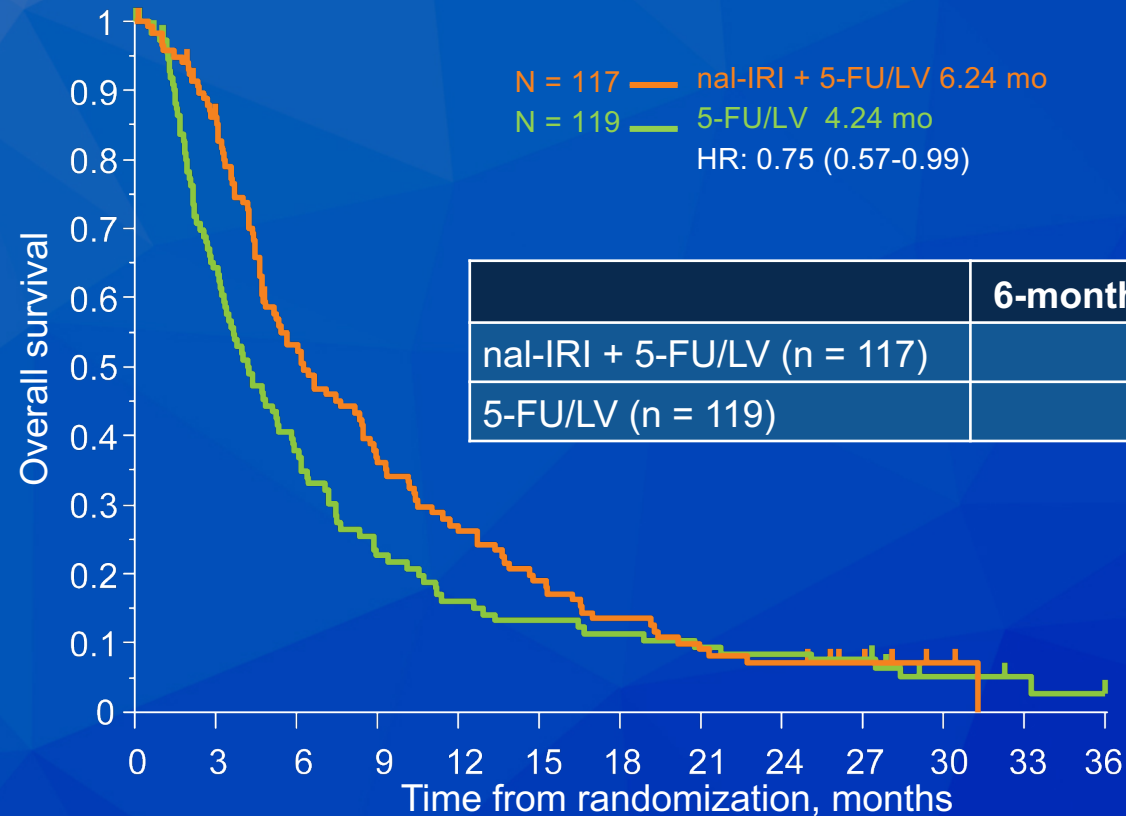
Quality of Life in Metastatic Pancreatic Cancer Patients Receiving Liposomal Irinotecan plus 5-Fluorouracil and Leucovorin²

¹ Wang-Gillam A et al.
Eur J Cancer 2019;108:78-87.

² Hubner RA et al.
Eur J Cancer 2019;106:24-33.



NAPOLI-1: Final Overall Survival and Tolerability with NaI-IRI/5-FU/LV vs 5-FU/LV as Second-Line Therapy



- Grade 3 and 4 adverse events with nal-IRI + 5-FU/LV included neutropenia (15.4%), diarrhea (9.4%), vomiting (6.0%) and fatigue (6.8%)
- Health-related quality of life was maintained with nal-IRI + 5-FU/LV

Editorial — Dr Bekaii-Saab

A nanoliposomal formulation of irinotecan (nal-IRI) added to 5-FU was shown to improve all efficacy outcomes vs. 5-FU alone following gemcitabine failure in first line. Survival benefits were maintained with long-term follow up while QOL did not seem to be compromised with the combination of nal-IRI and 5-FU. The collective interpretation of the initial and long-term outcomes suggests that the combination of nal-IRI and 5-FU should be considered as the preferred option for all patients who fail prior gemcitabine-based regimens. These results should also encourage us to consider gemcitabine and *nab*-paclitaxel (including biweekly schedule) as the preferred first-line regimen for most patients since sequential exposure to the regimens allows for improved tolerability while maintaining outcomes, as shown in multiple real-world observational studies. This paradigm should exclude those with known BRCA1/2 and PALB2 mutations where FOLFIRINOX would be preferred.

Efficacy of Pembrolizumab in Patients with Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results from the Phase II KEYNOTE-158 Study¹

Pembrolizumab for Advanced Anal Squamous Cell Carcinoma (ASCC): Results from the Multicohort, Phase II KEYNOTE-158 Study²

¹ Marabelle A et al.
J Clin Oncol 2020;38(1):1-10.

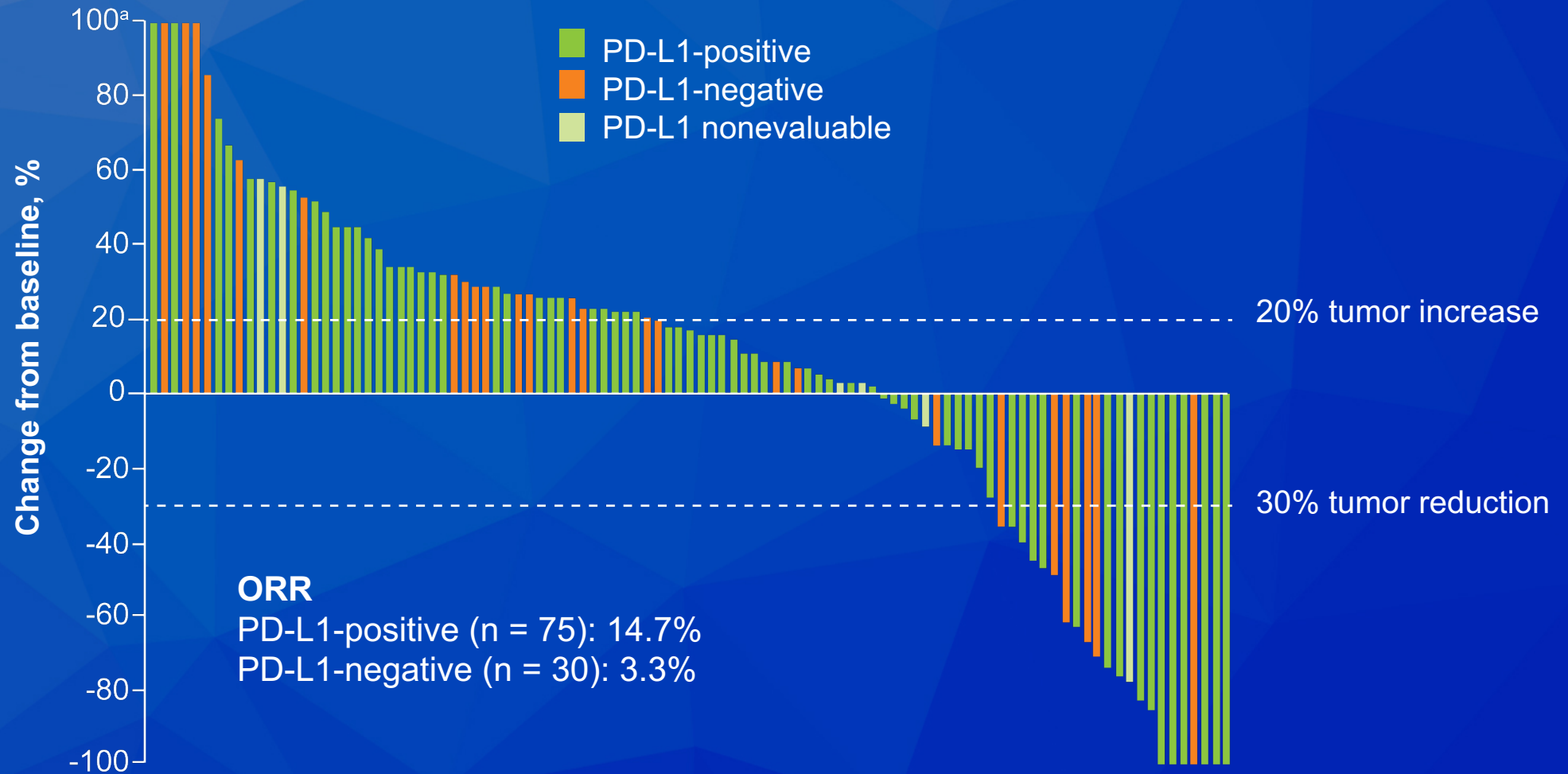
² Marabelle A et al.
Gastrointestinal Cancers Symposium 2020;Abstract 1.

KEYNOTE-158: Pembrolizumab for Noncolorectal dMMR/MSI-H Cancer

Tumor type	ORR	Median PFS	Median OS	Median DOR
Endometrial (n = 49)	57.1%	25.7 mo	NR	NR
Gastric (n = 24)	45.8%	11.0 mo	NR	NR
Cholangiocarcinoma (n = 22)	40.9%	4.2 mo	24.3 mo	NR
Pancreatic (n = 22)	18.2%	2.1 mo	4.0 mo	13.4 mo
Small intestine (n = 19)	42.1%	9.2 mo	NR	NR
Anal SCC (n = 112)	10.7%	2.0 mo	11.9 mo	NR
Ovarian (n = 15)	33.3%	2.3 mo	NR	NR
Brain (n = 13)	0%	1.1 mo	5.6 mo	—

NR = not reached

KEYNOTE-158: Tumor Response with Pembrolizumab in Patients with ASCC Based on PD-L1 Status



^a Percentage changes from baseline >100% are presented as 100%.
Data cutoff date: June 27, 2019.

Gastrointestinal Cancers – Drs Bendell, Marshall and Wainberg

Hepatocellular Carcinoma

Cholangiocarcinoma

Colorectal Cancer

Pancreatic Cancer

Gastroesophageal Cancer

Pembrolizumab with or without Chemotherapy versus Chemotherapy for First-Line Treatment of Advanced Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma: The Phase 3 KEYNOTE-062 Study¹

Pembrolizumab with or without Chemotherapy versus Chemotherapy for Advanced Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma: The Phase III KEYNOTE-062 Study²

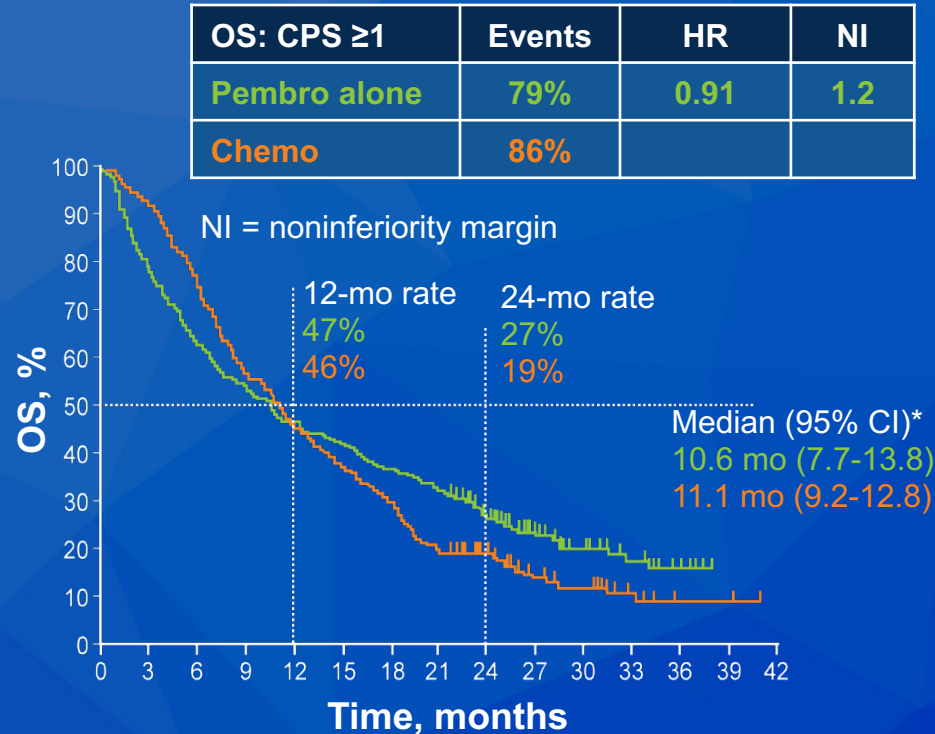
Tabernero J et al.

¹*Proc ESMO World GI Cancer Congress 2019;Abstract LBA-002.*

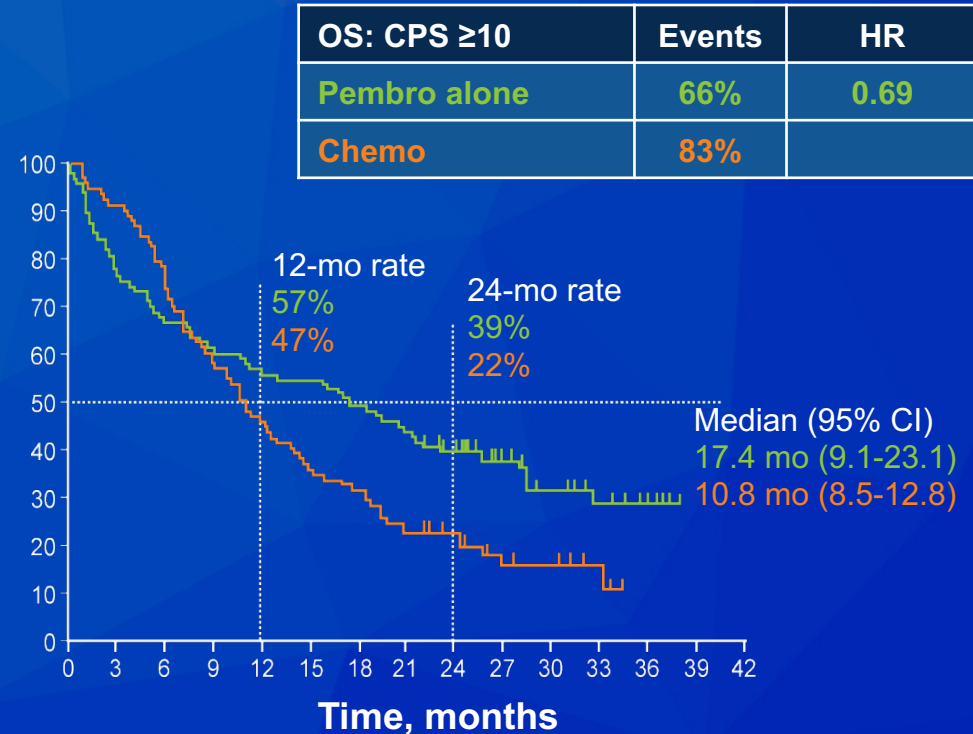
²*Proc ASCO 2019;Abstract LBA4007.*



KEYNOTE-062: A Phase III Trial of Pembrolizumab with and without Chemotherapy as First-Line Treatment for Advanced Gastric or GEJ Adenocarcinoma



* HR (95% CI) = 0.91 (0.74-1.10); $p = 0.162$ for superiority of pembro vs chemo



- Pembrolizumab was noninferior to chemotherapy for OS in patients with CPS ≥ 1 , and a clinically meaningful improvement in OS was reported with pembro vs chemo for patients with CPS ≥ 10 .
- Pembrolizumab + chemotherapy did not show superior OS and PFS for patients with CPS ≥ 1 and OS for CPS ≥ 10 .

Editorial — Dr Bendell

The KEYNOTE-062 study was a trial for patients with first-line metastatic gastric cancer that looked at pembrolizumab with or without chemotherapy versus chemotherapy. Patients with HER2-negative and PD-L1 positive disease (CPS ≥ 1) were randomized to pembrolizumab versus pembrolizumab plus chemotherapy, with the chemotherapy consisting of fluorouracil plus platinum, or placebo plus chemotherapy. Interestingly, looking at the comparison of the combination of pembrolizumab plus chemotherapy versus chemotherapy, there was really no difference seen in overall survival between the two arms. However, looking at the comparison between pembrolizumab alone and chemotherapy alone, the trial did meet its pre-specified noninferiority margin, showing that pembrolizumab was noninferior to chemotherapy for overall survival. For patients who had CPS ≥ 10 the improvement in median overall survival with pembrolizumab versus chemotherapy alone showed a hazard ratio of 0.69.

Editorial — Dr Bendell (continued)

Of note, for patients with CPS ≥ 1 the overall response rate for pembrolizumab alone was 15% versus 37% with chemotherapy alone, and for patients with CPS ≥ 10 the response rate for pembrolizumab alone was 25% and chemotherapy alone 38%. So while pembrolizumab versus chemotherapy met noninferiority, in making a treatment decision one does need to consider if the patient needs a response and what the CPS score is. But we do now see a role for certain selected patients of using pembrolizumab alone as first-line treatment for advanced gastric cancer.

Editorial — Dr Wainberg

This long-awaited trial was the largest trial to date comparing checkpoint inhibitors to chemo in patients with newly diagnosed metastatic gastric cancer. There were 3 arms in this study, and only patients with PDL1+ (CPS >1) were enrolled. There were multiple gated primary endpoints in this study with complex statistics. Patients were randomized to either chemo alone (5-FU/cis or cape/cis), pembro alone or the combination. Surprisingly, there was no significant benefit in the combination group over chemo alone, even among the CPS ≥ 10 patient population. One of the primary endpoints of the study was noninferiority of pembro vs chemo in the PDL1+ patient population. In this trial, this endpoint was met with similar OS rates of pembro (10.6 months), vs chemo (11.1 months). In the CPS ≥ 10 population, there was a benefit of pembro, but this study was not powered to do this analysis. However, both PFS and response rate were superior in the chemo group compared to pembro.

Editorial — Dr Wainberg (continued)

In a subset analysis of MSI patients, there was a clear benefit of pembro over chemo in all objective categories, although the small numbers preclude detailed statistical analysis. Overall, this study left many questions unanswered: Why was there no improvement at all with the combination of chemo + pembro even among PDL1+ patients? Is there a complete lack of synergy between infusional 5-FU and pembro? In this trial, as we have been accustomed to seeing, the survival curves cross, indicating a high percentage of patients in the investigational arm progressed quickly, but there was a “tail of the curve.”

FDA Approves Trifluridine/Tipiracil for Recurrent, Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma

Press Release – February 22, 2019

“The Food and Drug Administration approved trifluridine/tipiracil tablets a fixed combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor—for adult patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

Approval was based on TAGS (NCT02500043), an international, randomized, double-blind, placebo-controlled trial in 507 patients with metastatic gastric or GEJ adenocarcinoma previously treated with at least two prior lines of chemotherapy.”

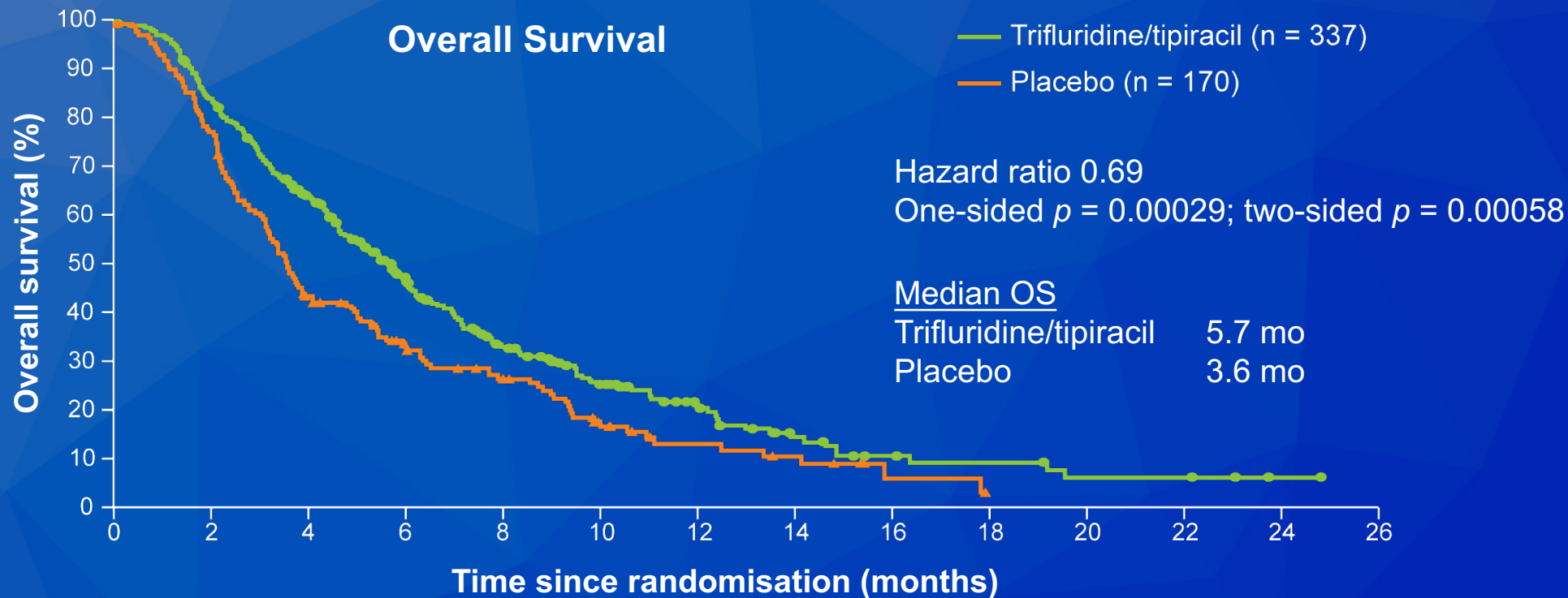
Trifluridine/Tipiracil versus Placebo in Patients with Heavily Pretreated Metastatic Gastric Cancer (TAGS): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial

Shitara K et al.

Lancet Oncol 2018;19(11):1437-48.



TAGS: Outcome Summary



Clinical variable	TAS-102	Placebo	HR	p-value
Median PFS (n = 337, 170)	2.0 mo	1.8 mo	0.57	<0.0001
ORR (n = 290, 145)	4.0%	2.0%	—	0.28

- Most frequent Grade ≥ 3 AEs of any cause with trifluridine/tipiracil were neutropenia (34%) and anemia (19%).

Editorial — Dr Bendell

TAS-102, or trifluridine/tipiracil, is a nucleoside metabolic inhibitor combined with a thymidine phosphorylase inhibitor. We have seen activity of TAS-102 in patients with refractory colorectal cancer who had already progressed on a fluoropyrimidine. The TAGS study assessed the activity of TAS-102 in a refractory gastric cancer patient population. This study randomized patients with refractory metastatic gastric adenocarcinoma to TAS-102 versus placebo. An improvement in overall survival with a hazard ratio of 0.69 was seen. Median overall survival was 5.7 months in the treatment group and 3.6 months in the placebo group. Adverse events were similar to those seen in patients with colorectal cancer treated with TAS-102, including neutropenia and anemia. Because of this improvement in survival status, TAS-102 was FDA approved in February of 2019 for the treatment of patients with refractory gastroesophageal cancers.

Editorial — Dr Wainberg

The oral cytotoxic chemotherapy drug TAS-102 has been approved in metastatic CRC for many years and was studied in the TAGS trial in metastatic gastric cancer. In this global Phase III trial, 337 patients were randomized to TAS-102 and 170 to placebo. This patient population included patients who had at least 2 prior lines of therapy. Of the group enrolled, approximately 35% of patients received 2 prior lines, 35% received 3 prior lines and approximately 25% received ≥ 4 prior lines. In this trial, the primary endpoint of overall survival was met with an increase from 3.6 months to 5.7 months (HR of 0.69). There was also a small statistically significant advantage of PFS, but no difference in response rate was seen. Overall, similar to metastatic CRC, this trial met its primary endpoint and accordingly was FDA approved. Also similar to CRC, the primary toxicities were cytopenias and fatigue. The dose studied and approved was the same dose approved for metastatic CRC. This represents an additional option for patients with metastatic gastric cancer.

Pembrolizumab Approved as Monotherapy for Recurrent Locally Advanced or Metastatic Squamous Cell Carcinoma of the Esophagus

Press Release – July 31, 2019

“The US Food and Drug Administration has approved pembrolizumab as monotherapy for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

The approval was based on data from KEYNOTE-181, a multicenter, randomized, open-label, active-controlled trial [for] patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease.”

The Phase 3 KEYNOTE-181 Study: Pembrolizumab versus Chemotherapy as Second-Line Therapy for Advanced Esophageal Cancer¹

Pembrolizumab versus Chemotherapy as Second-Line Therapy for Advanced Esophageal Cancer: Phase III KEYNOTE-181 Study²

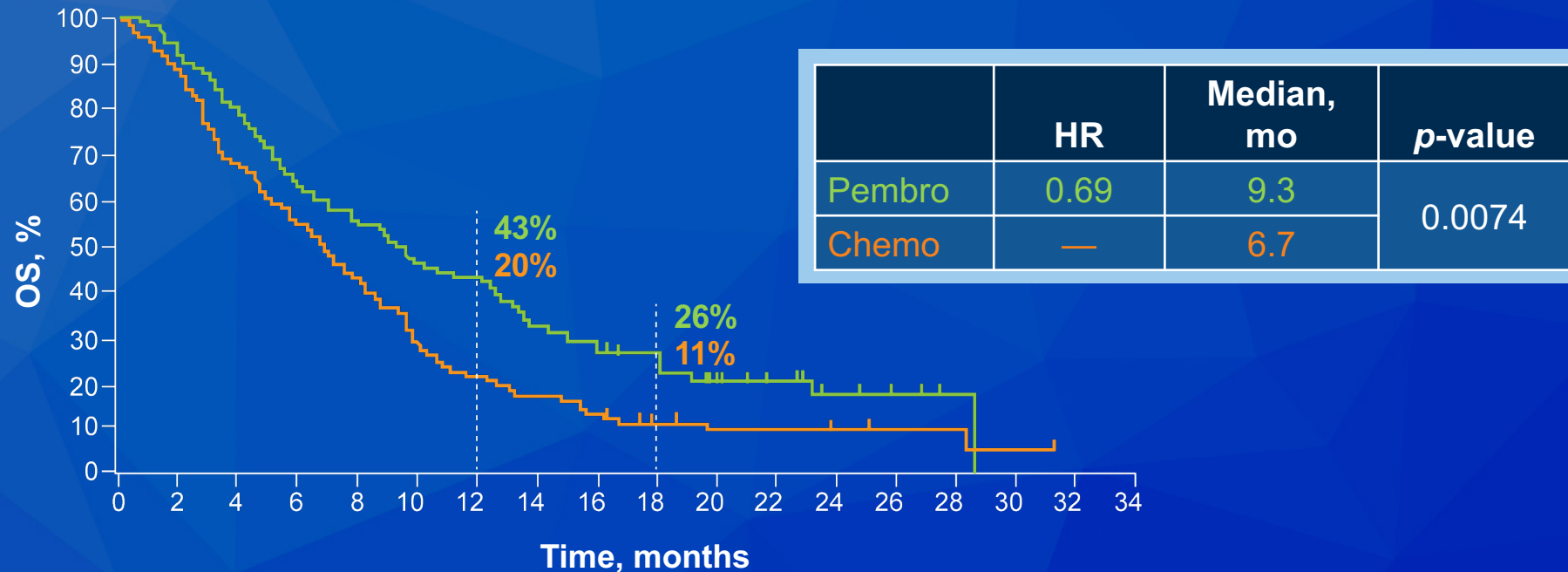
¹ Metges J et al. *Proc ESMO World GI Congress* 2019; Abstract O-012.

² Kojima T et al. *Gastrointestinal Cancers Symposium* 2019; Abstract 2.



KEYNOTE-181: A Phase III Trial of Second-Line Pembrolizumab Compared to Chemotherapy for Advanced Esophageal Cancer

Overall Survival (PD-L1 CPS ≥ 10) for Patients with Squamous Cell Carcinoma



- ORR higher with pembrolizumab than with chemotherapy for patients with CPS ≥ 10 (21.5% vs 6.1%)
- Lower frequency of Grade 3-5 treatment-related adverse events with pembrolizumab than with chemotherapy (18.2% vs 40.9%); no new safety signals observed

Editorial — Dr Wainberg

Over the last few years, we have seen several trials in both adeno and squamous cell of the esophagus. The KEYNOTE-181 study compared single-agent pembro vs investigator's choice chemo in a large, randomized Phase 3 trial. All patients were PDL1+, and there were both SCC and adenocarcinoma patients enrolled. In the SCC patients of PDL1 (CPS >10), there was roughly a 4-month improvement in OS (HR of 0.64). The results in adeno were less convincing, and therefore the FDA granted approval for patients with SCC of the esophagus (PDL1 CPS \geq 10). The ATTRACTION-3 trial randomized 419 SCC patients (no adeno) to single-agent nivo vs investigator's choice chemo. This study met its primary endpoint, and nivolumab improved OS from 10.9 months (nivo) vs 8.4 months (chemo). This 2.5-month improvement in OS (HR of 0.77) met its primary endpoint.

Editorial — Dr Wainberg (continued)

Several factors must be considered. Similarly to ATTRACTION-2, this trial enrolled exclusively in Asia. In this trial, there was a survival advantage reported in both PDL1+ and PDL1- patients, although the cutoffs have been reported as <1 and >1 . Overall, the toxicity profiles in both trials favored the checkpoint inhibitor over chemo, and therefore this represents a new option for treatment in these patients.

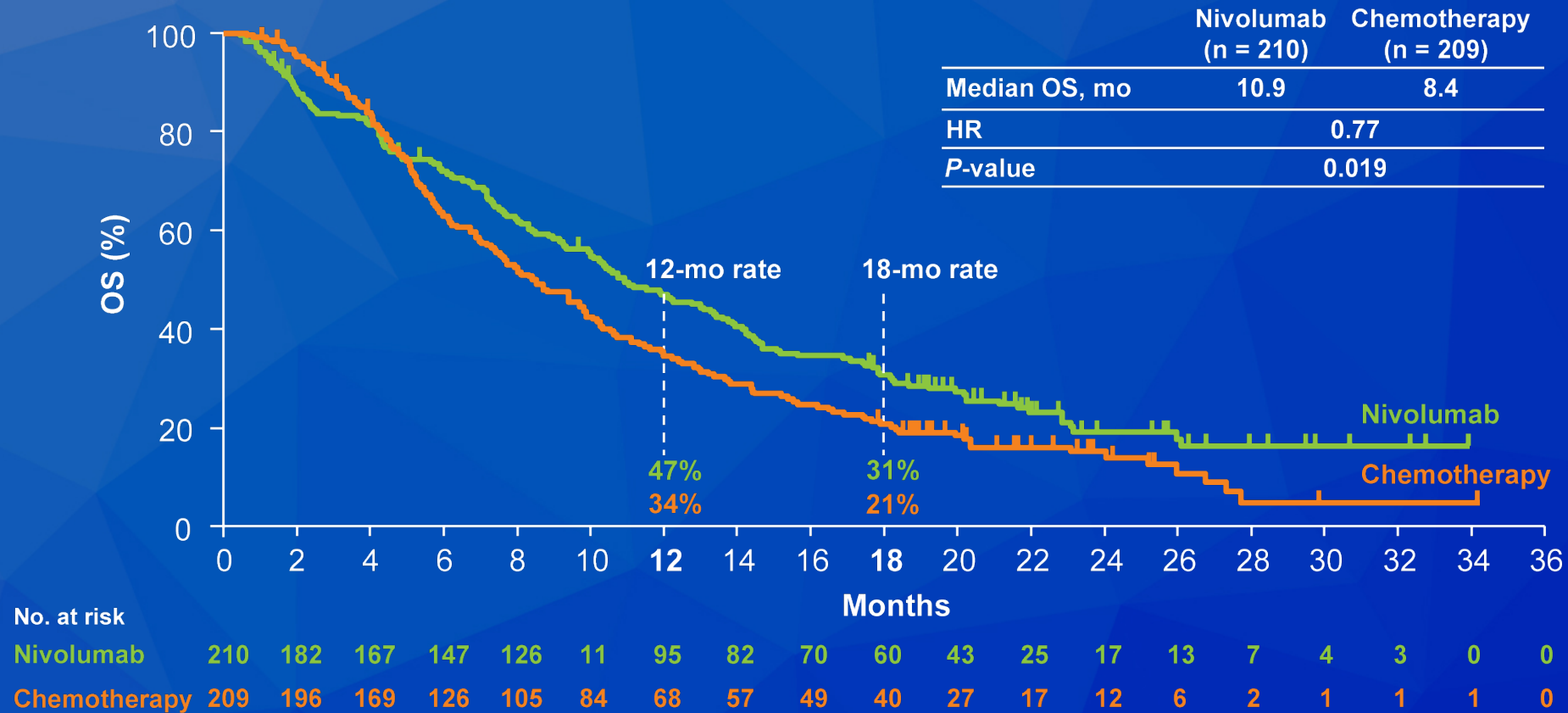
Nivolumab versus Chemotherapy in Patients with Advanced Oesophageal Squamous Cell Carcinoma Refractory or Intolerant to Previous Chemotherapy (ATTRACTION-3): A Multicentre, Randomised, Open-Label, Phase 3 Trial

Kato K et al.

Lancet Oncol 2019;20(11):1506-17.



ATTRACTION-3: Overall Survival



- 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

Editorial — Dr Bendell

Recently trials evaluating new treatments for gastroesophageal cancer patients have split gastroesophageal cancers into esophageal cancers (including Siewert I GEJ cancers) and cancers of the GE junction (Siewert II and III) and stomach. Trials of checkpoint inhibitors have now been done in a purely esophageal cancer population. The KEYNOTE-180 study was a phase II study that looked at treating patients with refractory esophageal cancer with pembrolizumab. In a heavily pretreated population there was an overall response rate of 10%, but for the squamous cell population the response rate was 14.3%. The randomized phase III KEYNOTE-181 study took this data further, randomizing patients with esophageal cancer to either pembrolizumab or investigator's choice of paclitaxel, docetaxel, or irinotecan therapy. Patients with squamous cell esophageal cancer and PD-L1 expression CPS ≥ 10 showed an improvement in median overall survival using pembrolizumab versus chemotherapy, with a hazard ratio of 0.64 and a response rate of 22%.

Dr Marshall's Perspective on Recent Advances in GI Cancer

Wonderful Surprises

The advances in precision medicine and immuno-oncology are breathtaking and transformative. Never before in the history of cancer research have we witnessed such dramatic results in so short of a time. In many ways, none of this was predicted just a decade ago. As we started the previous decade, immune therapy was seen as a crazy concept that will never work. Today it is seen as a miracle. Precision medicine was only limited to known, established biomarkers such as ER/PR. Today virtually every patient with advanced disease should undergo broad molecular testing to find the ever-increasing needles hidden in the haystack. And as we look forward, we are seeing unexpected results as we combine older agents such as VEGF inhibitors with immuno-oncology treatments, discovering new mechanisms of action and remarkable improved clinical activity. No more is the phase 3 randomized trial essential; now correctly enriched studies can be small as long as the benefit is large.

Dr Marshall's Perspective on Recent Advances in GI Cancer (continued)

The world of clinical trial design has been turned on its head. All of this is represented in these 4 papers. Dr Le's paper, supported by the work of Marabelle and colleagues, transforms not only our concepts of trial design, it transforms our concept of diagnosis: the first ever treatment for patients whose tumors harbor a specific genetic change, MSI replacing our traditional designations based on tissue of origin. The work by Dr Kopetz has started to turn BRAF-mutated colon cancer from the most dreaded subtype into one where we have new therapeutic options. Each of these fundamental results came with rapidly performed, innovative trial designs. Wonderfully, our regulatory agencies in the US are keeping pace, recognizing the shifts in drug development, and granting rapid approvals so our patients can rapidly access these novel therapies. Finally, the work by Cheng and colleagues may be the most surprising: the combination of IO and VEGF therapies in HCC, one of the most recalcitrant cancers, providing major improvements and a new standard of care. After so many attempts to move the survival bar in HCC, we now take a major leap forward.

Dr Marshall's Perspective on Recent Advances in GI Cancer (continued)

Finally, the work by Cheng and colleagues may be the most surprising: the combination of IO and VEGF therapies in HCC, one of the most recalcitrant cancers, providing major improvements and a new standard of care. After so many attempts to move the survival bar in HCC, we now take a major leap forward. These and other results leave me starting the new decade with more hope than I have ever had in my 30 years of practice. As we now fold into our science the impact of the microbiome into cancer treatments, I feel true cures are just ahead.

Le DT et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. J Clin Oncol 2019 Nov 14 [epub ahead of print]

Kopetz S et al. Encorafenib, Binimetinib, and Cetuximab in BRAFV600E-Mutated Colorectal Cancer. N Engl J Med. 2019 Oct 24;381(17):1632-1643.

Dr Marshall's Perspective on Recent Advances in GI Cancer (continued)

Marabelle A, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2019; Nov 4 [epub ahead of print]

A-L Cheng et al. 'IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). ESMO ASIA 2019; Abstract LBA3.