Year in Review

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

Saturday, February 24, 2018, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Research To Practice®

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Disclosures

Contracted Research	Abbott Laboratories, AbbVie Inc, Agios Pharmaceuticals Inc, Apexigen, ARMO BioSciences, Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Celldex Therapeutics, CytomX Therapeutics, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Five Prime Therapeutics Inc, Forty Seven Inc, Genentech BioOncology, Gilead Sciences Inc, GlaxoSmithKline, Incyte Corporation, Kolltan Pharmaceuticals Inc, Leap Therapeutics Inc, Lilly, MacroGenics Inc, MedImmune Inc, Merck, Nektar, Novartis, OncoMed Pharmaceuticals Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Roche Laboratories Inc, Sanofi Genzyme, Stemcentrx, SynDevRx Inc, Taiho Oncology Inc, Takeda Oncology

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Advisory Committee	Amgen Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Genentech BioOncology, Roche Laboratories Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Eisai Inc, Genentech BioOncology

Analysis of Over 100,000 Patients with Cancer for *CD274* (*PD-L1*) Amplification: Implications for Treatment with Immune Checkpoint Blockade

Goodman A et al.
Proc ASCO-SITC 2017;Abstract 47.

Analysis of CD274 (PD-L1) Gene Amplification in Patients with Cancer

- Analysis of CD274 gene copy number amplification (CNA) in >100,000 patient samples from Foundation Medicine database and UC San Diego.
- CD274 CNA detected in 0.7% of all tumor samples

Select tumor type	Total no. of patients	Percent with CD274 CNA
Soft tissue sarcoma undifferentiated	313	3.8
Thyroid anaplastic sarcoma	165	3.0
Lung adenocarcinoma	≥10,000	0.6
Breast cancer	2,000-9,999	2.0
Colon cancer	2,000-9,999	0.2
Prostate cancer	2,000-9,999	0.2

- 9 patients with CD274 CNA were treated with PD-1/PD-L1 blockade at UC San Diego
  - Response rate = 6/9 (67%); median PFS = 15.1 months

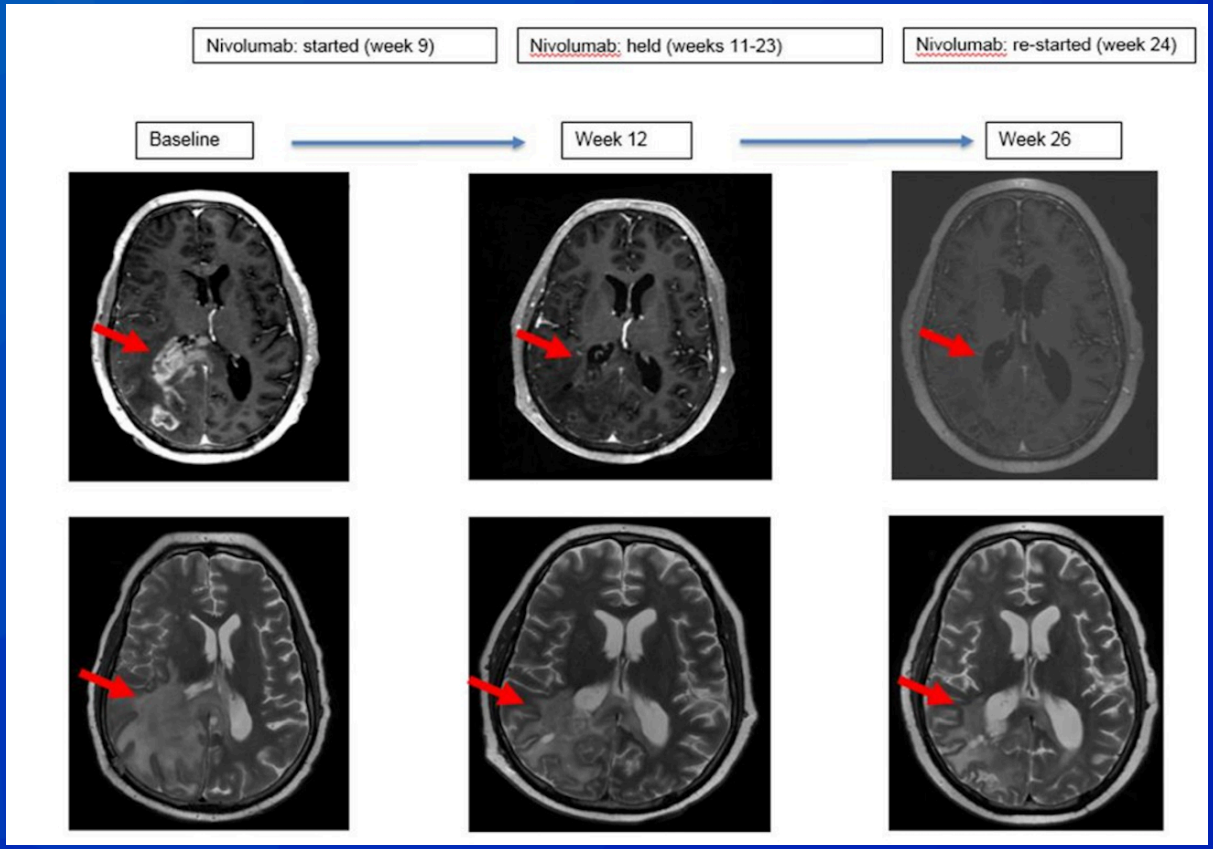
Goodman A et al. *Proc ASCO-SITC* 2017;Abstract 47.

Patient #4: 40-year-old man with progressive glioblastoma

Progressive disease after:
- Surgery
- XRT/temozolomide

Genomics:
- 12 alterations
- PD-L1 amplification
- PD-L2 amplification
- JAK2 amplification

Ongoing PR of 5.2 months



Goodman A et al. *Proc ASCO-SITC* 2018;Abstract 47.

Select Recently Approved Agents in Gastrointestinal Cancers

Colorectal cancer		
Agent	**Approval date**	**Indication**
Pembrolizumab	5/23/17	MSI-H or dMMR CRC that has progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan
Nivolumab	7/31/17	dMMR and MSI-H mCRC that has progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan
Gastric cancer		
Agent	**Approval date**	**Indication**
Pembrolizumab	9/22/17	PD-L1-positive recurrent locally advanced or metastatic gastric or GEJ cancer that has progressed on or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.

Pembrolizumab approved 5/23/17 for patients with unresectable or metastatic MSI-H/dMMR solid tumors that have progressed on prior therapy and have no satisfactory alternative treatment options

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm

Select Recently Approved Agents in Gastrointestinal Cancers (continued)

Hepatocellular carcinoma		
Agent	**Approval date**	**Indication**
Nivolumab	9/22/17	HCC previously treated with sorafenib
Regorafenib	4/27/17	HCC previously treated with sorafenib
GI neuroendocrine tumors		
Agent	**Approval date**	**Indication**
Telotristat ethyl	2/28/17	In combination with somatostatin analogue (SSA) therapy for the treatment of patients with carcinoid syndrome diarrhea that SSA therapy alone has inadequately controlled

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm

Gastrointestinal Cancers — Drs Bendell and Grothey

Colorectal Cancer

Gastric Cancer

Hepatocellular Carcinoma

Pancreatic Cancer

GI Neuroendocrine Tumors (GI NET)

Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration

Oxaliplatin-based chemotherapy for patients with stage III colon cancer: Disease free survival results of the three versus six months adjuvant IDEA France trial

FOLFOX4/CAPOX in stage II–III colon cancer: Efficacy results of the Italian Three or Six Colon Adjuvant trial TOSCA

Final DFS results of the SCOT study: An international Phase III randomised (1:1) non-inferiority trial comparing 3 versus 6 months of oxaliplatin based adjuvant chemotherapy for colorectal cancer

Shi Q et al. *Proc ASCO* 2017;Abstract LBA1.

Andre T et al. *Proc ASCO* 2017;Abstract 3500.

Sobrero AF et al. *Proc ASCO* 2017;Abstract 3501.

Iveson T et al. *Proc ASCO* 2017;Abstract 3502.

IDEA (*I*nternational *D*uration *E*valuation of *A*djuvant Chemotherapy) Collaboration

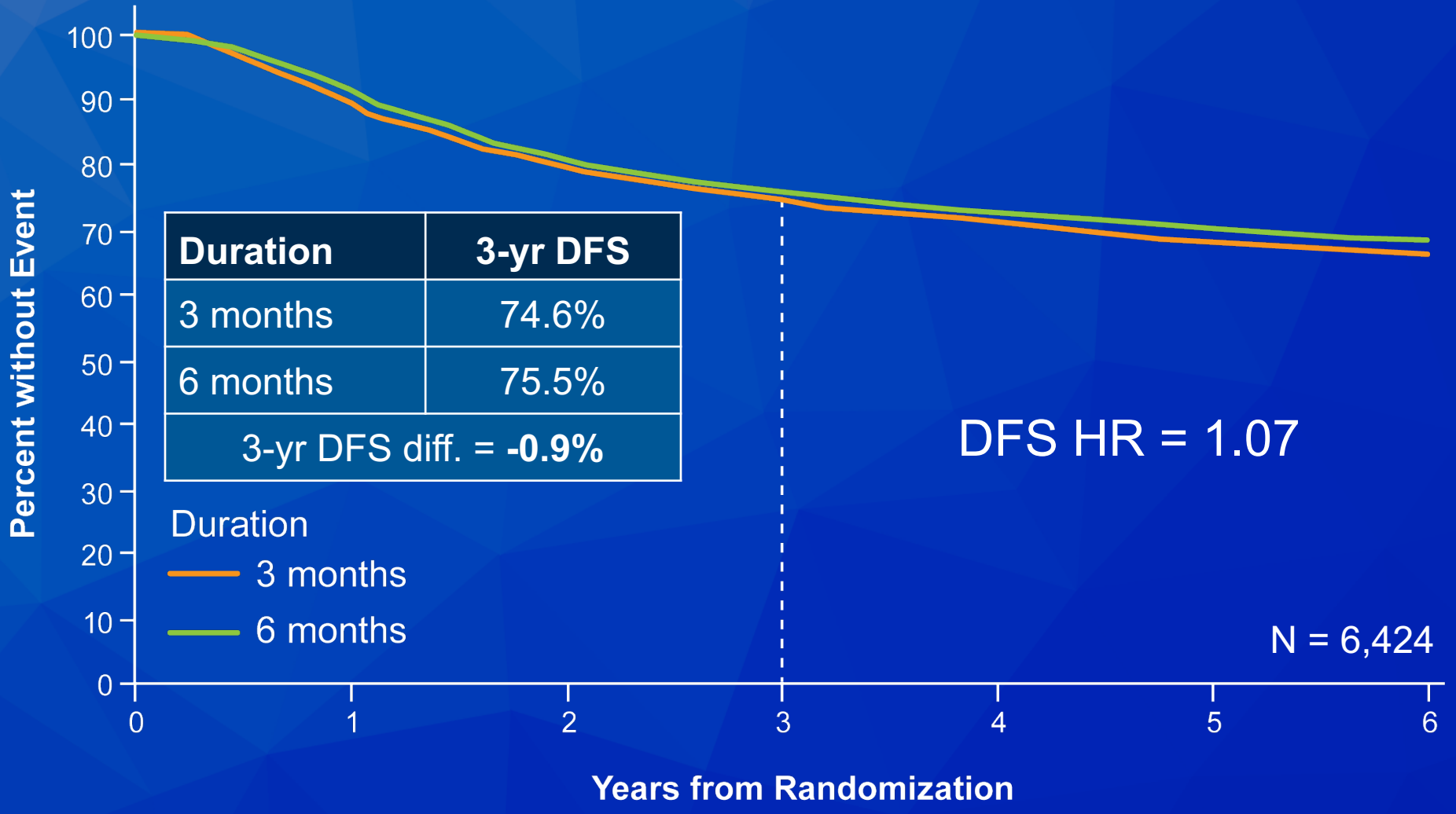
- Academic collaboration of clinicians and statisticians from six randomized Phase III trials

IDEA trials summary			
Trial	**Regimen(s)**	**Patients with Stage III colon cancer***	**Enrolling country**
TOSCA	CAPOX or FOLFOX4	2,402	Italy
SCOT	CAPOX or mFOLFOX6	3,983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2,010	France
C80702	mFOLFOX6	2,440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1,291	Japan

* Only patients with Stage III colon cancer were included in the pooled primary analysis

Shi Q et al. *Proc ASCO* 2017;Abstract LBA1.

IDEA: Primary Endpoint — Disease-Free Survival (DFS)



Duration	3-yr DFS
3 months	74.6%
6 months	75.5%
3-yr DFS diff. = **-0.9%**	

Shi Q et al. *Proc ASCO* 2017;Abstract LBA1.

Editorial — Dr Venook

The standard adjuvant treatment for stage III colon cancer patients is six months of FOLFOX or CAPOX, but 20%-25% of cured patients will have lifelong neuropathy related to oxaliplatin. However, a study to halve the exposure to oxaliplatin by comparing three to six months of therapy would require 10,000 randomized patients to be confident that cancer outcomes are not being compromised.

Mayo biostatistician Dan Sargent had a practical idea: pool worldwide results from six studies asking the duration question and let the large sample size balance cross-study differences and yield the answer.

Editorial — Dr Venook (continued)

Three of those studies — by Andre (France), Sobrero (Italy) and Iveson (rest of Europe) — are presented because of their contribution to the pool; studies in North America, Greece and Japan brought the sample size to 12,834 patients.

Because statisticians do not design studies without endpoints, IDEA's collaborators opted for non-inferiority of the three-month arm. As expected, neuropathy was rare in the shorter duration arms and 3-year disease-free survival curves were virtually identical (medians — 75.5% vs 74.6%.) However, the upper limits of the hazard ratio (1.15) exceeded the prespecified boundary of 1.12 that planners used to define non-inferiority.

Editorial — Dr Venook (continued)

Is this the place for statistical rigor? In the spirit of Dan Sargent, the master statistician whose idea this had been but who passed away before the results were in, the collaborators did not let perfect get in the way of practical: post-hoc analysis of low-risk patients led to the conclusion that three months is enough but not so for patients with higher risk.

Primary tumor location as an independent prognostic marker from molecular features for overall survival in patients with metastatic colorectal cancer: Analysis of CALGB/SWOG 80405 (Alliance)

Venook AP et al.
Proc ASCO 2017;Abstract 3503.

CALGB/SWOG 80405: Association Between Primary Tumor Location and Outcomes

Patient subgroups KRAS WT	Median OS		HR, *p*-value*
	Right 1^0	Left 1^0	
All patients (n = 293, 732)	19.4 mo	33.3 mo	1.55, <0.0001
Cetuximab (n = 143, 376)	16.7 mo	36.0 mo	1.87, <0.0001
Bevacizumab (n = 150, 356)	24.2 mo	31.4 mo	1.32, 0.01

* Adjusted for age, sex, biologic, chemotherapy, prior therapy, synchronous disease, in-place primary, liver metastases

- Significant interaction between side and biologic:
  - Left-sided primary: Cetux vs bev superiority ($p = 0.018$)
  - Right-sided primary: Bev vs cetux superiority ($p = 0.065$)
- Sidedness is also prognostic for patients with KRAS-mutant disease

Venook AP et al. *Proc ASCO* 2017;Abstract 3503; *Proc ASCO* 2016;Abstract 3504.

CALGB/SWOG 80405: Possible Indicators of Tumor Burden

	Right-sided (n = 167)	Left-sided (n = 330)	*p*-value
LDH Median Mean (SD)	 195.5 284.7 (225.2)	 196.5 404 (528)	—
# metastatic sites 1 2 3+	 53.9% 33.9% 11.5%	 55.9% 30.1% 13.1%	0.8168
Prior adjuvant therapy	12.0%	18.8%	0.0533
Primary in place at initiation of therapy	4.8%	1.8%	0.0937
Intent of treatment Palliative Curative	 86.4% 13.6%	 83.1% 16.9%	0.3408
Pattern of mets Liver only Liver mets plus Extrahepatic only	 30.3% 62.4% 37.0%	 38.3% 73.3% 25.8%	0.0136

Venook AP et al. *Proc ASCO* 2017;Abstract 3503.

CALGB/SWOG 80405: Multivariate Analysis Findings

Sidedness – Surrogate for Tumor Burden:

- No evidence in this population that patients with right-sided primary had greater tumor burden at the time of diagnosis.
- Differences in distribution of metastases and outcomes between right and left sidedness appear to reflect differences in tumor biology.

Conclusions/Take-Home Messages:

- Tumor location is independently prognostic when adjusted for factors described.
- Tumor sidedness should be a stratification factor in studies of colon cancer.
- Further work is needed to determine the mechanism by which sidedness remains an independent prognostic variable.

Venook AP et al. *Proc ASCO* 2017;Abstract 3503.

Editorial — Dr Venook

CALGB/SWOG 80405 compared first-line bevacizumab to cetuximab and found that patient survival was no different across arms. By banking thousands of bio-specimens and engaging scientists far and wide, this study's investigators held out the possibility of gaining insights into factors that determine how patients will do.

For all of the planning, however, this group's top priority has been explaining the unexpected observation of a 14-month survival difference favoring patients with metastatic disease arising from a left- vs right-sided primary cancer. This observation has been noted in many studies; similarly, studies have also confirmed the poor track record of antitumor efficacy of cetuximab in patients with right-sided primaries regardless of RAS status.

Editorial — Dr Venook (continued)

This report explores the possible features of right-sided colon cancer that might account for the difference in outcome. One often stated pearl is the idea that patients with right-sided tumors present later than those with left-sided primaries, presumably due to a longer time to symptoms. While not easily done without the full radiology series for each patient, analyses of sites of disease, CEA elevation, platelet count and other general markers of higher tumor burden did not show a difference in right vs left.

Editorial — Dr Venook (continued)

Assuming that “sidedness” is a surrogate for non-randomly distributed biological features, multivariable analyses of individual mutational states such as BRAF V600E, TP53 and MSI-H, as well as the primary cancer’s Consensus Molecular Subtypes (CMS I-IV), did not surpass sidedness, which remains an independent predictor of outcomes in patients with all RAS wild-type metastatic colorectal cancer.

Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study

Michael J Overman, Ray McDermott, Joseph L Leach, Sara Lonardi, Heinz-Josef Lenz, Michael A Morse, Jayesh Desai, Andrew Hill, Michael Axelson, Rebecca A Moss, Monica V Goldberg, Z Alexander Cao, Jean-Marie Ledeine, Gregory A Maglinte, Scott Kopetz, Thierry André**

Lancet Oncol 2017;18(9):1180-91.

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

N Engl J Med 2015;372(26):2509-20.

Objective Responses to Anti-PD-1 Antibodies in dMMR/MSI-H CRC

Nivolumab — Overman et al.[1]	dMMR/MSI-H per local assessment (n = 74)
Objective response rate (investigator assessed)	31.1%
DCR for ≥12 weeks	69%

Pembrolizumab — Le et al.[2]	dMMR CRC (n = 10)	pMMR CRC (n = 18)
Objective response rate	40%	0%
DCR ≥12 weeks	90%	11%

dMMR = DNA mismatch repair-deficient; MSI-H = microsatellite instability-high, pMMR = DNA mismatch repair-proficient; DCR = disease control rate

- NCCN (3/13/2017): For patients with dMMR or MSI-H tumors, nivolumab or pembrolizumab added as treatment options in subsequent therapy for patients appropriate for intensive therapy

[1] Overman MJ et al. *Lancet Oncol* 2017;18(9):1182-91; [2] Le DT et al. *N Engl J Med* 2015;372(26):2509-20.

Editorial — Dr Venook

The rules of drug development in cancer are well known. Choosing the disease, dose and schedule and endpoints and demonstrating safety is done on the faith that the ensuing clinical trial will show the agent to be effective. An investigator could work on a new drug for years only to be told to turn over the files because a more promising pipeline product needed attention.

Results on less than 100 patients remind us that it is the exceptions that make the rules, and in this case, they are the checkpoint inhibitors. Nivolumab and pembrolizumab block the PD-1 axis, the brakes that keep the immune system from attacking itself. Patients may have autoimmune manifestations, but unleashing the immune system can have remarkable effects.

Editorial — Dr Venook (continued)

Le et al introduced the subject at the opening session of ASCO 2014 (*NEJM* 2015). Pembrolizumab treatment of patients with MSI-H tumors of any GI origin led to a 62% response rate but induced no responses in MSS tumors. Overman et al reported an equally startling result from a 70-patient, single-arm study of nivolumab in MSI-H previously treated colon cancer patients. Just 31% had documented radiographic responses but no patient's disease progressed in the first 12 weeks on study.

A *Lancet Oncology* editorial in September 2017 stated the obvious. The Overman results heralded a new treatment for patients with MSI-H advanced colon cancer.

Editorial — Dr Venook (continued)

Unfortunately, this represented just 4%-5% of patients with metastatic colorectal cancer, and expanding the role of checkpoint inhibitors beyond this unique subset of patients was our next challenge.

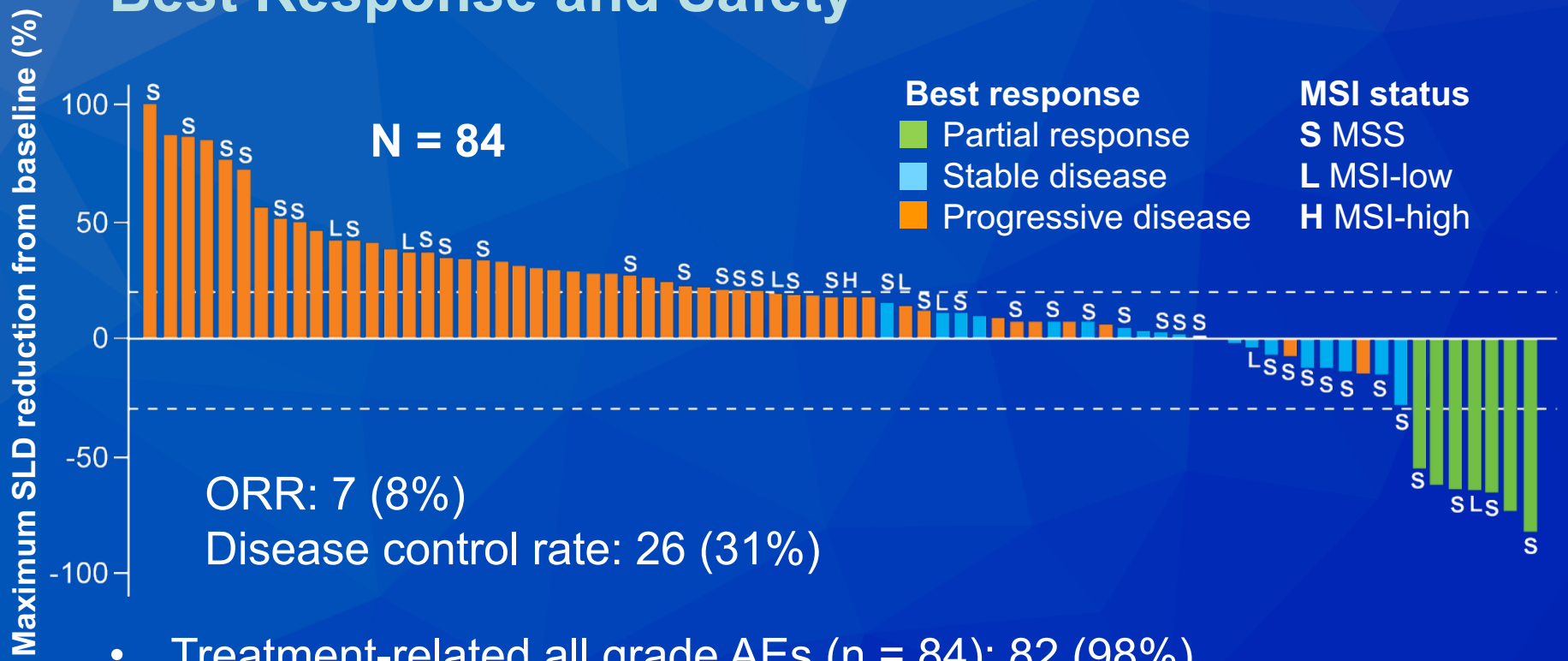
A Phase Ib Study of Safety and Clinical Activity of Atezolizumab (A) and Cobimetinib (C) in Patients (pts) with Metastatic Colorectal Cancer (mCRC)

Nivolumab + Ipilimumab Combination in Patients with DNA Mismatch Repair-Deficient/ Microsatellite Instability-High (dMMR/MSI-H) Metastatic Colorectal Cancer (mCRC): First Report of the Full Cohort from CheckMate-142.

Bendell J et al. Gastrointestinal Cancers Symposium 2018;Abstract 560.

Andre T et al. Gastrointestinal Cancers Symposium 2018;Abstract 553.

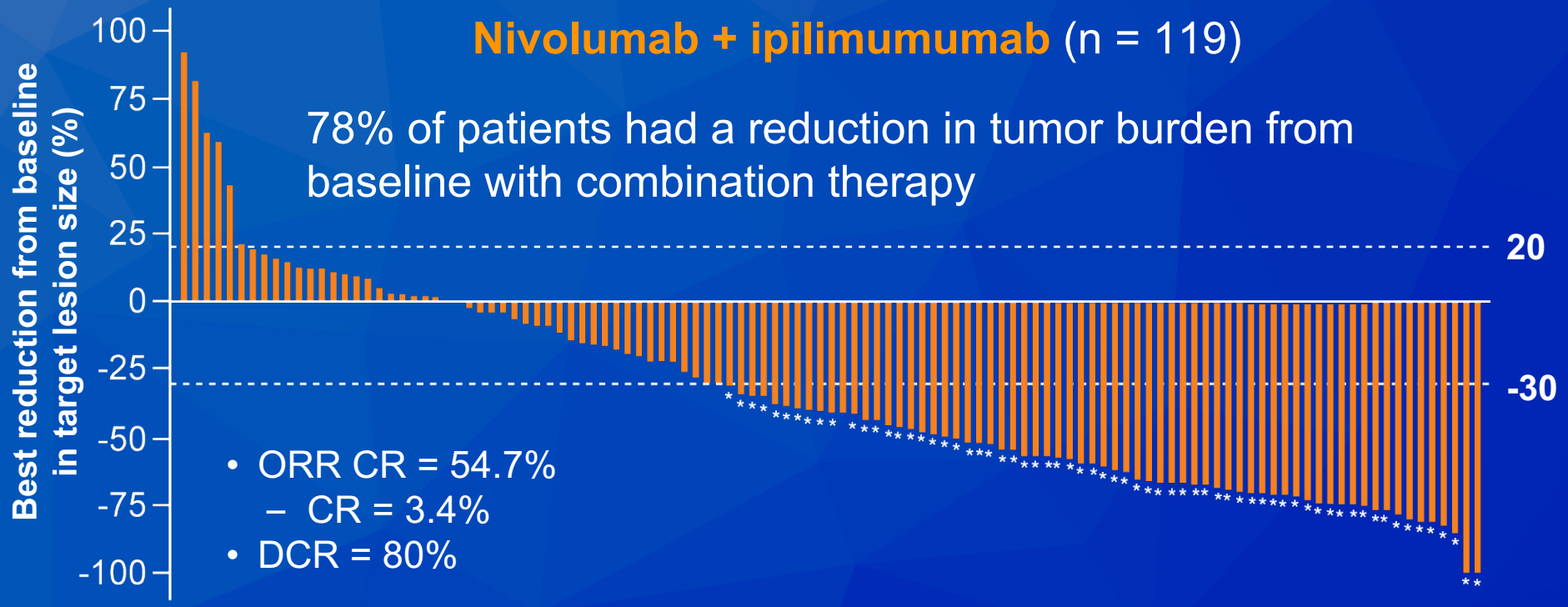
Phase Ib Trial of Atezolizumab and Cobimetinib: Best Response and Safety



- Treatment-related all grade AEs (n = 84): 82 (98%)
  - AEs leading to withdrawal of atezolizumab = 11 (13%)
  - AEs leading to withdrawal of cobimetinib = 20 (24%)
- Rash, diarrhea, fatigue and increased blood creatinine phosphokinase were the most frequent treatment-related Grade 3-4 AEs (5% each)

Bendell J et al. Gastrointestinal Cancers Symposium 2018;Abstract 560.

CheckMate 142: Response by INV Assessment



- Median time to response = 2.8 mo
- Responses were durable
- Median duration of response was not reached
- 94% of responders had ongoing responses at data cutoff

Andre T et al. Gastrointestinal Cancers Symposium 2018;Abstract 553.

Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406)

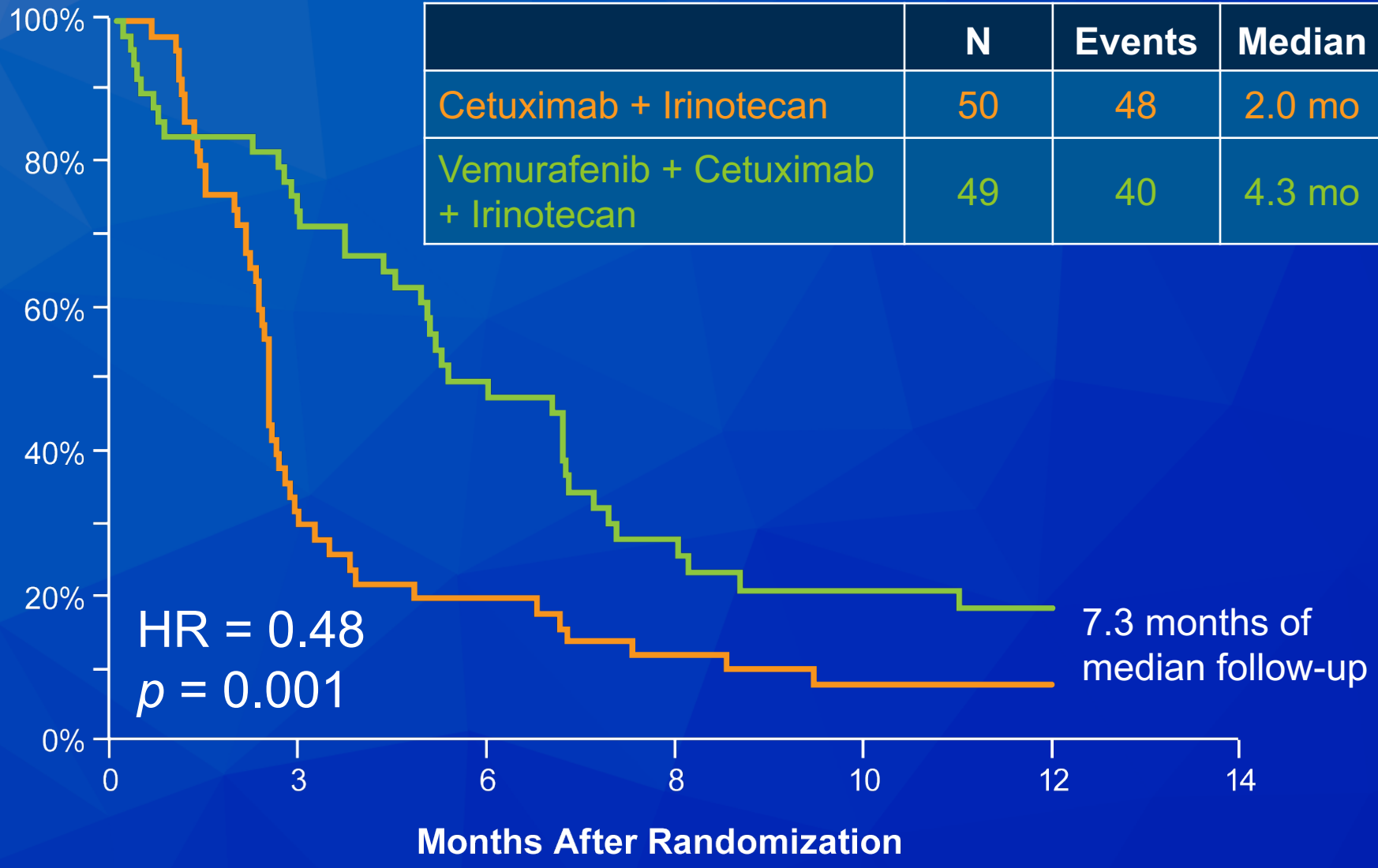
BEACON CRC: Safety lead-in (SLI) for the combination of binimetinib (BINI), encorafenib (ENCO), and cetuximab (CTX) in patients (Pts) with BRAF-V600E metastatic colorectal cancer (mCRC)

Kopetz S et al.
Proc ASCO 2017;Abstract 3505.

Huijberts S et al.
Proc ESMO 2017;Abstract 517P.

SWOG-S1406: Primary Endpoint — Progression-Free Survival

	N	Events	Median
Cetuximab + Irinotecan	50	48	2.0 mo
Vemurafenib + Cetuximab + Irinotecan	49	40	4.3 mo



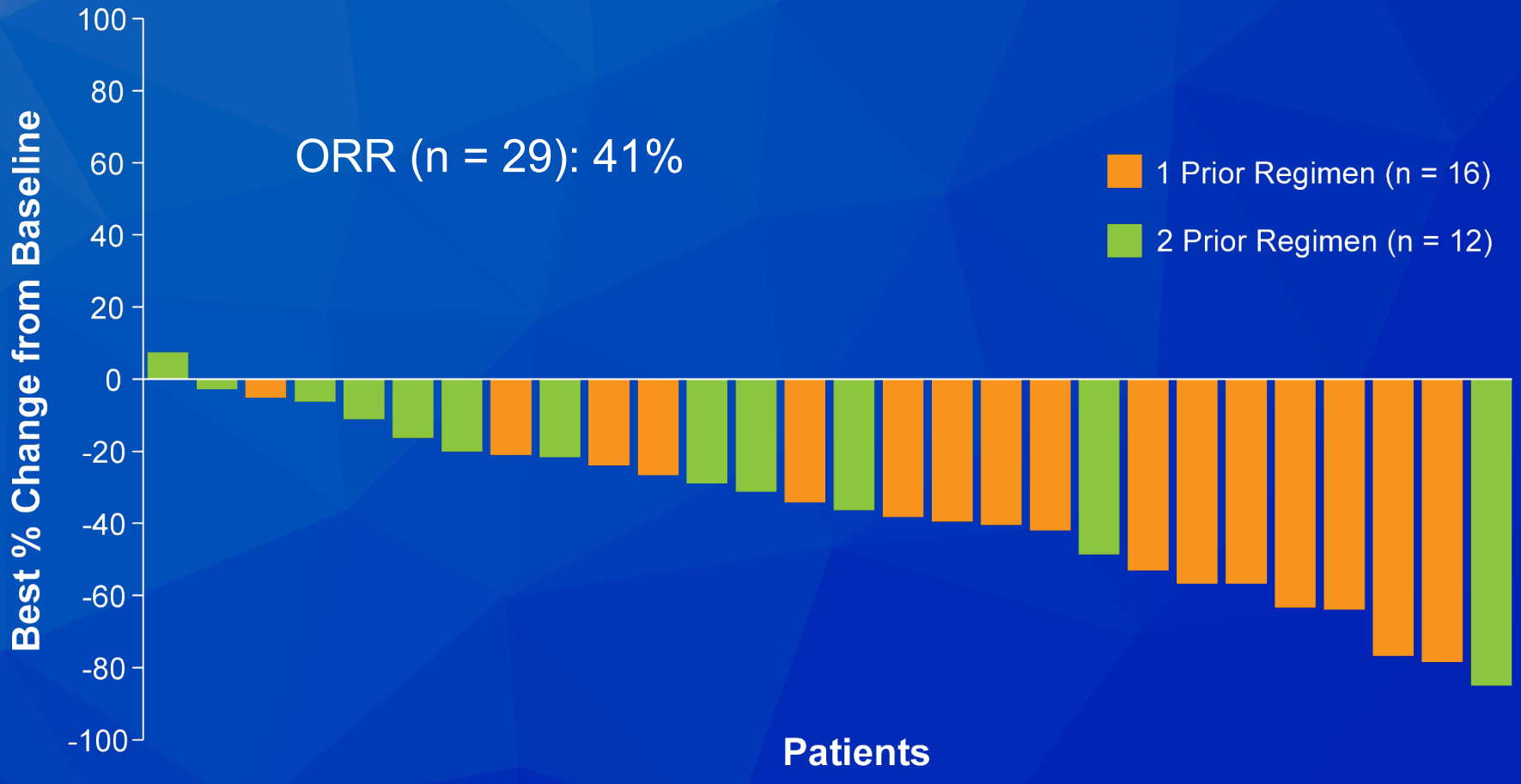
Kopetz S et al. *Proc ASCO* 2017;Abstract 3505.

SWOG-S1406: Grade 3 or 4 Adverse Events (AEs)

	Cetuximab + irinotecan (n = 46)	Vemurafenib + cetuximab + irinotecan (n = 46)
Anemia	**0 (0%)**	**6 (13%)**
Dehydration	3 (7%)	5 (11%)
Diarrhea	6 (13%)	11 (24%)
Febrile neutropenia	2 (4%)	5 (11%)
Fatigue	7 (15%)	7 (15%)
Neutropenia	**3 (7%)**	**15 (33%)**
Rash	3 (7%)	2 (4%)
Hypomagnesemia	2 (4%)	0 (0%)
Nausea	**1 (2%)**	**9 (20%)**
Arthralgia	0 (0%)	3 (7%)
Discontinued due to AE	3/50 (6%)	8/49 (16%)

Kopetz S et al. *Proc ASCO* 2017;Abstract 3505.

BEACON CRC: Response, Tumor Regression and Safety



- Most common adverse events: Diarrhea, nausea, dermatitis acneiform and fatigue

Huijberts S et al. *Proc ESMO* 2017;Abstract 517P.

Editorial — Dr Venook

The BRAF V600E mutation is found in about 5% of colorectal cancers that are wild-type KRAS and reflects a very poor prognosis. Specific inhibitors of this target, eg, vemurafenib, have demonstrable activity as single agents in patients with malignant melanoma but are inactive in colorectal cancer patients with the identical mutation. Built on molecular modeling suggesting escape routes through the EGFR pathway, Corcoran and Atreya demonstrated modest activity of a BRAF and MEK inhibitor combined, and other pilot studies had shown various triplet combinations to be feasible.

Editorial — Dr Venook (continued)

Kopetz et al presented the results of an ambitious randomized phase II trial led by SWOG. The study included 99 patients with disease progressing on first-line therapy with tumors harboring a BRAF V600E mutation. Patients who received the standard cetuximab/irinotecan combination with vemurafenib had a median progression-free survival of 4.3 months compared to 2.0 months for those receiving cetuximab/irinotecan alone (P = 0.001, HR = 0.48).

Huijberts et al reported on the safety of a different BRAF-related strategy using encorafenib. Having shown efficacy of the combination of encorafenib plus cetuximab, these investigators demonstrated the safety of that combination with the addition of a MEK inhibitor, binimetinib.

Editorial — Dr Venook (continued)

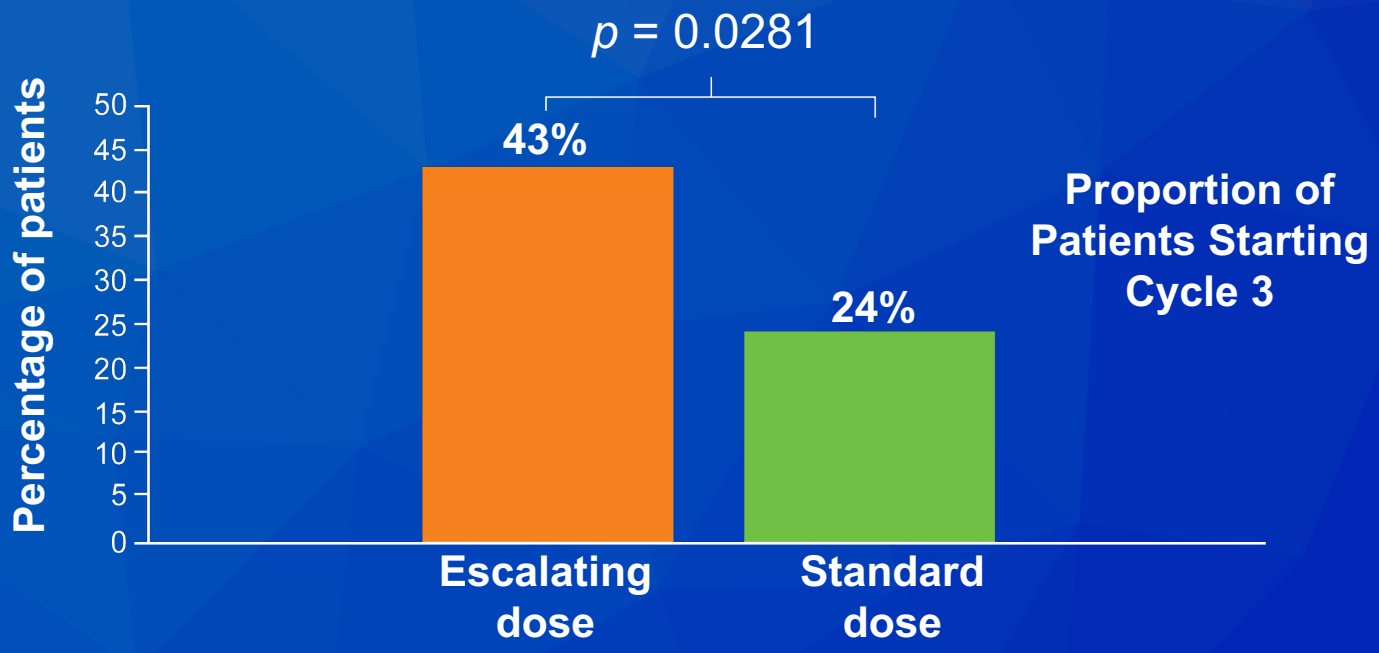
That combination is now in a phase III trial using a similar control arm to the Kopetz study.

Although the real efficacy of these combinations is not yet clear, these studies represent diligent and outstanding development work to potentially identify combination therapies that can replace the standard and mostly ineffective treatments now being used in patients with the BRAF V600E mutation.

Regorafenib Dose Optimization Study (ReDOS): Randomized Phase II Trial to Evaluate Dosing Strategies for Regorafenib in Refractory Metastatic Colorectal Cancer (mCRC) — An ACCRU Network Study

Bekaii-Saab TS et al.
Gastrointestinal Cancers Symposium 2018;Abstract 611.

ReDOS: Efficacy and Safety



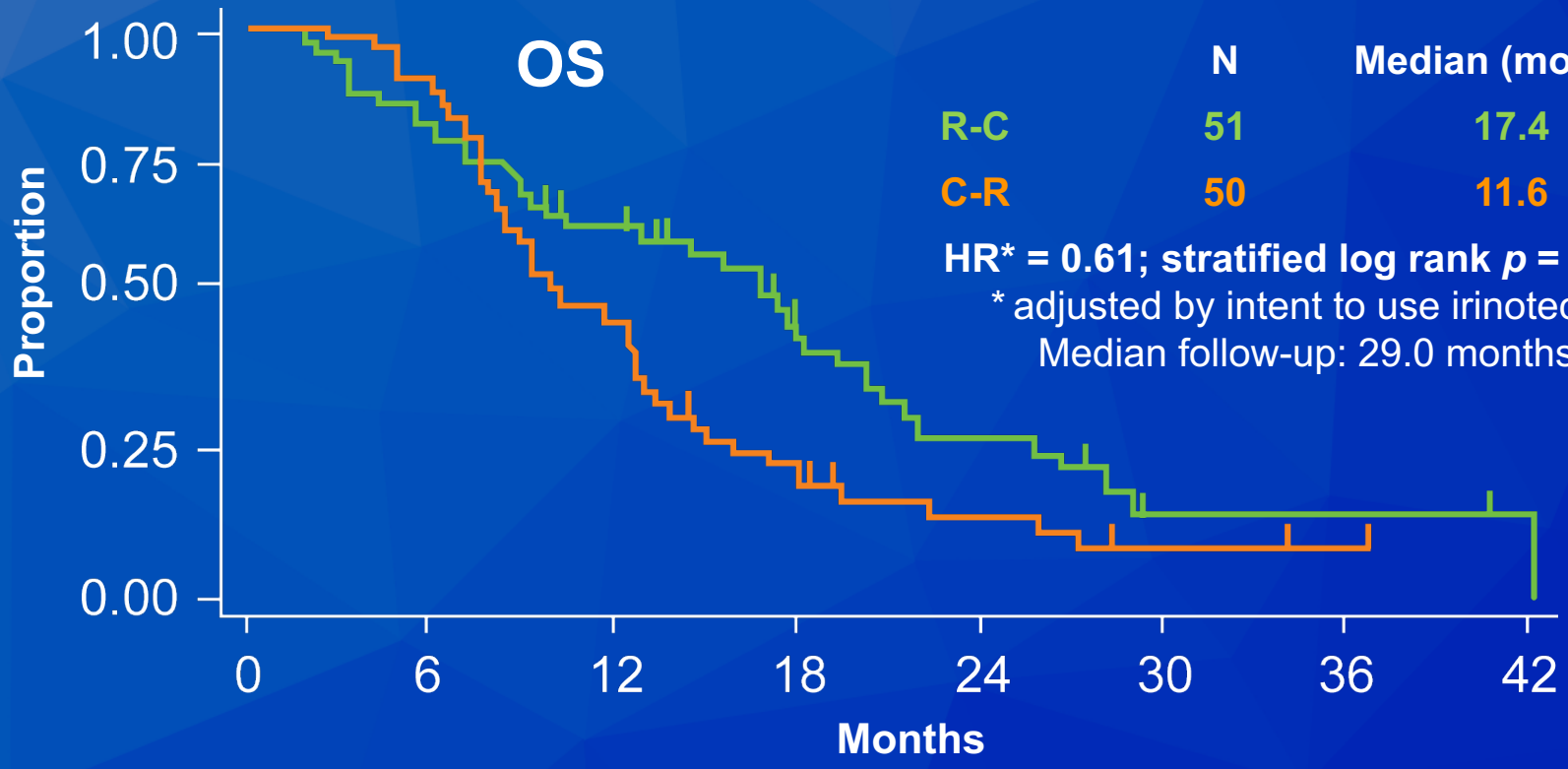
Clinical outcome	Escalating dose (n = 54)	Standard dose (n = 62)	HR	*p*-value
Median OS	9.0 mo	5.9 mo	0.65	0.0943
Median PFS	2.5 mo	2.0 mo	0.89	0.5534
Grade 3/4 AE	**Escalating dose (n = 54)**		**Standard dose (n = 62)**	
HFSR	8 (14.8%)		10 (16.1%)	
Hypertension	4 (7.4%)		9 (14.5%)	

Bekaii-Saab TS et al. Gastrointestinal Cancers Symposium 2018;Abstract 611.

REVERCE: Randomized Phase II Study of Regorafenib followed by Cetuximab versus the Reverse Sequence for Metastatic Colorectal Cancer Patients Previously Treated with Fluoropyrimidine, Oxaliplatin, and Irinotecan

Shitara K et al.
Gastrointestinal Cancers Symposium 2018;Abstract 557.

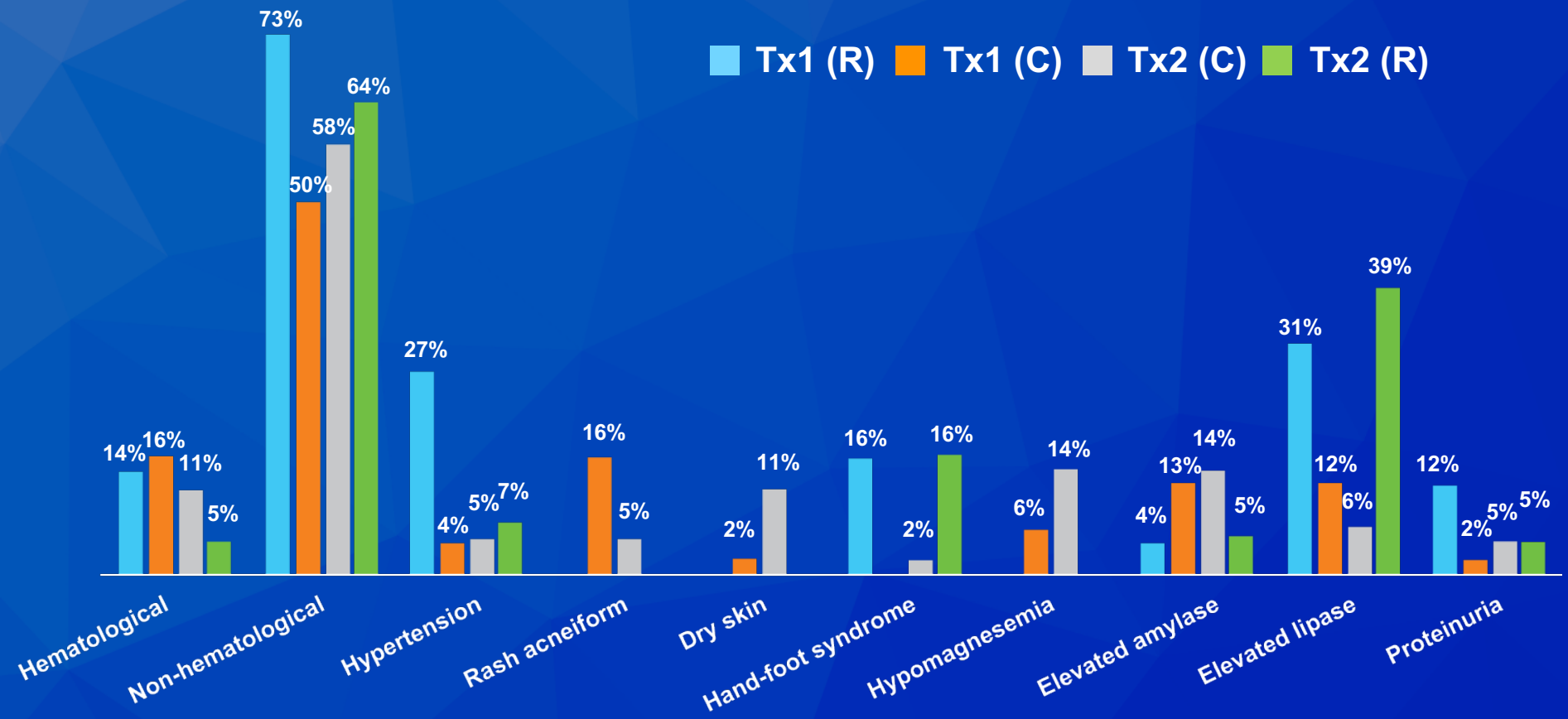
REVERCE: Survival Outcomes



Median PFS	Rego → Cetux	Cetux → Rego	HR	*p*-value
PFS1 (n = 51, 50)	2.4 mo	4.2 mo	0.97	0.91
PFS2 (n = 44, 43)	5.2 mo	1.8 mo	0.29	<0.0001

Shitara K et al. Gastrointestinal Cancers Symposium 2018;Abstract 557.

REVERCE: Adverse Events



No unexpected safety signals

Tx1 = Treatment 1 (regorafenib or cetuximab); Tx2 = Treatment 2 (cetuximab or regorafenib)

Shitara K et al. Gastrointestinal Cancers Symposium 2018;Abstract 557.

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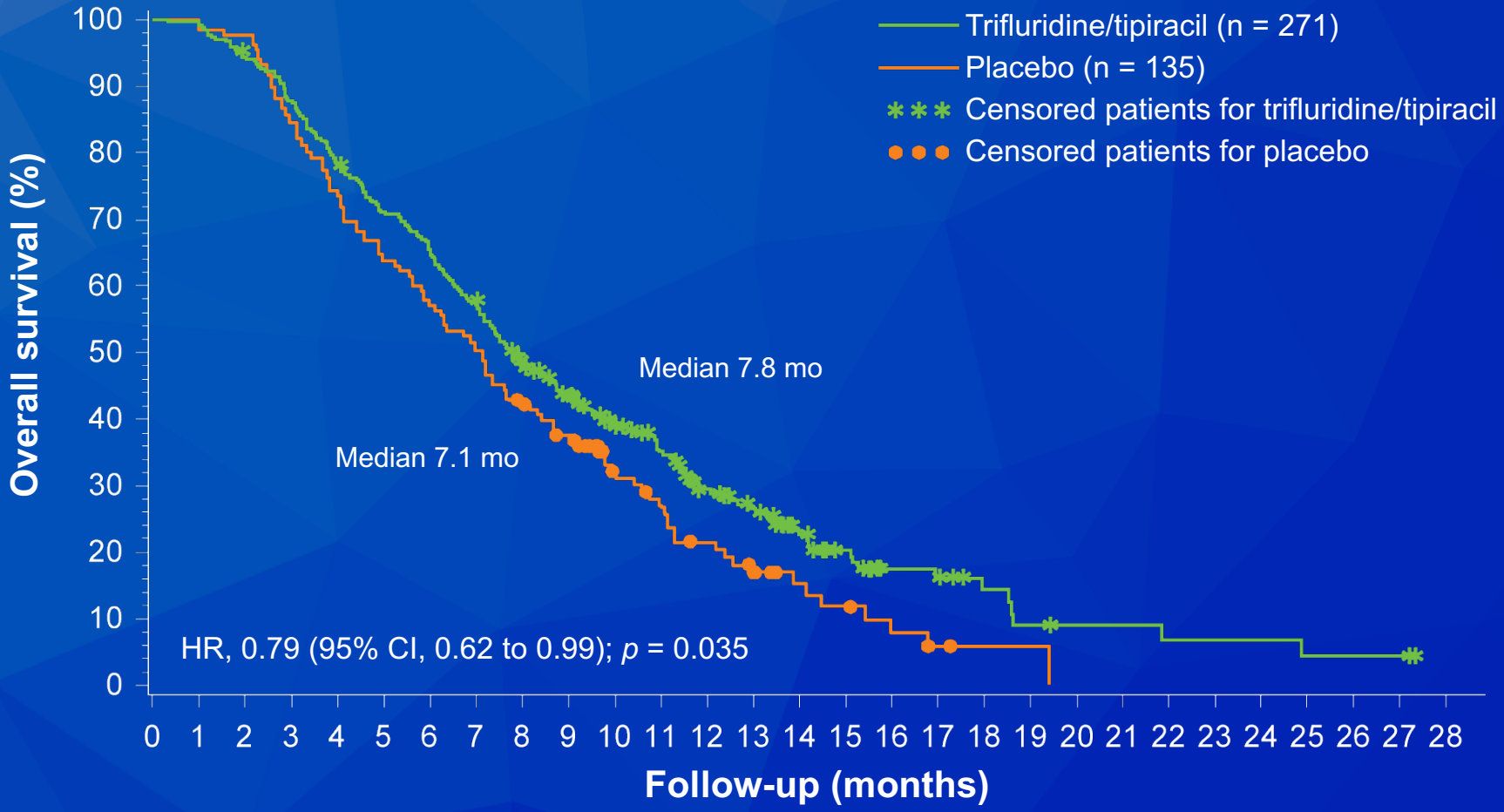
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study

Jianming Xu, Tae Won Kim, Lin Shen, Virote Sriuranpong, Hongming Pan, Ruihua Xu, Weijian Guo, Sae-Won Han, Tianshu Liu, Young Suk Park, Chunmei Shi, Yuxian Bai, Feng Bi, Joong Bae Ahn, Shukui Qin, Qi Li, Changping Wu, Dong Ma, Donghu Lin, and Jin Li

TERRA: Overall Survival with TAS-102 in Asian Patients with mCRC



- The incidence of serious adverse events was similar between the arms (TAS-102 = 23.2%; placebo = 23%)

Xu J et al. *J Clin Oncol* 2018;36(4):350-58.

Prolonged response to HER2-directed therapy in a patient with HER2-amplified, rapidly progressive metastatic colorectal cancer

Pertuzumab (P) + trastuzumab (H) + chemotherapy (CT) for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (mGC/GEJC): Final analysis of a Phase III study (JACOB)

Parikh A et al.
J Natl Compr Canc Netw 2017;15(1):3-8.

Tabernero J et al.
Proc ESMO 2017;Abstract 616O.

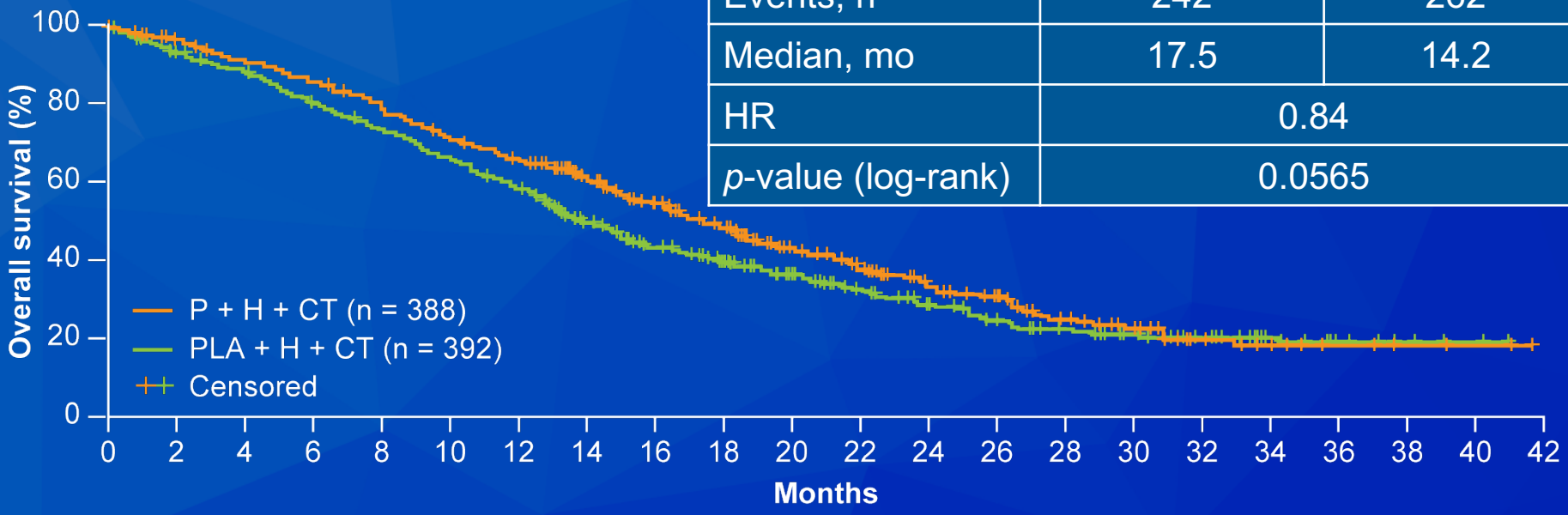
Case Report: Prolonged Response to HER2-Directed Therapy in a Patient with HER2-Amplified, Rapidly Progressive mCRC

- First-line therapy: FOLFIRI/cetuximab → disease progression after approximately 5 months
- Second-line therapy: CAPOX/bevacizumab → disease progression after 2 months
- NGS identified HER2 amplification
- Patient treated with T-DM1: Significant clinical benefit and radiographic disease control for 7 months prior to disease progression
  - Continued detection of HER2 amplification
- Patient treated with trastuzumab/pertuzumab for 6 cycles → disease progression
  - NGS demonstrated the loss of HER2 amplification
- First report of single-agent T-DM1 therapy demonstrating remarkable clinical benefit in the third line for a patient with HER2-amplified, refractory mCRC
  - Supports ongoing efforts to understand the role of HER2 in mCRC

Parikh A et al. *J Natl Compr Canc Netw* 2017;15(1):3-8.

JACOB: Primary Endpoint — Overall Survival

ITT Population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	242	262
Median, mo	17.5	14.2
HR	0.84	
p-value (log-rank)	0.0565	



Secondary endpoints	P + H + CT (n = 388)	PLA + H + CT (n = 392)	HR (*p*-value)
Median PFS	8.5 mo	7.0 mo	0.72 (NR)
ORR	56.7%	48.3%	—

NR = not reported

Tabernero J et al. *Proc ESMO* 2017;Abstract 616O.

Editorial — Dr Venook

The evolution of technology has led to a proliferation of assays that can analyze hundreds of genes on a tissue specimen in a few days. This discovery process may inform new treatments in the future, but it is an inefficient way to identify molecular features that are both critical to cancer progression and for which there are available therapies. While present in a minority of any one cancer, HER2 overexpression is found in many different settings and there are numerous studies informing us how to manage its presence in different diseases.

Tabernero et al presented the results of a randomized trial in gastric cancer that compared the current HER2 breast cancer regimen (trastuzumab, pertuzumab plus chemotherapy) to trastuzumab plus chemotherapy in gastric cancer patients.

Editorial — Dr Venook (continued)

Improvement in progression-free survival (8.5 v 7.0 mo, HR = 0.73) was significant, but the small sample size left the numerically better triplet arm (median OS 17.5 vs 14.2 mo) shy of statistical significance.

The case report by Parikh et al offers a different approach. A patient with refractory colon cancer had HER2 overexpression and gained access to trastuzumab-DM1. The patient had a dramatic albeit short-lived tumor response before progression. The patient failed to respond to subsequent trastuzumab and pertuzumab, and in fact, a repeat biopsy showed no evidence of HER2 overexpression.

Editorial — Dr Venook (continued)

While neither of these reports changes practice, the first reminds us that the site of the cancer still matters, and the second reminds us that the identification of unexpected molecular features may offer some opportunity to help some patients.

Phase Ib/II study of cancer stemness inhibitor napabucasin in combination with FOLFIRI +/- bevacizumab (bev) in metastatic colorectal cancer (mCRC) patients (pts)

A phase Ib/II study of cancer stemness inhibitor napabucasin in combination with gemcitabine (gem) & *nab*-paclitaxel (*nab*PTX) in metastatic pancreatic adenocarcinoma (mPDAC) patients (pts)

Bendell J et al.
Proc ESMO 2017 World Congress GI;Abstract LBA-003.

Bekaii-Saab T et al.
Proc ESMO 2017 World Congress GI;Abstract LBA-002.

Napabucasin with FOLFIRI +/- Bevacizumab for mCRC

Response	Evaluable patients (n = 66)
Disease control rate	83%
ORR	21%

- No dose-limiting or unexpected toxicity or significant PK interactions
- Napabucasin did not significantly add to or worsen the overall AE profile of FOLFIRI +/- bevacizumab

Bendell J et al. *Proc ESMO 2017 World Congress GI*;Abstract LBA-003.

Napabucasin with Gemcitabine/*Nab* Paclitaxel in Metastatic Pancreatic Adenocarcinoma

Response	Evaluable patients (n = 55)
Disease control rate	93%
ORR	55%

- No significant PK interactions, dose-limiting or unexpected toxicities
- Most common AEs: Grade 1 diarrhea, nausea, fatigue, neuropathy; Grade 2 alopecia; Grade 3 neutropenia

Bekaii-Saab T et al. *Proc ESMO 2017 World Congress GI*;Abstract LBA-002.

Editorial — Dr Venook

Being first in class is good, particularly when it means that you have the first of a class of drugs that targets a pathway in cancer development and progression. Napabucasin was identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells. The studies by O'Neil et al and Bekaii-Saab et al represent the first steps of the long road to determining whether this is a useful drug and what a path forward could be.

O'Neil reported on its combination with FOLFIRI and bevacizumab in 82 previously treated patients with metastatic colorectal cancer, while Bekaii-Saab reported on its combinability with gemcitabine and gem-*nab* paclitaxel in 66 patients with either untreated (N = 49) or previously treated (N = 17) advanced pancreatic cancer.

Editorial — Dr Venook (continued)

Each combination was safe and well tolerated. While efficacy in early phase trials is hard to interpret, the overall response rate in the colorectal group was 21%, even though many patients had progressed on the FOLFIRI/bevacizumab previously. Perhaps more encouraging is the 55% overall response rate in the cohort of pancreatic cancer patients; even though many were treatment-naïve, that level of activity in pancreas cancer is surprising.

These results mean only that napabucasin has potential as a drug. The real work will tell us if it actually inhibits stem cells and if so, what difference that can make in the treatment of cancer patients. The results mean we can anticipate napabucasin being tested in a variety of settings.

Gastrointestinal Cancers — Drs Bendell and Grothey

Colorectal Cancer

Gastric Cancer

Hepatocellular Carcinoma

Pancreatic Cancer

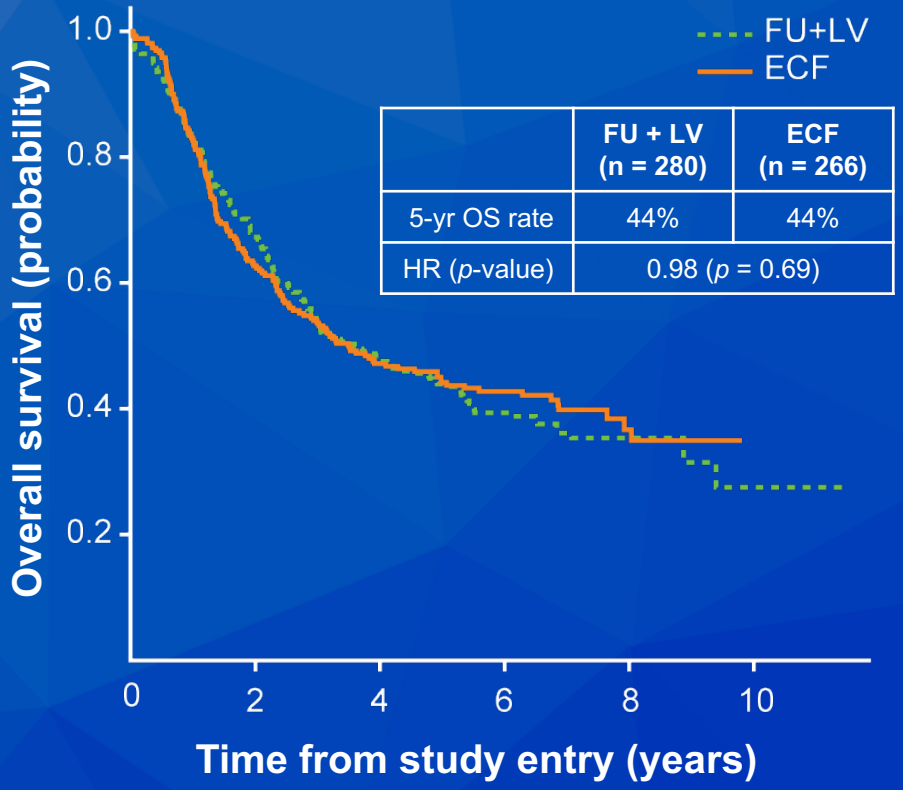
GI Neuroendocrine Tumors (GI NET)

Adjuvant Chemoradiotherapy with Epirucibin, Cisplatin, and Fluorouracil Compared with Adjuvant Chemotherapy with Fluorouracil and Leucovorin After Curative Resection of Gastric Cancer: Results from CALGB 80101 (Alliance)

Fuchs CS et al.
J Clin Oncol 2017;35(32):3671-7.

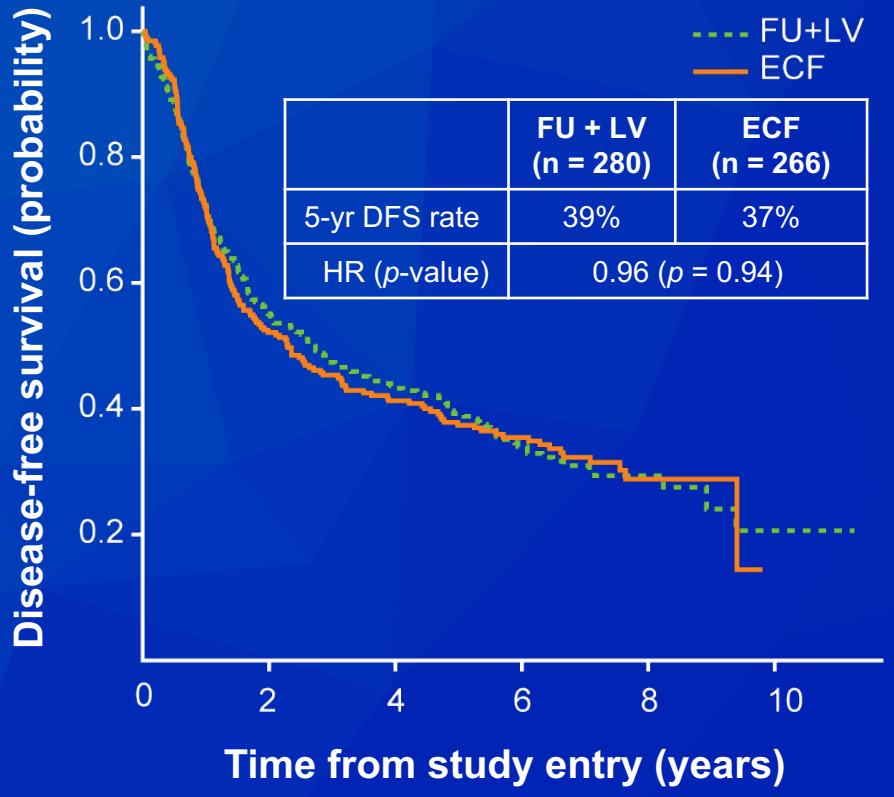
CALGB 80101: OS and DFS

OS



	FU + LV (n = 280)	ECF (n = 266)
5-yr OS rate	44%	44%
HR (*p*-value)	0.98 (*p* = 0.69)	

DFS



	FU + LV (n = 280)	ECF (n = 266)
5-yr DFS rate	39%	37%
HR (*p*-value)	0.96 (*p* = 0.94)	

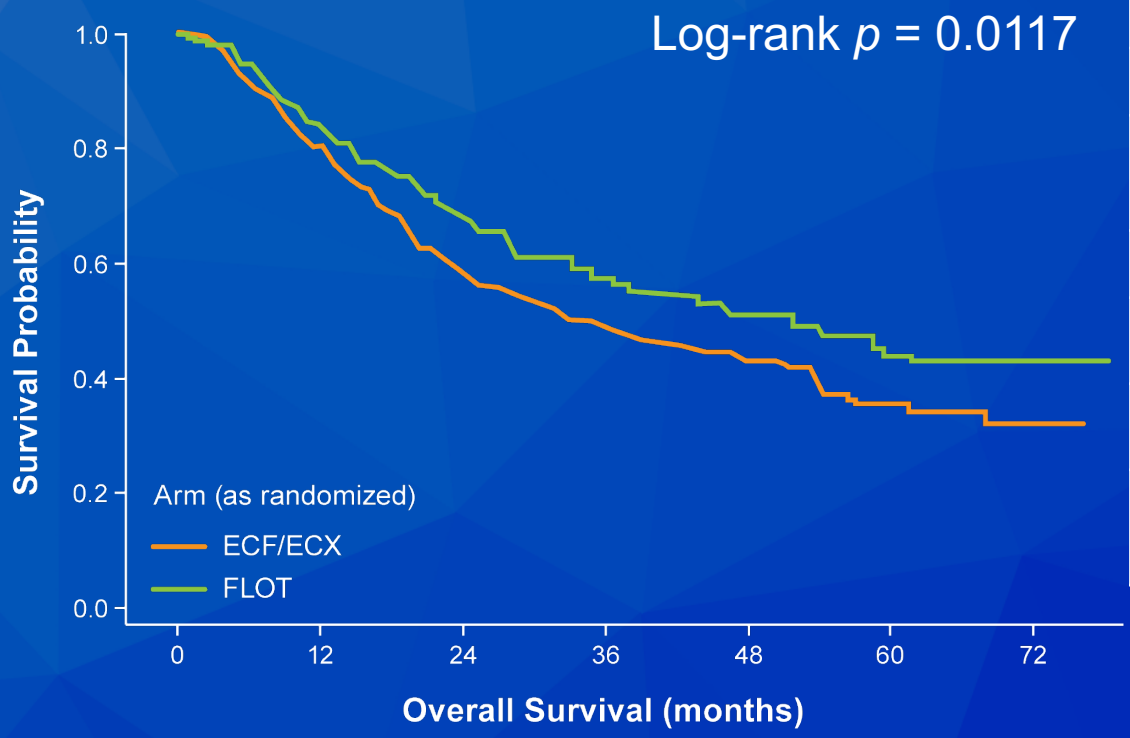
Median follow-up: 6.5 years

Fuchs CS et al. *J Clin Oncol* 2017;35(32):3671-7.

Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial

Al-Batran SE et al.
Proc ASCO 2017;Abstract 4004.

FLOT4-AIO: Primary Endpoint — Overall Survival



	ECF/ECX (n = 360)	FLOT (n = 356)
mOS months	35	50
HR	0.77 p = 0.012 (log rank)	
OS rate	**ECF/ECX**	**FLOT**
2y	59%	68%
3y	48%	57%
5y projected OS rates	36%	45%

Al-Batran SE et al. *Proc ASCO* 2017;Abstract 4004.

FLOT4-AIO: Select Chemotherapy-Related Toxicity

Grade 3-4 >5%	ECF/ECX (n = 354)	FLOT (n = 354)	*p*-value (chi-square)
Diarrhea	13 (4%)	34 (10%)	0.002
Vomiting	27 (8%)	7 (2%)	<0.001
Nausea	55 (16%)	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	NR
Infections	30 (9%)	63 (18%)	<0.001
Leukopenia	75 (21%)	94 (27%)	NR
Neutropenia	139 (39%)	181 (51%)	0.002
Thromboembolic	22 (6%)	9 (3%)	0.03
Anemia	20 (6%)	9 (3%)	0.04

Al-Batran SE et al. *Proc ASCO* 2017;Abstract 4004.

Editorial — Dr Philip

FLOT4 was a phase III trial of perioperative chemotherapy using a triplet of docetaxel, 5FU/leucovorin and oxaliplatin in patients with resectable (stages I-III, cT2-4/cN-any/cM0) gastric (G) or gastroesophageal junction (GEJ) cancer. The control arm was based on the previously reported MAGIC trial that established the ECF triplet as a treatment option in patients with resected G or GEJ cancer (without radiotherapy). Patients received chemotherapy preoperatively and following surgery. A total of 716 patients were enrolled. Overall survival favored FLOT (HR 0.77, p 0.012). Median OS and 3-year survival were 50 months and 57% versus 35 months and 48% in the control versus experimental arms, respectively.

Editorial — Dr Philip (continued)

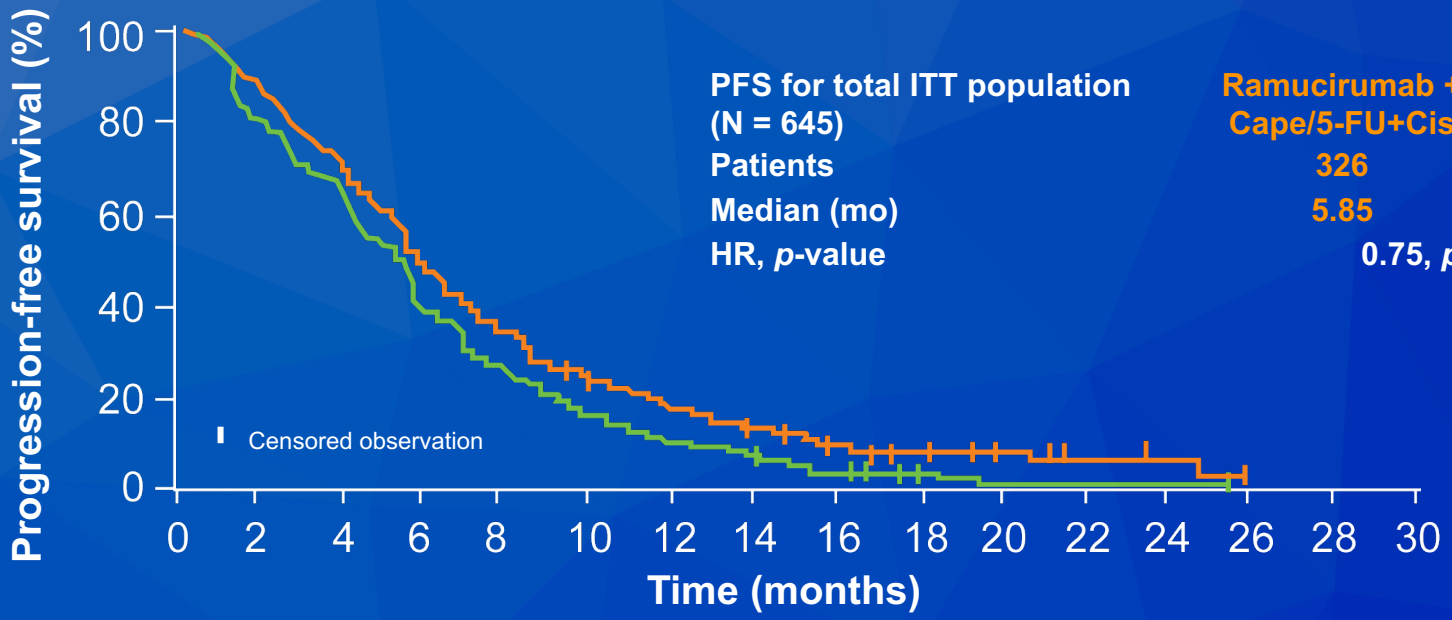
Grade 3 and 4 adverse events were higher in the FLOT group (diarrhea, infections, neutropenia). 46% and 37% of patients completed post-operative chemotherapy in the FLOT and control, respectively.

FLOT provides a modest benefit over ECF/ECX in resectable G and GEJ cancers. FLOT will be another treatment option for patients with resected G or GEJ cancer, probably in younger patients with good PS. However one has to consider the toxicity profile of this regimen relative to a doublet such as FOLFOX/CAPOX that is not infrequently used in the US. In treating resectable G and GEJ cancers, triplets may be considered in patients with good performance status and those who are younger after discussion with patients explaining the pros and cons of each regimen.

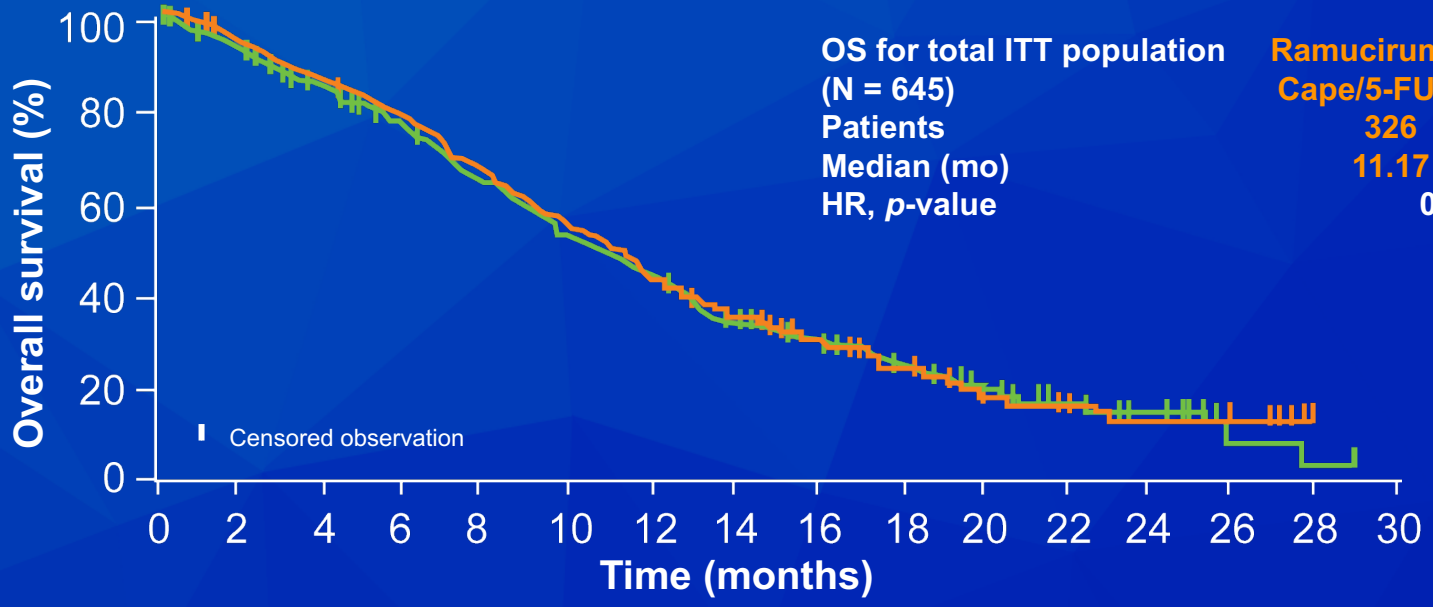
RAINFALL: A Randomized, Double-Blind, Placebo-Controlled Phase III Study of Cisplatin (Cis) plus Capecitabine (Cape) or 5FU with or without Ramucirumab (RAM) as First-Line Therapy in Patients with Metastatic Gastric or Gastroesophageal Junction (G-GEJ) Adenocarcinoma

Fuchs CS et al.
Gastrointestinal Cancers Symposium 2018;Abstract 5.

RAINFALL: Survival Outcomes



PFS for total ITT population (N = 645)	Ramucirumab + Cape/5-FU+Cis	Placebo + Cape/5-FU+Cis
Patients	326	319
Median (mo)	5.85	5.55
HR, *p*-value	0.75, *p* = 0.0024	



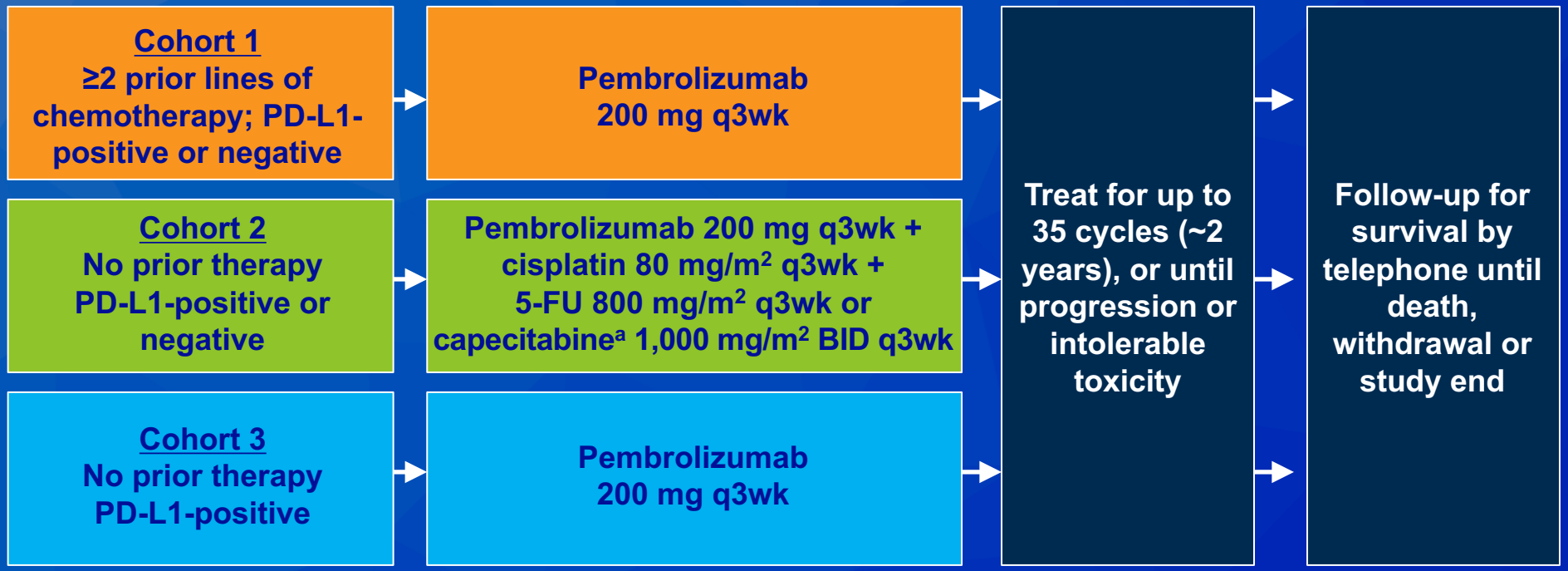
OS for total ITT population (N = 645)	Ramucirumab + Cape/5-FU+Cis	Placebo + Cape/5-FU+Cis
Patients	326	319
Median (mo)	11.17	10.74
HR, *p*-value	0.96, *p* = 0.68	

Fuchs CS et al. Gastrointestinal Cancers Symposium 2018;Abstract 5.

KEYNOTE-059 update: Efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal (G/GEJ) cancer

Wainberg ZA et al.
Proc ESMO 2017;Abstract LBA28_PR.

KEYNOTE-059 Study Design



Primary Endpoints: Safety, ORR

PD-L1-positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = the number of PD-L1-positive cells (tumor cells, lymphocytes and macrophages) divided by the total number of tumor cells x 100

[a] Capecitabine administered only in Japan

Wainberg ZA et al. *Proc ESMO* 2017;Abstract LBA28_PR.

KEYNOTE-059: Response and Survival with Pembrolizumab

Objective response rate	Cohort 1	Cohort 2	Cohort 3
All patients	12%	60%	26%
PD-L1-positive	16%	69%	
PD-L1-negative	6%	38%	N/A
Median overall survival	**Cohort 1**	**Cohort 2**	**Cohort 3**
All patients	5.5 mo	13.8 mo	20.7 mo
PD-L1-positive	5.8 mo	NR	
PD-L1-negative	4.6 mo	NR	N/A
Median PFS	**Cohort 1**	**Cohort 2**	**Cohort 3**
All patients	2.0 mo	6.6 mo	3.3 mo
PD-L1-positive	2.1 mo	NR	
PD-L1-negative	2.0 mo	NR	N/A

- Safety was manageable and consistent with that of previous reports: No new safety signals reported

Wainberg ZA et al. *Proc ESMO* 2017;Abstract LBA28_PR.

Editorial — Dr Venook

The US FDA is subjected to criticism about the time it takes to review applications and its inflexibility in allowing industry sponsors to take unconventional approaches to trial designs. It can refer skeptics to the path Merck followed in developing pembrolizumab in patients with gastric or gastroesophageal adenocarcinoma. Of course, it helps when the studies accrue rapidly, the data is consistent and patients realize clear-cut benefits.

Fuchs et al reported on the KEYNOTE-059 trial at ASCO this year. This was a super-sized phase II trial of pembrolizumab monotherapy in 259 patients with previously treated gastric cancer or GE junction cancer.

Editorial — Dr Venook (continued)

Actually, it was a series of phase I trials that explored differences in pembrolizumab toxicities and activity in cohorts of patients defined by prior lines of therapy and tumor expression of PD-L1. The overall response rate was 11.1% and the toxicities were as we expect with this class of agents.

Just two months later, Wainberg et al presented an update on cohort 1 and new results on cohorts 2 and 3 of the same KEYNOTE-059 trial. The data in the cohort 1 patients was more granular, although the response rate did not change.

Editorial — Dr Venook (continued)

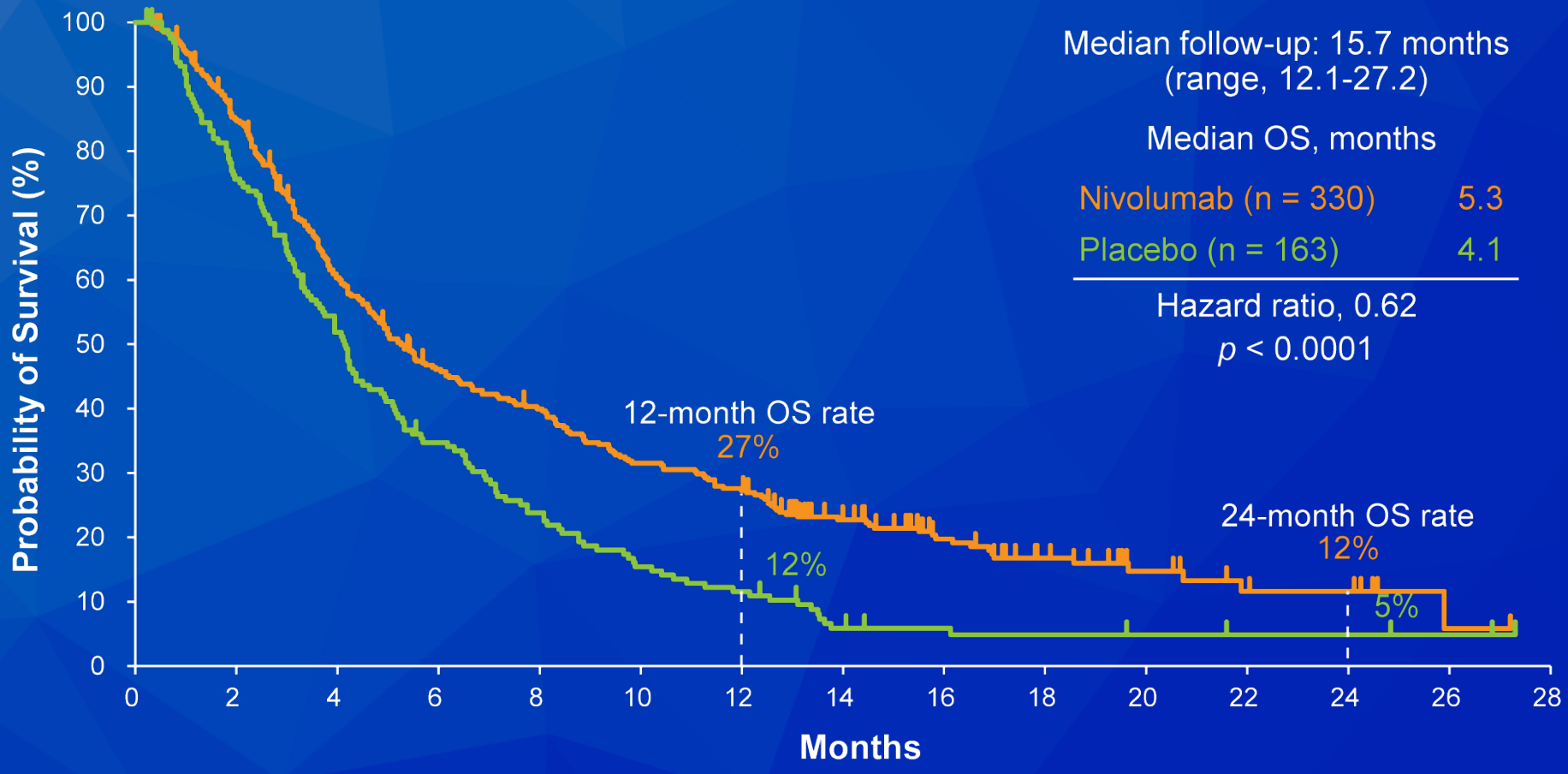
Cohort 2 included 25 treatment-naïve patients who received pembrolizumab in combination with cisplatin and a fluoropyrimidine; PD-L1 positive patients (N=16) had a 69% response rate while PD-L1 negative patients a 38% overall response rate. Cohort 3, treatment-naïve patients with PD-L1 positive tumors, had a response rate of 26%.

Next step: accelerated approval.

A Phase 3 study of nivolumab (Nivo) in previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Updated results and subset analysis by PD-L1 expression (ATTRACTION-02)

Boku N et al.
Proc ESMO 2017;Abstract 617O.

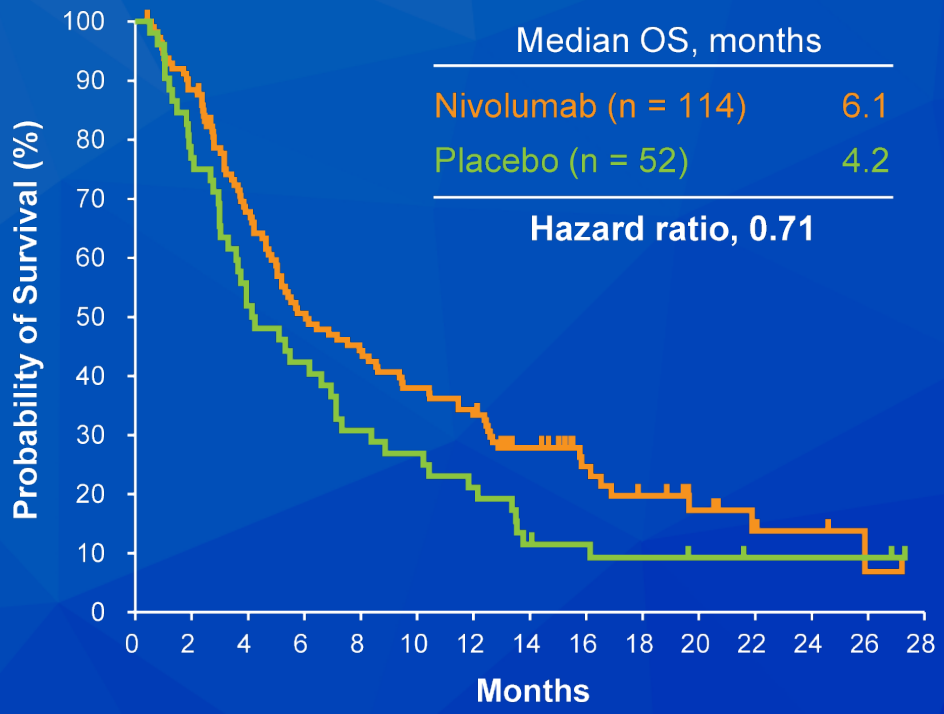
ATTRACTION-02: Updated Overall Survival (OS)



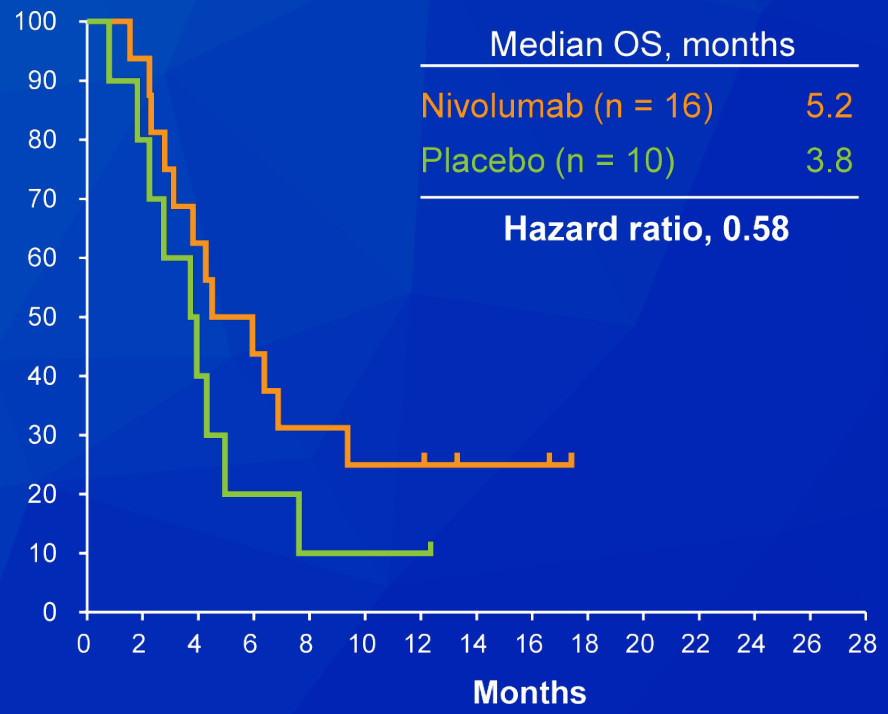
Boku N et al. *Proc ESMO* 2017;Abstract 617O.

ATTRACTION-02: OS by PD-L1 Expression

PD-L1 <1%



PD-L1 ≥1%



Boku N et al. *Proc ESMO* 2017;Abstract 617O.

Editorial — Dr Venook

It would be difficult to level any criticism at the design of the ATTRACTION-02 study in Asian patients with gastric or GE junction cancer. With a median follow-up of less than nine months, the 493-patient study that randomized patients 2:1 to nivolumab vs placebo, was terminated because an overall survival difference had already been realized (median OS, 5.3 vs 4.1 months, $p < 0.0001$).

Such a rapid and robust result could disrupt the study conduct and patient participation and preclude the analysis of secondary endpoints. In this case, for example, the planned analysis of possible correlations between tumor PD-L1 expression and outcomes, the duration of response and/or the nature of early compared to late toxicities could be missed.

Editorial — Dr Venook (continued)

That did not happen in this study, however. Boku et al reported on these secondary analyses in this ESMO abstract. Most important, and disappointing, is the lack of any correlation between tumor PD-L1 expression (<1% vs ≥1%) and patient outcomes — the presence of the receptor does not appear to be informative in predicting response. On the positive side, however, the overall survival difference was maintained with eight more months of follow-up (median OS, 6.3 vs 4.1 mos); this is not surprising given that the median response duration was 9.8 months. And as has been seen in most other studies with this class of agent, toxicities in general either happen early or not at all.

And now the next study: moving this class of drugs into the first line in these diseases.

Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study

Nivolumab monotherapy in patients with advanced gastric or gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study

Janjigian YY et al.
Proc ASCO 2017;Abstract 4014.

Calvo E et al.
Proc ESMO 2017 World Congress GI;Abstract O-007.

CheckMate 032: Antitumor Activity

	Nivo 3 (n = 59)	Nivo 1 + Ipi 3 (n = 49)	Nivo 3 + Ipi 1 (n = 52)
ORR	12%	24%	8%
Median PFS	1.4 mo	1.4 mo	1.6 mo
12-month PFS rate	8%	17%	10%
Median OS	6.2 mo	6.9 mo	4.8 mo
18-month OS rate	25%	28%	13%

Nivo 3 = Nivo 3 mg/kg q2wk
Nivo 1 + Ipi 3 = Nivo 1 mg/kg + Ipi 3 mg/kg q3wk
Nivo 3 + Ipi 1 = Nivo 3 mg/kg + Ipi 1 mg/kg q3wk

Janjigian YY et al. *Proc ASCO* 2017;Abstract 4014.

CheckMate 032: Treatment-Related Adverse Events (TRAEs)

Patients, n %	Nivo 3 (n = 59)		Nivo 1 + Ipi 3 (n = 49)		Nivo 3 + Ipi 1 (n = 52)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs	6 (10)	3 (5)	21 (43)	17 (35)	13 (25)	9 (17)
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥15% of patients in any treatment arm						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

- One Grade 5 TRAE was reported (tumor lysis syndrome in a patient treated with Nivo 3 + Ipi 1)

Janjigian YY et al. *Proc ASCO* 2017;Abstract 4014.

CheckMate 032: Subanalysis

	Nivolumab 3 mg/kg (n = 42)	
	INV	BICR
ORR	16.7%	7.1%
Complete response	4.8%	0%
Partial response	11.9%	7.1%
Stable disease	16.7%	31.0%
Median PFS	1.4 mo	1.5 mo

INV = investigator review; BICR = blinded independent central review

Calvo E et al. *Proc ESMO 2017 World Congress GI*;Abstract O-007.

Editorial — Dr Venook

ATTRACTION-2, which demonstrated activity of nivolumab in gastric and GE junction cancers, was conducted in Asia. Prior randomized studies (such as with bevacizumab) in these diseases had different outcomes across continents, suggesting that Western and Asian patients may be different.

CheckMate 032 included numerous cohorts with gastric or GE junction cancer, differentiated by prior lines of therapy, PD-L1 tumor expression and the addition of ipilimumab. To get a sense if immunotherapies had differential effects in patients based on demographics or genetics or other factors that might differ in Asian vs Western patients, a series of analyses were presented.

Editorial — Dr Venook (continued)

Janjigian et al reported on 160 heavily pretreated Western patients who received nivolumab +/- ipilimumab and matched them to approximate the results relative to Asian patients. Overall response rate and OS in PD-L1 positive or negative patients tracked similarly to the Asian patients, eg, overall survival: ATTRACTION-2, 5.3 mos; CheckMate 4.8, 6.2 mos. Ott et al did a similar analysis of a nivolumab monotherapy population of Western patients who had received at least two prior systemic therapies. A subset of 42 patients had comparable results to the ATTRACTION-2 population in terms of response rate, duration of response, overall survival and safety.

Editorial — Dr Venook (continued)

It is difficult to make much of this data given the relatively crude comparisons that are presented. Only a randomized study including both Asian and Western patients could address this issue directly, but there is no suggestion from these data sets that there is likely to be a huge disparity between these populations.

Updated Results from Phase III KEYNOTE-061 Trial of Pembrolizumab in Previously Treated Gastric or GEJ Adenocarcinoma

Press Release — December 14, 2017

The pivotal Phase III KEYNOTE-061 trial investigating pembrolizumab as a second-line treatment for patients with advanced gastric or GEJ adenocarcinoma did not meet its primary endpoint of overall survival (OS) (HR, 0.82; p=0.042 [one-sided]) in patients whose tumors expressed PD-L1 [Combined Positive Score (CPS) ≥ 1].

Additionally, progression free survival (PFS) in the PD-L1 positive population did not show statistical significance.

http://investors.merck.com/news/press-release-details/2017/Merck-Provides-Update-on-KEYNOTE-061-a-Phase-3-Study-of-KEYTRUDA-pembrolizumab-in-Previously-Treated-Patients-with-Gastric-or-Gastroesophageal-Junction-Adenocarcinoma/default.aspx.

Updated Results from Phase III JAVELIN Gastric 300 Trial of Avelumab in Previously Treated Gastric or GEJ Adenocarcinoma

Press Release — November 28, 2017

The Phase III JAVELIN Gastric 300 trial did not meet its primary endpoint of superior overall survival with single-agent avelumab compared with physician's choice of chemotherapy. The trial investigated avelumab as a third-line treatment for unresectable, recurrent or metastatic gastric or GEJ adenocarcinoma patients whose disease progressed following two prior therapeutic regimens, regardless of programmed death ligand-1 (PD-L1) expression.

The safety profile of avelumab was consistent with that observed in the overall JAVELIN clinical development program.

https://www.pfizer.com/news/press-release/press-release-detail/merck_kgaa_darmstadt_germany_and_pfizer_provide_update_on_phase_iii_javelin_gastric_300_study_in_patients_with_pre_treated_advanced_gastric_cancer

Gastrointestinal Cancers — Drs Bendell and Grothey

- Colorectal Cancer
- Gastric Cancer
- Hepatocellular Carcinoma
- Pancreatic Cancer
- GI Neuroendocrine Tumors (GI NET)

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

Masatoshi Kudo, Richard S Finn, Shukui Qin, Kwang-Hyub Han, Kenji Ikeda, Fabio Piscaglia, Ari Baron, Joong-Won Park*, Guohong Han*, Jacek Jassem, Jean Frederic Blanc, Arndt Vogel, Dmitry Komov, T R Jeffry Evans, Carlos Lopez, Corina Dutcus, Matthew Guo, Kenichi Saito, Silvija Kraljevic, Toshiyuki Tamai, Min Ren, Ann-Lii Cheng*

Kudo M et al. *Lancet* 2018;[Epub ahead of print].

REFLECT: Primary and Secondary Endpoints

	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR/odds ratio	*p*-value
Median OS	13.6 mo	12.3 mo	0.92	NR
Median PFS	7.4 mo	3.7 mo	0.66	<0.00001
Median TTP	8.9 mo	3.7 mo	0.63	<0.00001
ORR	24.1%	9.2%	3.13*	<0.00001

NR = not reported; TTP = time to progression

* Odds ratio

- Lenvatinib is noninferior to sorafenib with regard to OS and achieves statistically significant and clinically meaningful improvements in PFS, TTP and ORR as first-line therapy for unresectable HCC.

Kudo M et al. *Lancet* 2018;[Epub ahead of print]. Cheng AL et al. *Proc ASCO* 2017;Abstract 4001.

REFLECT: Select Treatment-Emergent AEs

Adverse event, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Palmar-plantar erythrodysesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (0)	57 (12)	0 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (N/A)	119 (25)	0 (N/A)

Cheng AL et al. *Proc ASCO* 2017;Abstract 4001.

Editorial — Dr Philip

REFLECT study was a global phase III trial of oral lenvatinib versus sorafenib in the first-line setting in patients with advanced HCC. Lenvatinib targets multiple kinases (VEGFR1-3, FGFR1-4, PDGFRalpha, and KIT). Primary endpoint was OS. The study was designed as a noninferiority trial and included 954 previously untreated patients who had Child Pugh A score, PS ≤1, and BCLC stage B or C. Approximately half of the patients had documented hepatitis B infection. Dose of lenvatinib was either 8 mg or 12 mg per day based on weight. Sorafenib was at the standard dose of 400 mg twice daily.

Results of the study demonstrated noninferiority of lenvatinib versus sorafenib (13.6 months versus 12.3 months, respectively).

Editorial — Dr Philip (continued)

There was, however, significant improvement in PFS (HR 0.66), TTP (HR 0.63), and objective response rate with lenvatinib. Objective responses were seen in 24.1% versus 9.1% in lenvatinib and sorafenib arms, respectively. Comparisons of toxicity revealed a higher frequency of hypertension in lenvatinib arm and a higher incidence of hand-foot rash in the sorafenib arm. Other toxicities were comparable. However, more serious adverse events were reported with lenvatinib. Median duration of treatment was longer in the lenvatinib arm by 2 months.

Lenvatinib appears to be an appropriate treatment option for patients with advanced HCC with favorable PS and liver reserve.

Editorial — Dr Philip (continued)

The study did not demonstrate a survival benefit, but several secondary outcome measures favored lenvatinib. The latter may favor the front-line use of lenvatinib but must also be considered in the context of its toxicity profile relative to sorafenib. A biomarker based selection is not possible at this time.

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial

Updated overall survival (OS) analysis from the international, phase 3, randomized, placebo-controlled RESORCE trial of regorafenib for patients with hepatocellular carcinoma (HCC) who progressed on sorafenib treatment

Bruix J et al.
Lancet 2017;389(10064):56-66.

Bruix J et al.
Proc ESMO 2017 World Congress GI;Abstract O-009.

RESORCE: Efficacy

	Regorafenib (n = 379)	Placebo (n = 194)	HR	*p*-value
Median PFS[1]	3.1 mo	1.5 mo	0.46	<0.0001
Median OS (primary analysis)[1]	10.6 mo	7.8 mo	0.63	<0.0001
Median OS (updated analysis)[2]	10.7 mo	7.9 mo	0.61	<0.0001
ORR (mRECIST)[1]	11%	4%	—	0.0047
Disease control rate[1]	65%	36%	—	<0.0001

- Data cutoff for primary analysis: February 29, 2016
- Data cutoff for updated OS analysis: January 23, 2017

[1] Bruix J et al. *Lancet* 2017;389(10064):56-66; [2] Bruix J et al. *Proc ESMO 2017 World Congress GI*;Abstract O-009.

Editorial — Dr Philip

This was a double-blind phase 3 trial of regorafenib in patients with advanced HCC who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), experienced disease progression on sorafenib and had Child-Pugh A liver function and favorable performance status. Patients were randomized to either oral regorafenib 160 mg/day or placebo once daily during weeks 1-3 of each 4-week cycle. The primary endpoint was overall survival. A total of 573 were enrolled.

Regorafenib improved overall survival (HR 0.63, $p < 0.0001$); median survival was 10.6 months for regorafenib versus 7.8 months for placebo. Progression-free survival was also significantly improved (HR 0.46, $p < 0.0001$). Time to progression was doubled with regorafenib.

Editorial — Dr Philip (continued)

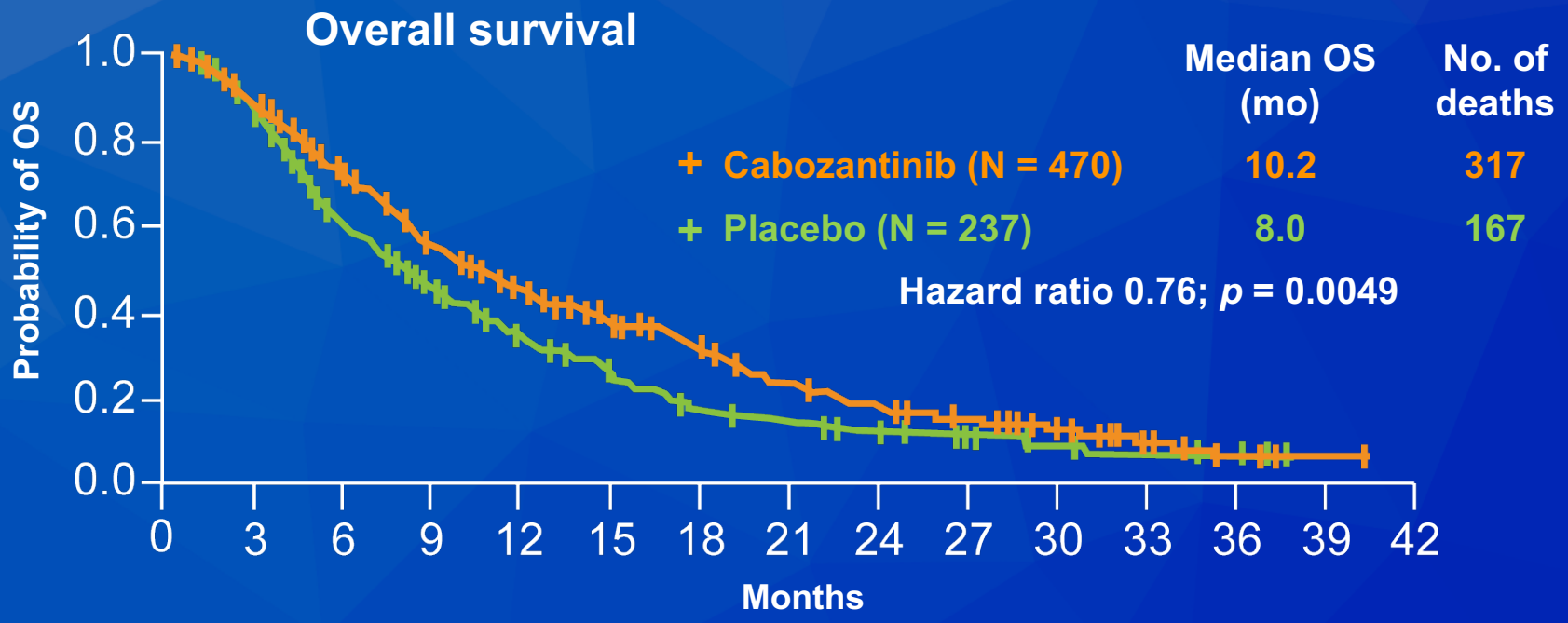
The most common clinically relevant grade 3 or 4 treatment-emergent events due to regorafenib were hypertension, hand-foot skin reaction, fatigue.

At this time regorafenib is the only systemic treatment shown to provide survival benefit of a clinically meaningful value in HCC patients progressing on sorafenib treatment. Subgroup analyses demonstrates benefit in all patient categories. Regorafenib at a dose of 160 mg may not be well tolerated by the average patients with advanced HCC, who may require dose reductions. At a minimum, patients must be closely monitored during the first few weeks of therapy.

Cabozantinib (C) versus Placebo (P) in Patients (pts) with Advanced Hepatocellular Carcinoma (HCC) Who Have Received Prior Sorafenib: Results from the Randomized Phase III CELESTIAL Trial

Abou-Alfa GK et al.
Gastrointestinal Cancers Symposium 2018;Abstract 207.

CELESTIAL: Clinical Outcomes



All patients	Cabozantinib (n = 470)	Placebo (n = 237)	HR	*p*-value
Median PFS	5.2 mo	1.9 mo	0.44	<0.0001
Prior sorafenib only	**n = 331**	**n = 164**	**HR**	
Median OS	11.3 mo	7.2 mo	0.70	—
Median PFS	5.5 mo	1.9 mo	0.40	—

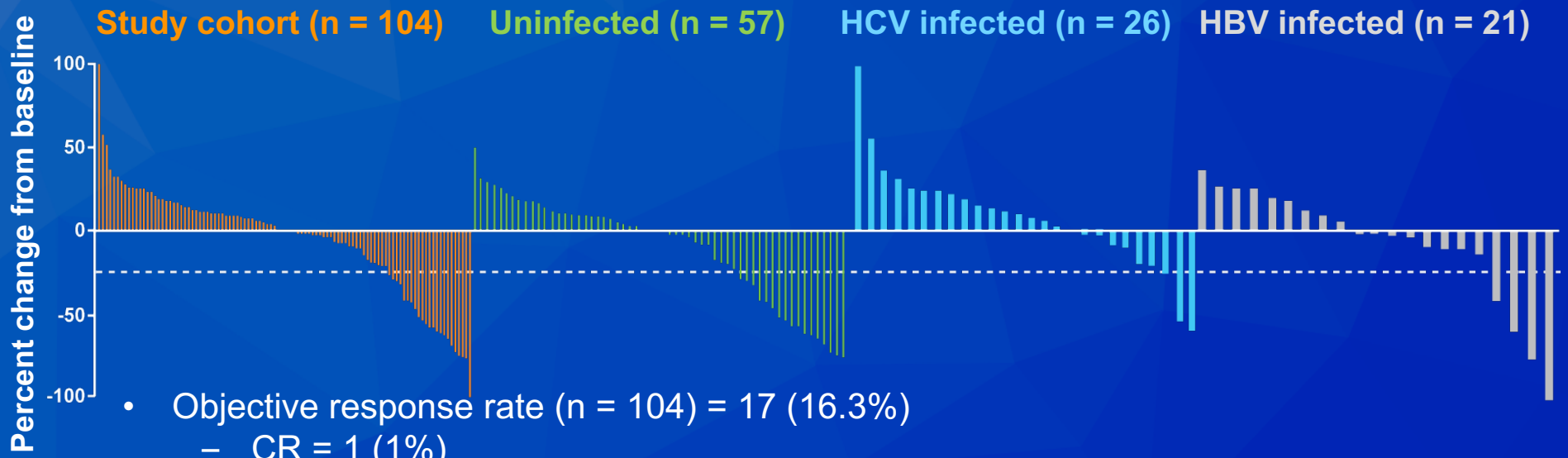
Abou-Alfa GK et al. Gastrointestinal Cancers Symposium 2018;Abstract 207.

KEYNOTE-224: Pembrolizumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib

Zhu AX et al.
Gastrointestinal Cancers Symposium 2018;Abstract 209.

KEYNOTE-224: Response and Survival

Maximum Percentage Changes from Baseline in Target Lesions



- Objective response rate (n = 104) = 17 (16.3%)
  - CR = 1 (1%)

- Disease control rate (n = 104) = 64 (61.5%)
- Median time to response = 2.1 mo
- Median duration response = 8.2 mo
- Median OS = not reached
- Median PFS = 4.8 mo

Zhu AX et al. Gastrointestinal Cancers Symposium 2018;Abstract 209.

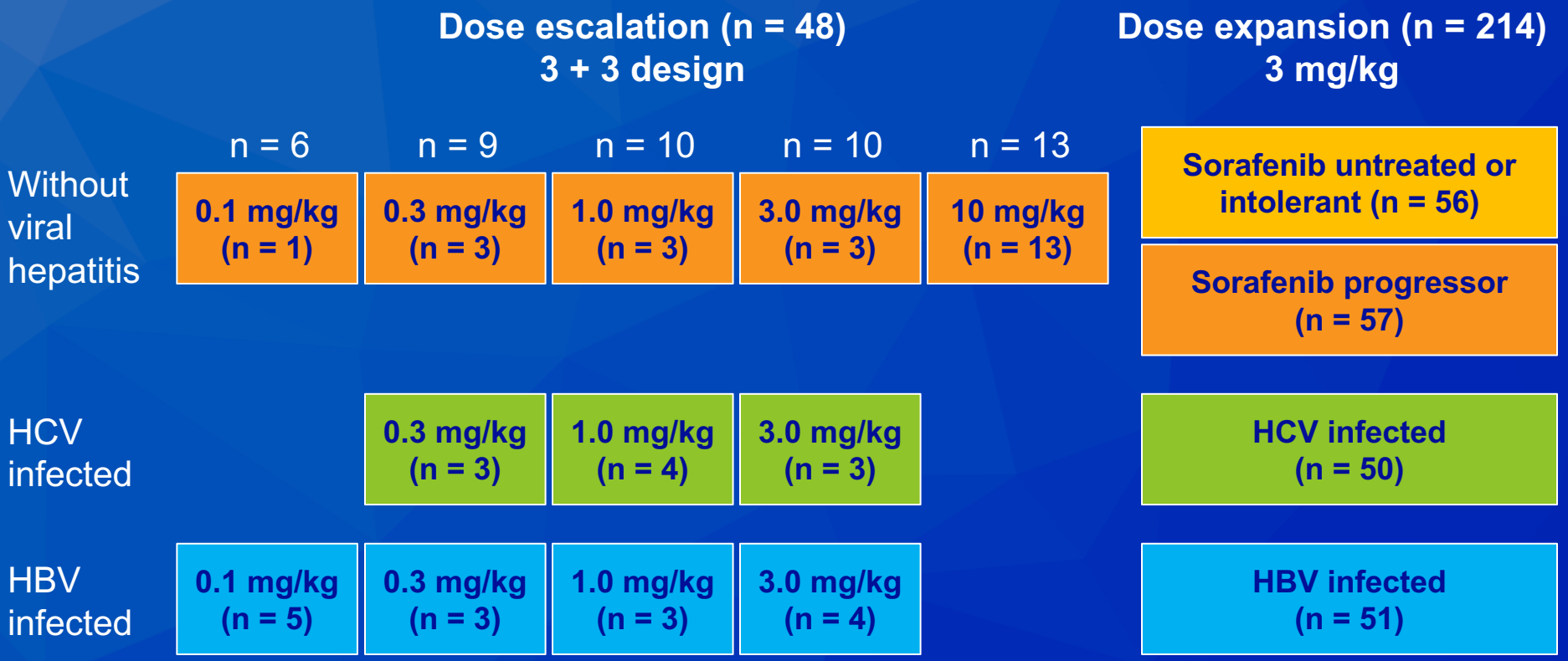
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Efficacy and safety of nivolumab in patients with advanced hepatocellular carcinoma analyzed by patient age: A sub-analysis of the CheckMate 040 study

El-Khoueiry AB et al.
Lancet 2017;389(10088):2492-502.

Melero I et al.
Proc ESMO 2017 World Congress GI;Abstract O-008.

CheckMate 040 Study Design



HCV = hepatitis C virus; HBV = hepatitis B virus

El-Khoueiry AB et al. *Lancet* 2017;389(10088):2492-502.

CheckMate 040: Dose-Expansion Phase

	All patients (n = 214)	Uninfected untreated/intolerant (n = 56)	Uninfected progressor (n = 57)	HCV infected (n = 50)	HBV infected (n = 51)
ORR	20%	23%	12%	20%	14%
CR	3%	0%	4%	0%	2%
PR	18%	23%	18%	20%	12%
SD	45%	52%	40%	46%	41%
mDOR	9.9 mo	8.4 mo	NYR	9.9 mo	NYR
Disease control	64%	75%	61%	66%	55%
9-mo OS	74%	82%	63%	81%	70%

ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; mDOR = median duration of response; OS = overall survival; NYR = not yet reached

El-Khoueiry AB et al. *Lancet* 2017;389(10088):2492-502.

CheckMate 040: Grade 3-4 Dose-Expansion TRAEs

Event	Uninfected untreated/ intolerant (n = 56)	Uninfected progressor (n = 57)	HCV infected (n = 50)	HBV infected (n = 51)	All patients (n = 214)
Rash	1 (2%)	1 (2%)	0	0	2 (1%)
Pruritus	0	0	1 (2%)	0	1 (<1%)
Diarrhea	1 (2%)	1 (2%)	0	1 (2%)	3 (1%)
Decreased appetite	0	0	1 (2%)	0	1 (<1%)
Fatigue	1 (2%)	1 (2%)	1 (2%)	0	3 (1%)
Nausea	0	0	0	0	0
Dry mouth	0	0	0	0	0
Increased AST	2 (4%)	2 (4%)	5 (10%)	0	9 (4%)
Increased ALT	0	2 (4%)	3 (6%)	0	5 (2%)

El-Khoueiry AB et al. *Lancet* 2017;389(10088):2492-502.

CheckMate 040: Subanalysis by Patient Age

N = 262	<65 y (n = 142)	65 y to <75 y (n = 89)	≥65 y (n = 120)	≥75 y (n = 31)
ORR by BICR	16.9%	18.0%	16.7%	12.9%
Sorafenib naïve	21.1%	26.7%	19.0%	0%
Sorafenib experienced	15.4%	13.6%	15.4%	21.1%
ORR by INV	19.7%	22.5%	20.0%	12.9%
Sorafenib naïve	21.1%	33.3%	23.8%	0%
Sorafenib experienced	19.2%	16.9%	17.9%	21.1%

- Nivolumab efficacy did not appear to be affected by patient age in patients with advanced HCC, and a manageable safety profile was observed across patient age groups.

Melero I et al. *Proc ESMO 2017 World Congress GI*;Abstract O-008.

Editorial — Dr Philip

CheckMate 040 was a phase 1/2, open-label, noncomparative, dose-escalation and expansion trial of the PD-1 inhibitor nivolumab in patients with advanced hepatocellular carcinoma (HCC). Previous sorafenib treatment was allowed. Eligible patients had a Child-Pugh score of 7 or less (Child-Pugh A or B7) for the dose-escalation phase and 6 or less (Child-Pugh A) for the dose-expansion phase, and an ECOG PS of 1 or less. Patients received intravenous nivolumab 0.1-10 mg/kg every 2 weeks in the dose-escalation phase (3+3 design). Nivolumab 3 mg/kg was given every 2 weeks in the dose-expansion phase to patients in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressor without viral hepatitis, HCV infected, and HBV infected.

Editorial — Dr Philip (continued)

Primary endpoints were safety and tolerability for the escalation phase and objective response rate for the expansion phase. 262 patients were treated (48 patients in the dose-escalation phase and 214 in the dose-expansion phase). 202 (77%) of 262 patients have completed treatment and follow-up is ongoing.

During dose escalation, nivolumab showed a manageable safety profile, including acceptable tolerability. In this phase, 46 (96%) of 48 patients discontinued treatment, 42 (88%) due to disease progression. Incidence of treatment-related adverse events did not seem to be associated with dose and no maximum tolerated dose was reached. 12 (25%) of 48 patients had grade 3/4 treatment-related adverse events.

Editorial — Dr Philip (continued)

Three (6%) patients had treatment-related serious adverse events (pemphigoid, adrenal insufficiency, liver disorder). Nivolumab 3 mg/kg was chosen for dose expansion. The objective response rate was 20% (95% CI, 15-26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI, 6-28) in the dose-escalation phase.

This study demonstrates a benefit for the PD-1 inhibitor nivolumab 3 mg/kg in patients with HCC. No immune biomarker was defined to predict outcome or select patients at this time. It certainly adds to our treatment armamentarium and expands treatment options.

Editorial — Dr Philip (continued)

The durability of the responses supports using nivolumab in treatment of advanced HCC in first or later lines of therapy. One has to note also that the eligible patients in this trial had good PS and favorable liver reserve, and therefore one would question the safety and efficacy of nivolumab in patients with less favorable hepatic reserve and/or unfavorable performance status.

Gastrointestinal Cancers — Drs Bendell and Grothey

Colorectal Cancer

Gastric Cancer

Hepatocellular Carcinoma

Pancreatic Cancer

GI Neuroendocrine Tumors (GI NET)

Select Ongoing Phase III Trials in the Adjuvant and Locally Advanced Settings of Pancreatic Adenocarcinoma

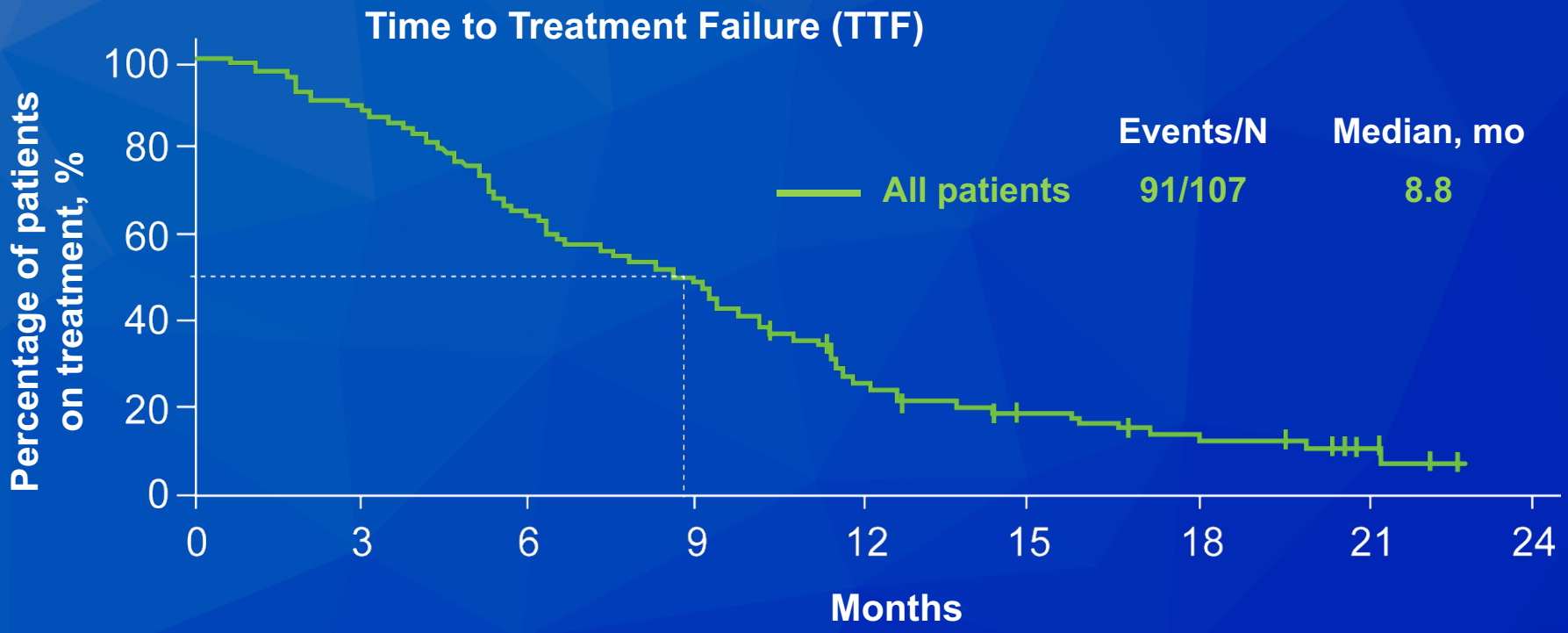
Trial identifier	N	Setting	Randomization
APACT (NCT01964430)	866	Adjuvant	• *Nab* paclitaxel + gemcitabine • Gemcitabine
CSPAC-010 (NCT02506842)	300	Second-line adjuvant	• *Nab* paclitaxel + gemcitabine • Oxaliplatin/folinic acid/flourouracil
PANC0015 (NCT01926197)	172	Locally advanced	• mFOLFIRINOX + SBRT • mFOLFIRINOX
CONKO-007 (NCT01827553)	830	Locally advanced	• Gemcitabine or FOLFIRINOX → chemoRT • Gemcitabine or FOLFIRINOX
NEOPAN (NCT02539537)	170	Locally advanced	• FOLFIRINOX • Gemcitabine

www.clinicaltrials.gov; Accessed October 2017.

Phase II LAPACT Trial of nab-Paclitaxel (*nab*-P) plus Gemcitabine (G) for Patients with Locally Advanced Pancreatic Cancer (LAPC)

Hammel P et al.
Gastrointestinal Cancers Symposium 2018;Abstract 204.

LAPACT: Clinical Outcomes



Survival	n = 107
Median PFS	10.8 mo
12-mo OS	72%

Hammel P et al. Gastrointestinal Cancers Symposium 2018;Abstract 204.

Select Ongoing Phase III Trials in the Adjuvant and Locally Advanced Settings of Pancreatic Adenocarcinoma

Trial identifier	N	Setting	Randomization
APACT (NCT01964430)	866	Adjuvant	• *Nab* paclitaxel + gemcitabine • Gemcitabine
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NEOPAN (NCT02539537)	170	Locally advanced	• FOLFIRINOX • Gemcitabine

www.clinicaltrials.gov; Accessed October 2017.

Original Article

Second-Line Treatment in Patients With Pancreatic Ductal Adenocarcinoma: A Meta-Analysis

Mohamad Bassam Sonbol, MD; Belal Firwana, MD; Zhen Wang, PhD; Diana Almader-Douglas; Mitesh J. Borad, MD; Issam Makhoul, MD; Ramesh K. Ramanathan, MD; Daniel H. Ahn, DO; and Tanios Bekaii-Saab, MD

Cancer 2017;123(23):4680-6.

Meta-analysis: OS and PFS

- 5 trials (N = 895 patients) were identified comparing second-line fluoropyrimidine (FP) alone to FP combinations including either oxaliplatin (FPOX) or irinotecan formulations (FPIRI) for PDAC.
- **FPOX vs FP** demonstrated a modest improvement in PFS but not OS:
  - PFS HR = 0.81; $p = 0.02$
  - OS HR = 1.03; $p = 0.90$
- **FPIRI vs FP** demonstrated an improvement in both PFS and OS:
  - PFS HR = 0.64; $p = 0.005$
  - OS HR = 0.70; $p = 0.004$
- Combination of FP with oxaliplatin or various irinotecan formulations appears to improve PFS in comparison to single-agent FP.
- FPIRI, but not FPOX, appears to confer an OS advantage.

Sonbol MB et al. *Cancer* 2017;123(23):4680-6.

Editorial — Dr Philip

In this study the authors searched the PubMed, EMBASE, and Cochrane databases to identify randomized controlled trials comparing fluoropyrimidine (FP) monotherapy versus FP combination therapy that included either oxaliplatin or various irinotecan formulations in patients with pancreatic cancer whose disease progressed after first-line treatment. The authors performed a meta-analysis to determine the effectiveness of adding oxaliplatin (OX) or various irinotecan (IRI) formulations to a fluoropyrimidine (FP) after first-line treatment progression in patients with PDAC. Outcomes of interest included overall survival (OS) and progression-free survival (PFS). Five studies (895 patients) were identified.

Editorial — Dr Philip (continued)

Patients randomized to receive a FP-based combination had a significantly improved PFS and a trend toward improved OS compared with those who received FP monotherapy. When comparing irinotecan plus FP versus FP, there was an improvement in both PFS (hazard ratio, 0.64; P = .005) and OS (hazard ratio, 0.70; P = .004) in patients who received the combination. Conversely, oxaliplatin/FP produced only a modest improvement in PFS with no improvement in OS.

In this meta-analysis it appears that the combination of FP with irinotecan formulations may represent the optimum next line of treatment after gemcitabine-based chemotherapy regimens.

Editorial — Dr Philip (continued)

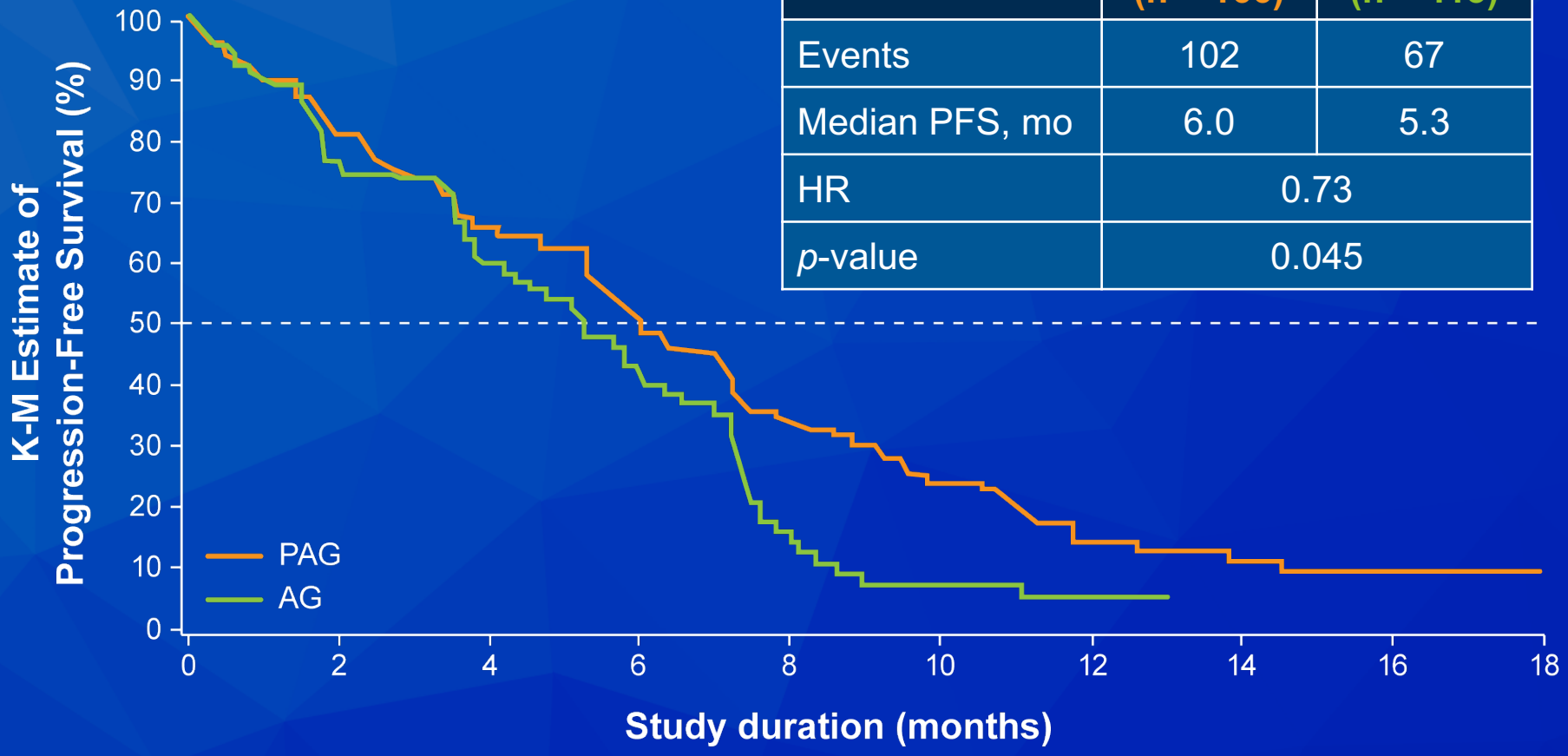
However, the benefits are still very modest and there is a need to consider clinical trials in all patients progressing on front-line therapy. At this time nanoliposomal irinotecan plus 5FU/LCV is an FDA-approved regimen in patients progressing on gemcitabine based therapy based on the NAPOLI-1 phase III trial. No prospective data is available for the other irinotecan formulations in the second-line setting.

Randomized phase II study of PEGPH20 plus *nab*-paclitaxel/gemcitabine (PAG) vs AG in patients (Pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDA)

Hingorani SR et al.
Proc ASCO 2017;Abstract 4008.

HALO-202: Primary Endpoint — PFS (Combined Stages 1 and 2)

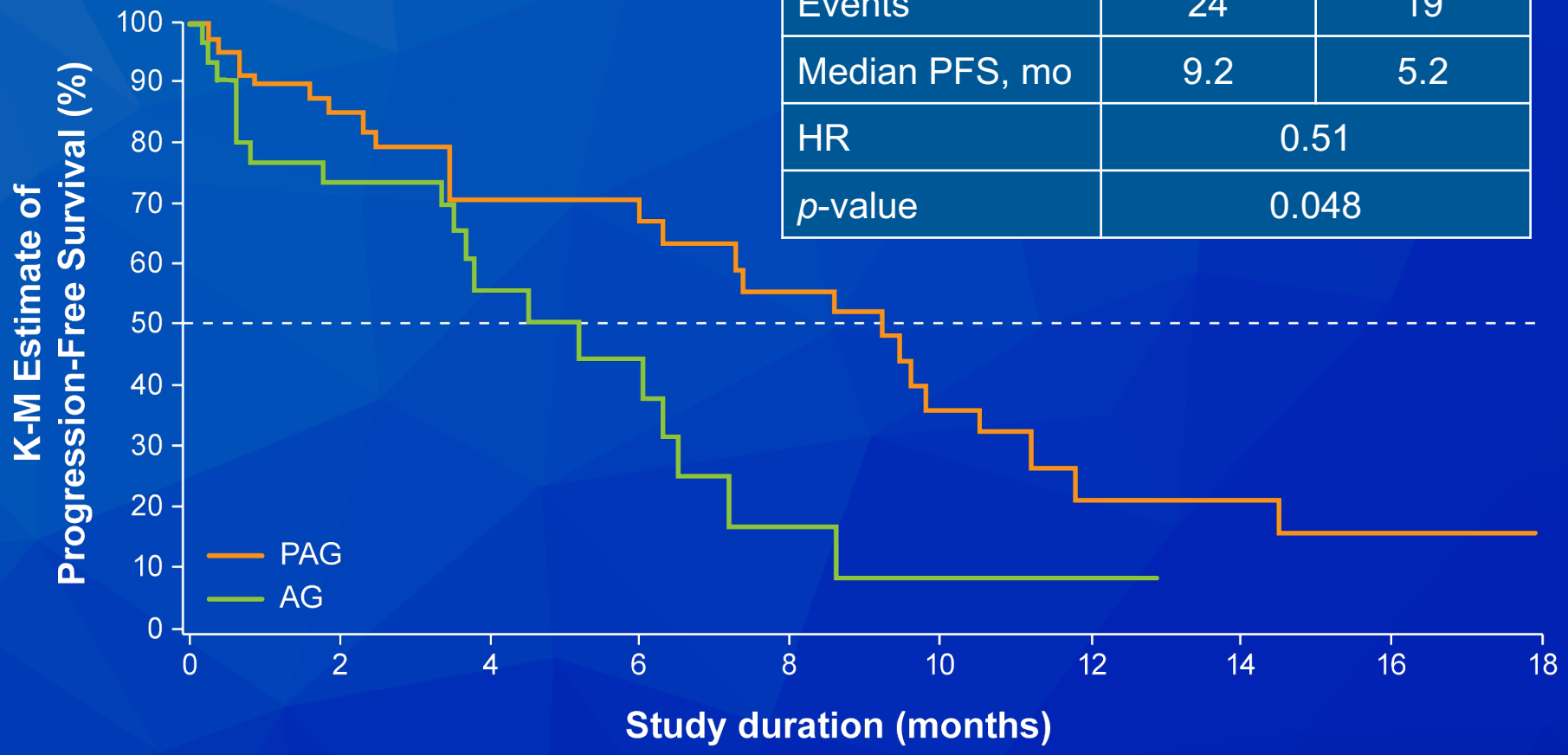
	PAG (n = 166)	AG (n = 113)
Events	102	67
Median PFS, mo	6.0	5.3
HR	0.73	
p-value	0.045	



Hingorani SR et al. *Proc ASCO* 2017;Abstract 4008.

HALO-202: Secondary Endpoint — PFS HA-High (Combined Stages 1 and 2)

	PAG (n = 49)	AG (n = 35)
Events	24	19
Median PFS, mo	9.2	5.2
HR	0.51	
p-value	0.048	



Hingorani SR et al. *Proc ASCO* 2017;Abstract 4008.

HALO-202: Select TRAEs

n (%)	PAG (n = 160)		AG (n = 100)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	115 (72)	33 (21)	66 (66)	16 (16)
Peripheral edema	101 (63)	8 (5)	26 (26)	4 (4)
Muscle spasms	89 (56)	20 (13)	3 (3)	1 (1)
Nausea	79 (49)	8 (5)	47 (47)	4 (4)
Diarrhea	64 (40)	11 (7)	39 (39)	5 (5)
Anemia	62 (39)	27 (17)	38 (38)	20 (20)
Alopecia	60 (38)	1 (0.6)	39 (39)	0
Decreased appetite	59 (37)	7 (4)	25 (25)	2 (2)
Neutropenia	54 (34)	47 (29)	19 (19)	18 (18)
Neuropathy peripheral	47 (29)	10 (6)	31 (31)	8 (8)
Vomiting	46 (29)	5 (3)	27 (27)	2 (2)
Dysgeusia	45 (28)	0	19 (19)	0
Myalgia	41 (26)	8 (5)	7 (7)	0
Thrombocytopenia	41 (26)	26 (16)	17 (17)	9 (9)

Hingorani SR et al. *Proc ASCO* 2017;Abstract 4008.

Editorial — Dr Philip

This was a pilot randomized phase II study testing the combination of gemcitabine plus *nab* paclitaxel with or without human recombinant pegylated hyaluronidase (PEGPH20) in patients with metastatic pancreatic adenocarcinoma. PEGPH20 targets hyaluronan, a matrix protein. Preclinical studies demonstrated the significantly improved antitumor effect with the combination of gemcitabine and PEGPH20. Patients (ECOG PS 0-1) had no prior systemic therapy for metastatic disease. The primary endpoint of the study was progression-free survival and was modified to also include the frequency of venous thromboembolic events because of the initial observation of a significant increase in VTEs in patients who were randomized to the PEGPH20 containing arm.

Editorial — Dr Philip (continued)

All patients had their tumors evaluated for the expression of hyaluronan by IHC.

In the subset of 80 patients whose tumors expressed high levels of hyaluronan PEGPH20 resulted in statistically significant and clinically meaningful prolongation of median progression-free survival (9.2 months versus 5.2 months). Treatment-related adverse events for trial participants included peripheral edema (63% of those receiving PEGPH20 vs 26% for the control group), muscle spasms (56% vs 3%), neutropenia (34% vs 19%), and myalgia (26% vs 7%). The use of low molecular weight heparin equalized the incidence of the VTEs between the two arms.

Editorial — Dr Philip (continued)

The survival data were not mature at time of the presentation and we need to wait for information. However, this study formed the basis of a launch of a global phase III trial in patients with metastatic pancreatic cancer in the front-line setting that also includes the administration of low molecular weight heparin. A major eligibility criterion is the tumoral expression of hyaluronan using IHC. Hyaluronan-directed therapy will hopefully be the first successful targeted therapy in pancreatic cancer in patients who are selected by a biomarker. Such a subgroup will be fewer than 50% of patients with metastatic pancreatic cancer.

Personalized Medicine and Imaging

Clinical Cancer Research

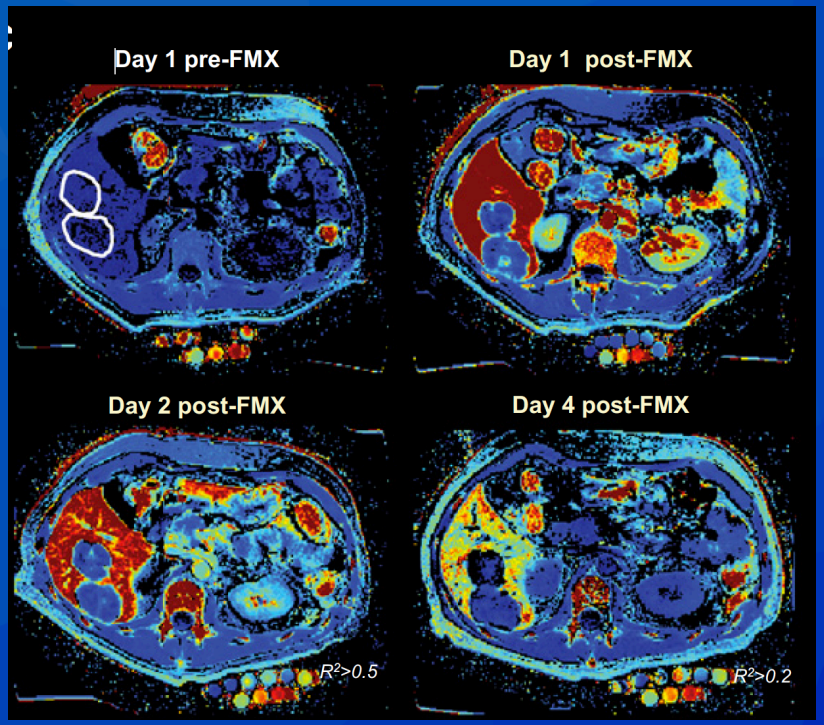
Correlation between Ferumoxytol Uptake in Tumor Lesions by MRI and Response to Nanoliposomal Irinotecan in Patients with Advanced Solid Tumors: A Pilot Study

Ramesh K. Ramanathan, Ronald L. Korn, Natarajan Raghunand, Jasgit C. Sachdev, Ronald G. Newbold, Gayle Jameson, Gerald J. Fetterly, Joshua Prey, Stephan G. Klinz, Jaeyeon Kim, Jason Cain, Bart S. Hendriks, Daryl C. Drummond, Eliel Bayever, and Jonathan B. Fitzgerald.

Clin Cancer Res 2017;23(14):3638-48.

Correlation between Ferumoxytol (FMX) Uptake in Tumor Lesions and Response to Nal-IRI

- FMX deposition was quantified by FMX MRI in 13 evaluable patients with previously treated solid tumors.



Representative pseudocolored maps from patient images before and after FMX dosing

- After FMX quantification, patients received nal-IRI (70 mg/m^2 every 2 weeks) until disease progression.
- Higher post-FMX levels were significantly associated with reduction in lesion size at 1 hour ($p < 0.001$) and 24 hours ($p < 0.003$).

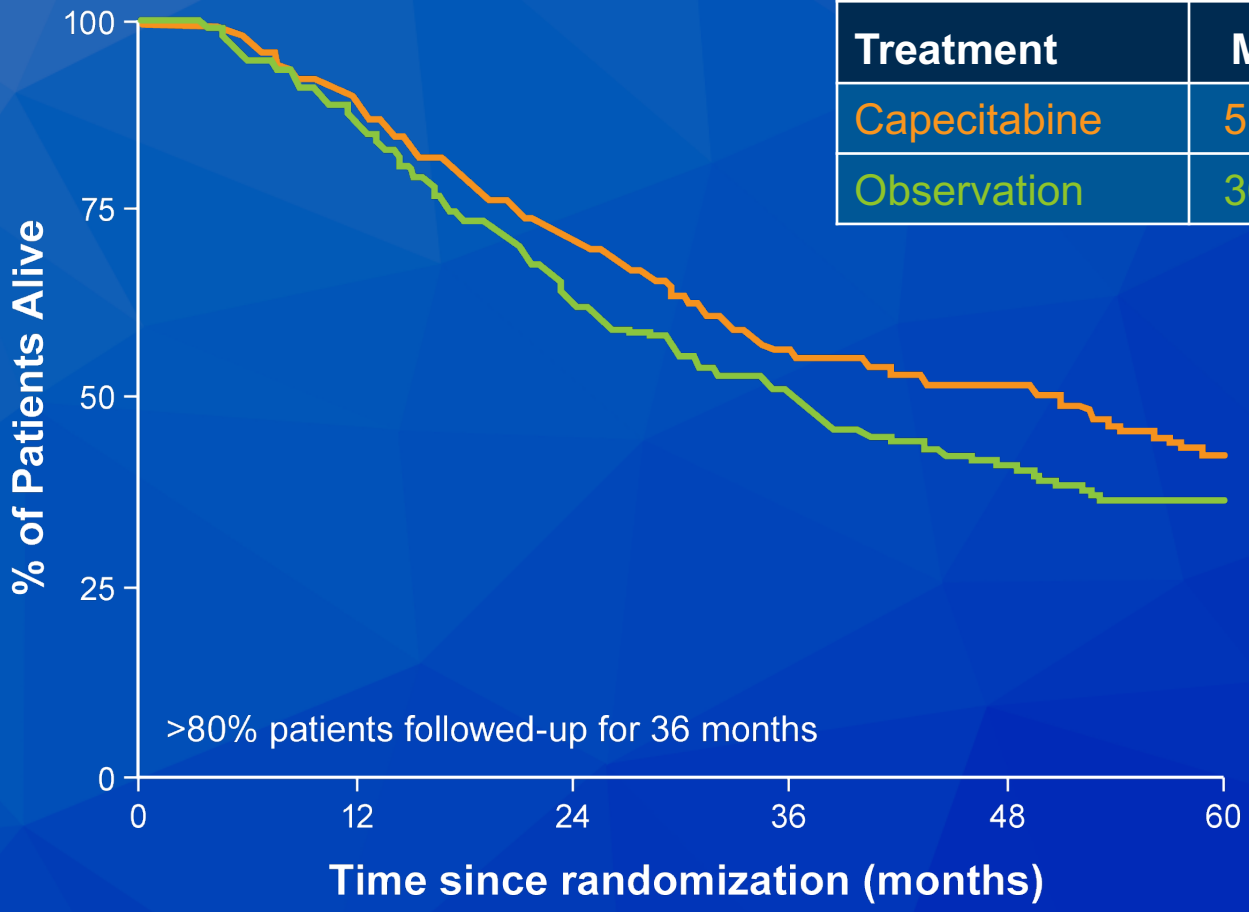
Ramanathan RK et al. *Clin Cancer Res* 2017;23(14):3638-48.

Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study

Primrose JN et al.
Proc ASCO 2017;Abstract 4006.

BILCAP: Primary Endpoint — OS

Treatment	Median OS	HR (*p*-value)
Capecitabine	51.1 months	0.81 (0.097)
Observation	36.4 months	



Sensitivity analyses

Adjusting for further prognostic factors (nodal status, disease grade, gender)

HR 0.70

$p = 0.007$

Primrose JN et al. *Proc ASCO* 2017;Abstract 4006.

BILCAP: Select AEs

Toxicity type	All grades		Grades 1 & 2		Grades 3 & 4	
	n	%	n	%	n	%
Fatigue	175	82	159	75	16	8
Plantar-palmar erythema	174	82	130	61	44	21
Diarrhea	137	64	121	57	16	8
Nausea	108	51	106	50	2	1
Mucositis/stomatitis	96	45	94	44	2	1
Vomiting	50	24	49	23	1	0.5
Neutropenia	49	23	45	21	4	2
Bilirubin	45	21	42	20	3	1
Thrombocytopenia	26	12	25	12	1	0.5
Alopecia	20	9	20	9	0	0

Primrose JN et al. *Proc ASCO* 2017;Abstract 4006.

Editorial — Dr Philip

BILCAP was a phase III trial of capecitabine given adjuvantly in patients with resected biliary tract cancers, a therapeutic area lacking phase III data. Eligibility included intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, muscle invasive gallbladder cancer, and lower common bile duct cancer. It also included R0 and R1 resected patients. Patients received 8 cycles of capecitabine 2,500 mg/m^2/day (2 weeks on/one week off) versus observation. Overall survival was the primary endpoint of the study. A total of 430 patients (ECOG PS ≤2) were enrolled.

Results showed that there was an improvement in the overall survival of patients treated with capecitabine (52.7 months versus 36.1 months, HR 0.75, p 0.028).

Editorial — Dr Philip (continued)

Of note, primary analysis was performed after a minimum 2-year follow-up. Treatment was well tolerated. Adjuvant radiotherapy was not part of the protocol.

Of note, ampullary cancers and mucosal gallbladder cancers (T1a) were excluded from the study. Approximately a third and half of patients had R1 resection or lymph node positive disease, respectively. Approximately 55% of patients received the eight cycles of capecitabine.

Capecitabine single agent is a standard for patients with resected biliary cancers and the preferred option over gemcitabine (with or without cisplatin). Additional studies are needed to define the role of adjuvant radiotherapy and the benefit of combination therapies in this setting.

Gastrointestinal Cancers — Drs Bendell and Grothey

Colorectal Cancer

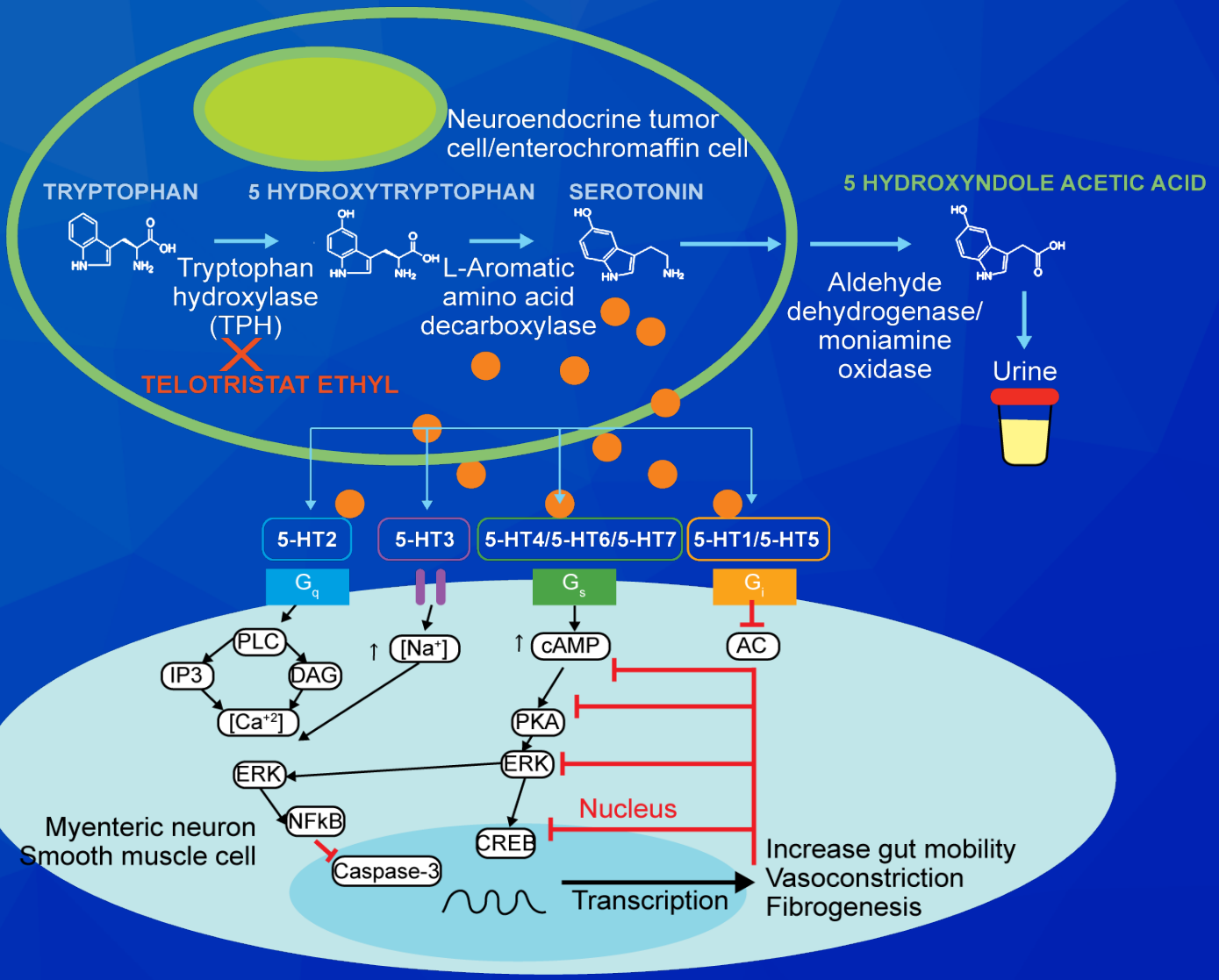
Gastric Cancer

Hepatocellular Carcinoma

Pancreatic Cancer

GI Neuroendocrine Tumors (GI NET)

Telotristat Ethyl (TE)
A Tryptophan Hydroxylase (TPH) Inhibitor



Molina-Cerrillo J et al. *The Oncologist* 2016;21:701-7.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

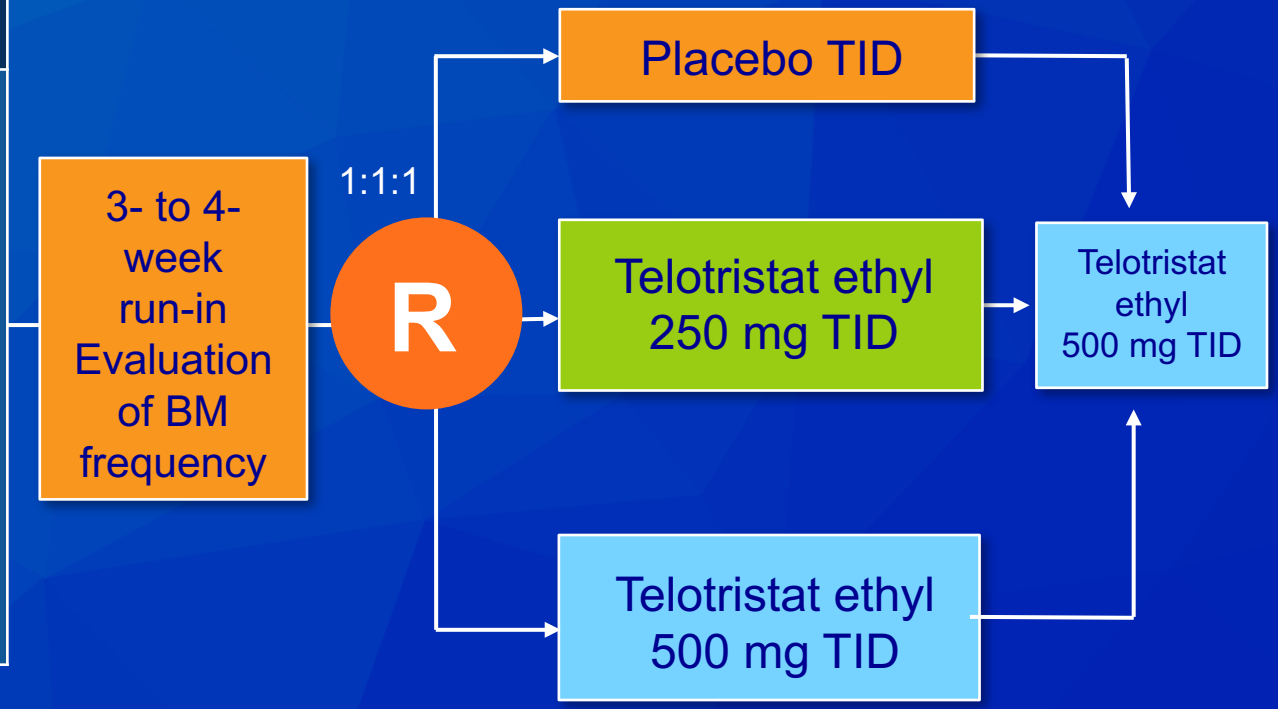
Matthew H. Kulke, Dieter Hörsch, Martyn E. Caplin, Lowell B. Anthony, Emily Bergsland, Kjell Öberg, Staffan Welin, Richard R.P. Warner, Catherine Lombard-Bohas, Pamela L. Kunz, Enrique Grande, Juan W. Valle, Douglas Fleming, Pablo Lapuerta, Phillip Banks, Shanna Jackson, Brian Zambrowicz, Arthur T. Sands, and Marianne Pavel

TELESTAR: Phase III Trial Schema

Trial Identifier: NCT01677910
Enrollment: 135

Eligibility

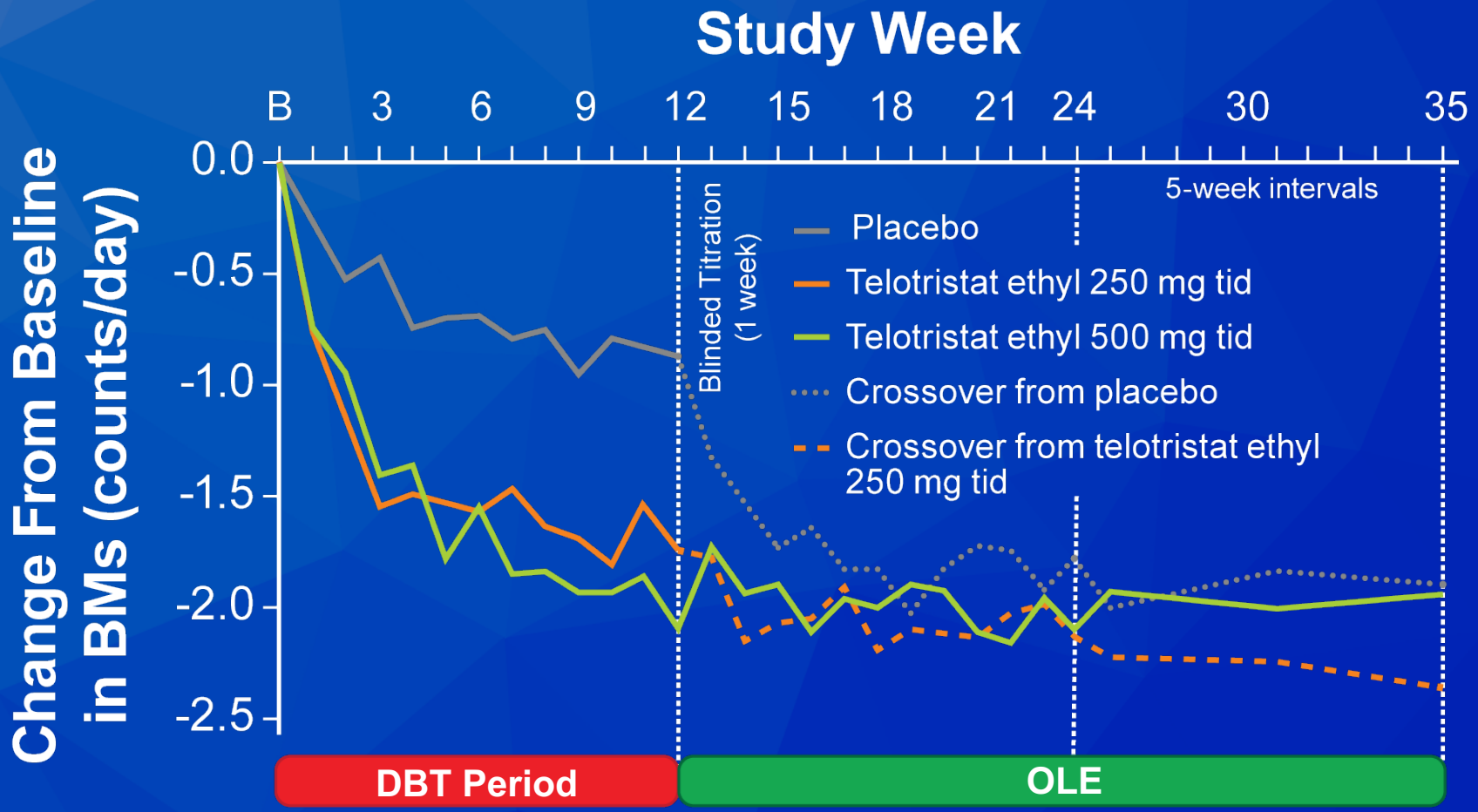
- Carcinoid syndrome
- Experiencing ≥4 bowel movements (BMs) per day despite stable-dose somatostatin analogue (SSA) therapy
- Continue SSA throughout study period



Primary endpoint: Change from baseline in BM frequency

Kulke MH et al. *J Clin Oncol* 2017;35(1):14-23.

TELESTAR: Change from Baseline in BMs Per Day

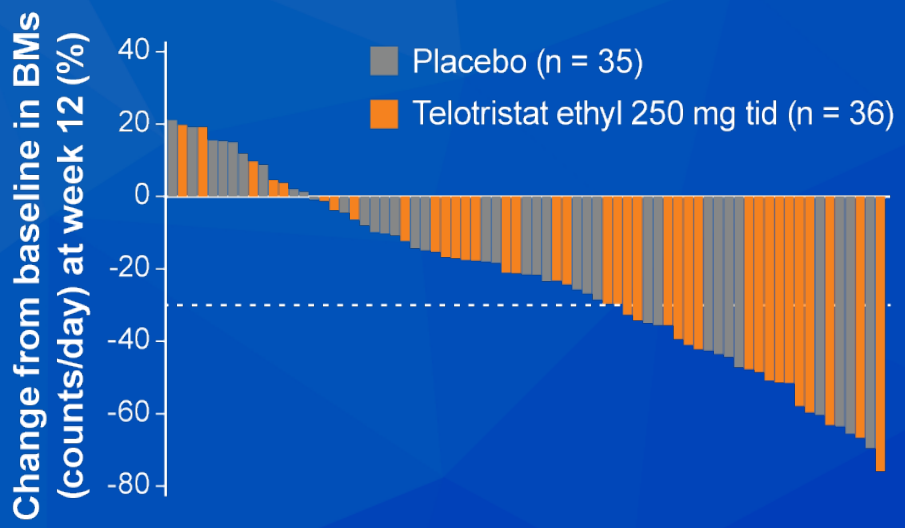


Double-Blind Treatment

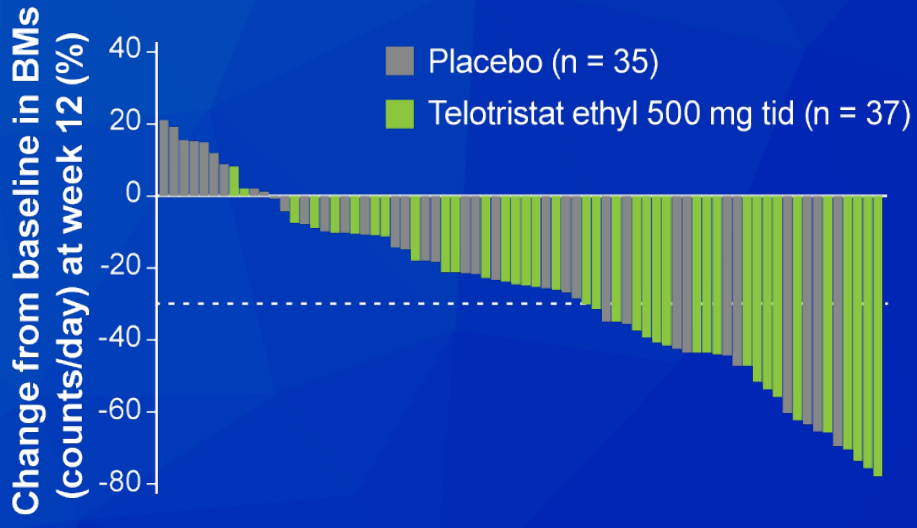
Open-Label Extension

Kulke MH et al. *J Clin Oncol* 2017;35(1):14-23.

TELESTAR: Change in Frequency of BMs from Baseline to Week 12



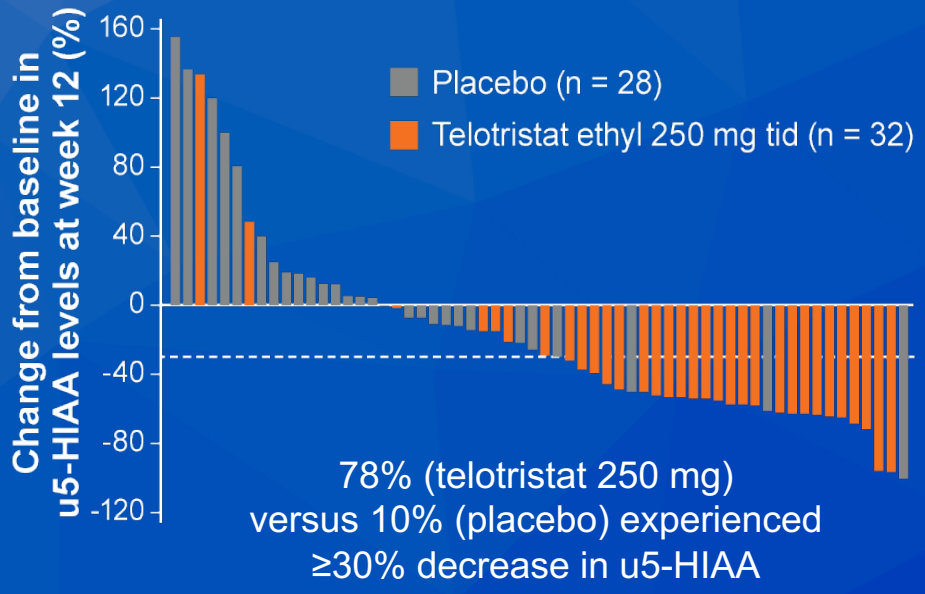
Mean reduction in daily BM frequency from baseline to week 12
250 mg three times per day: -1.7
Placebo: -0.9

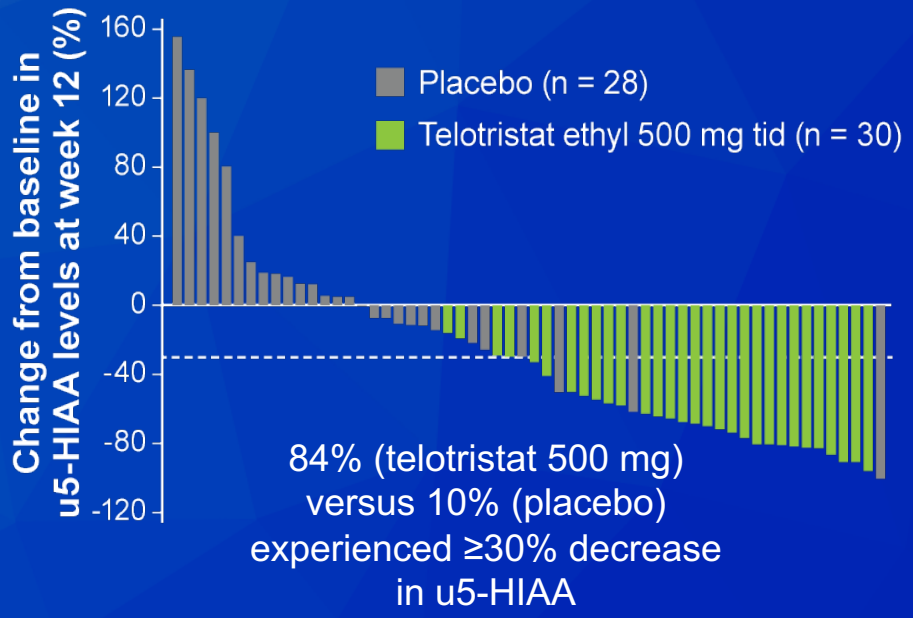


Mean reduction in daily BM frequency from baseline to week 12
500 mg three times per day: -2.1
Placebo: -0.9

Kulke MH et al. *J Clin Oncol* 2017;35(1):14-23.

TELESTAR: Percentage Change from Baseline in Urinary 5-Hydroxyindoleacetic Acid (u5-HIAA) Levels at Week 12





- Broader clinical significance of decreasing systemic serotonin levels, as determined by u5-HIAA levels, in patients with carcinoid syndrome has not been fully established
- However, serotonin stimulates fibroblast proliferation and has been linked to cardiac valvular fibrosis in patients with carcinoid syndrome
- Serotonin may also mediate mesenteric fibrosis often observed in patients with small intestine NETs

Kulke MH et al. *J Clin Oncol* 2017;35(1):14-23.

Editorial — Dr Philip

This was a phase III placebo-controlled study of oral telotristat ethyl in patients with the carcinoid syndrome. Telotristat ethyl is a tryptophan hydroxylase inhibitor, and the hypothesis was that it would reduce bowel movement (BM) frequency in patients with this syndrome because of inhibition of serotonin production by inhibiting the key enzyme in conversion of tryptophan to serotonin. 135 were enrolled. Eligibility included four or more BMs per day despite stable-dose somatostatin analogue therapy. They were randomized to receive placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg three times per day orally during a 12-week double-blind treatment period.

Editorial — Dr Philip (continued)

The primary endpoint was change from baseline in BM frequency. In an open-label extension, 115 patients subsequently received telotristat ethyl 500 mg.

Responses, predefined as a BM frequency decrease by ≥30% from baseline for ≥50% of the double-blind treatment period, were observed in 20%, 44%, and 42% of patients given placebo, telotristat ethyl 250 mg, and telotristat ethyl 500 mg, respectively. Both telotristat ethyl dosages significantly reduced mean urinary 5-hydroxyindoleacetic acid (5HIAA) versus placebo at week 12 ($P < .001$). Side effects of telotristat ethyl included mild nausea and asymptomatic increases in gamma-glutamyl transferase in some patients.

Editorial — Dr Philip (continued)

Of note, the FDA-approved dose of telotristat ethyl is 250 mg three times a day.

Telotristat ethyl, a well tolerated oral treatment, offers patients with carcinoid syndrome that is not adequately controlled by somatostatin analogues a treatment option. Patients with NET and diarrhea have to be evaluated for the cause of diarrhea because apart from the carcinoid syndromes resulting from serotonin excess, other causes such as short bowel syndrome or steatorrhea have to be excluded. Additional follow-up is needed to determine the potential long-term benefits of reduction in serotonin production on complications of NETs (eg, carcinoid heart disease, mesenteric fibrosis).

FDA approves lutetium Lu 177 dotatate for treatment of GEP-NETS

Press Release — January 26, 2018

"On January 26, 2018, the Food and Drug Administration approved lutetium Lu 177 dotatate, a radiolabeled somatostatin analog, for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Approval was based on data from NETTER-1 (NCT01578239), a randomized, multicenter, open-label, active-controlled trial in 229 patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm594105.htm

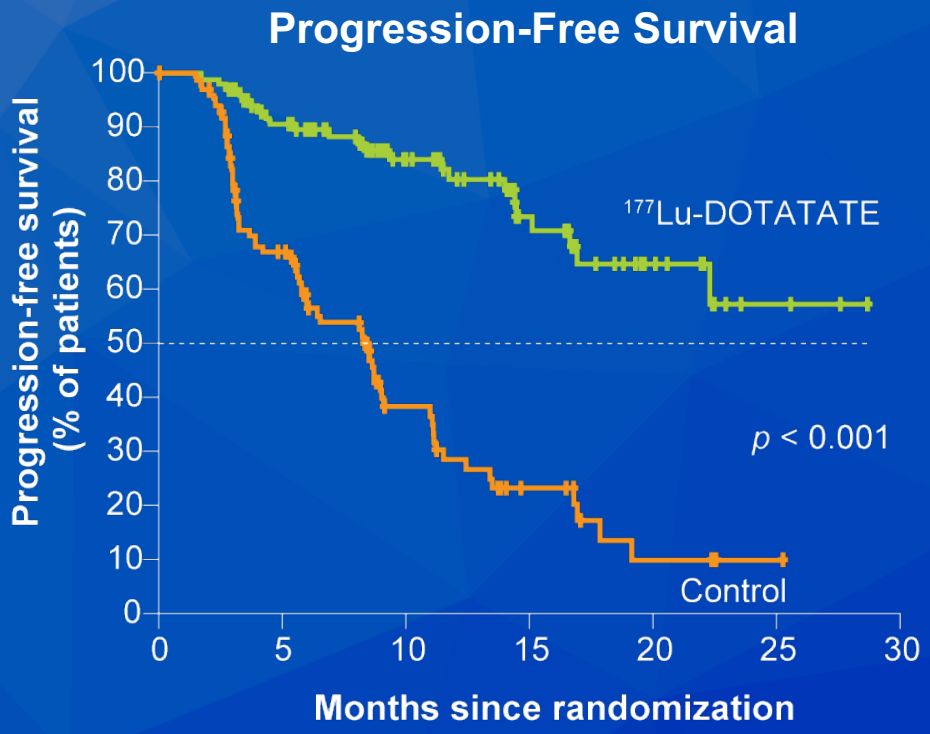
ORIGINAL ARTICLE

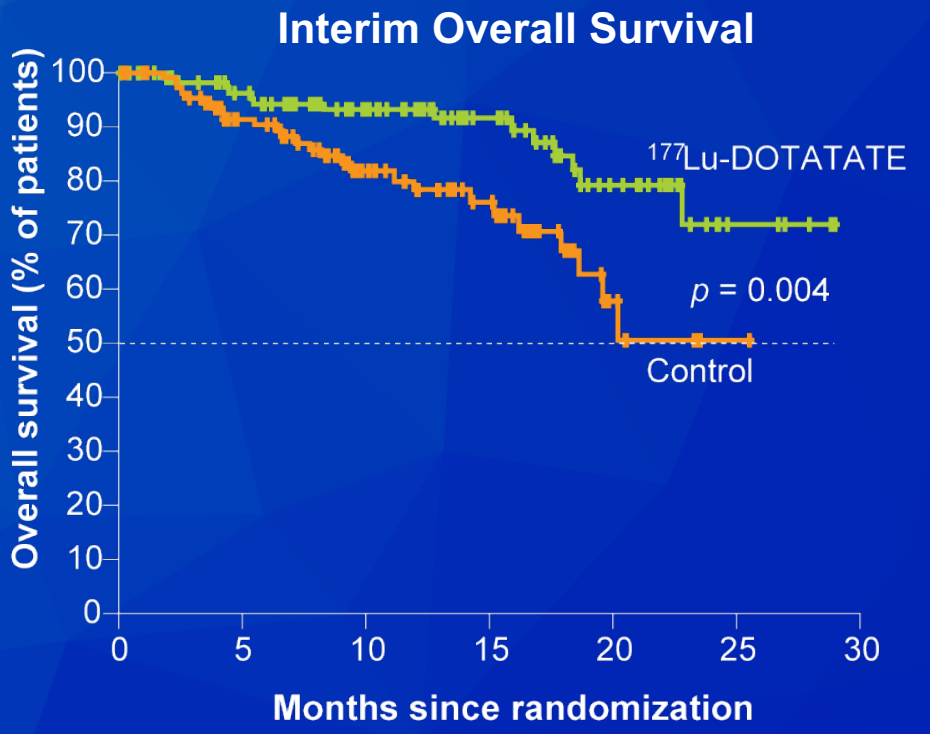
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

N Engl J Med 2017;376(2):125-35.

NETTER-1 Phase III Trial: Survival Analysis of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors





Endpoint	^{177}Lu-Dotatate (n = 116)	Control (n = 113)	Hazard ratio	*p*-value
Median PFS	Not reached	8.4 mo	0.21	<0.001
20-mo estimated PFS	65.2%	10.8%	—	—
Interim OS analysis	14 deaths	26 deaths	0.40	0.004

Strosberg J et al. *N Engl J Med* 2017;376(2):125-35.

NETTER-1: Select AEs

	^{177}Lu-Dotatate (n = 111)		Control (n = 110)	
	Any grade	**Grade 3/4**	**Any grade**	**Grade 3/4**
Nausea	59%	4%	12%	2%
Vomiting	47%	7%	10%	1%
Fatigue or asthenia	40%	2%	25%	2%
Thrombocytopenia	25%	2%	1%	0%
Anemia	14%	0%	5%	0%
Lymphopenia	18%	9%	2%	0%
Leukopenia	10%	1%	1%	0%
Neutropenia	5%	1%	1%	0%

Strosberg J et al. *N Engl J Med* 2017;376(2):125-35.

Editorial — Dr Philip

NETTER-1 was a phase III trial of lutetium-177 (^{177}Lu)-Dotatate in patients with advanced, progressive, somatostatin-receptor–positive, well-differentiated midgut neuroendocrine tumors. 229 patients received either ^{177}Lu-Dotatate at a dose of 7.4 GBq every 8 weeks (four intravenous infusions) plus octreotide long-acting (at a dose of 30 mg) or octreotide LAR 60 mg alone.

The estimated progression-free survival (primary endpoint) at month 20 was 65.2% in the ^{177}Lu-Dotatate group and 10.8% in the control group. The median progression-free survival had not yet been reached in the ^{177}Lu-Dotatate group and was 8.4 months in the control group (hazard ratio for disease progression or death with ^{177}Lu-Dotatate vs control, 0.21; 95% CI, 0.13 to 0.33; $P<0.001$).

Editorial — Dr Philip (continued)

The objective response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group ($P<0.001$). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the ^{177}Lu-Dotatate group. There was a trend in survival improvement.

^{177}Lu-Dotatate represents an exciting new drug development in patients with well-differentiated NET and a viable treatment option for patients progressing on somatostatin analogs. Moreover, for the first time we see therapy that can reduce tumor bulk in well-differentiated midgut NETs.

Editorial — Dr Philip (continued)

Of note, a major eligibility criterion was the proof of somatostatin receptor expression by nuclear imaging that can be achieved by either an octreotide scan or the recently introduced 68-Gallium PET. Longer follow-up is necessary to determine the impact on survival and also the safety with respect to certain toxicities such as bone marrow effects. NETTER-1 also confirmed the lack of benefit of higher doses of octreotide LAR with regard to controlling disease progression.