Year in Review

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

October 28, 2017, 8:00 AM – 4:00 PM
Orlando, Florida

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Contracted Research	Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Eisai Inc, Genentech BioOncology

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 Grothey and Berlin

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

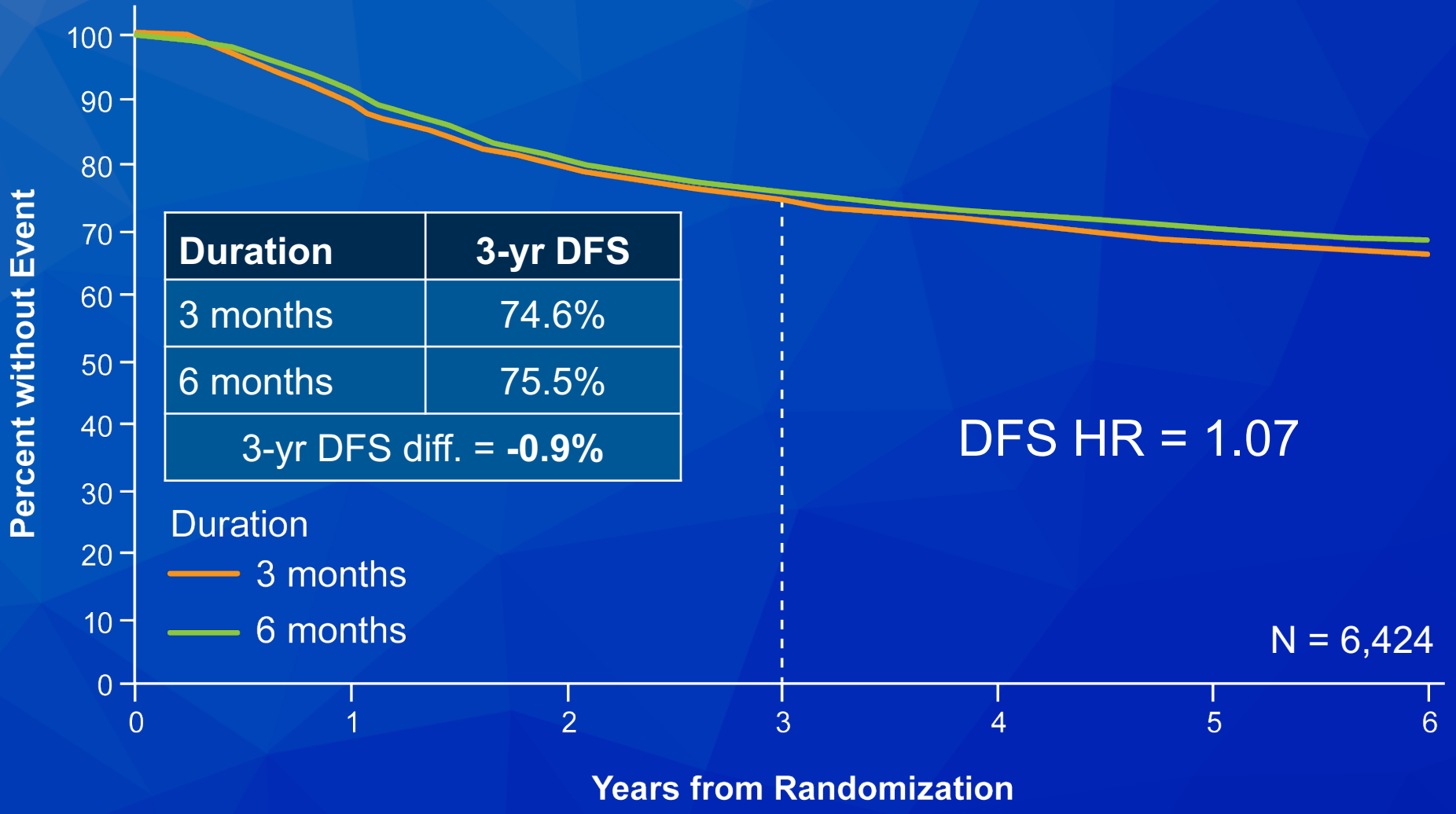
- Academic collaboration of clinicians and statisticians from six randomized Phase III trials

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 Grothey

Since 2004, the standard adjuvant therapy in stage III colon cancer had consisted of 6 months of a fluoropyrimidine/oxaliplatin combination, in form of either FOLFOX or CAPOX (capecitabine/oxaliplatin). The IDEA collaboration (International Duration Evaluation in Adjuvant therapy) is a prospective pooled analysis of 6 randomized trials concurrently conducted in 12 countries which investigated the non-inferiority of 3 months of adjuvant oxaliplatin-based therapy compared with standard 6 months duration to lower the risk of cumulative neurotoxicity of oxaliplatin. The upper limit of the non-inferiority margin as hazard ratio for disease-free survival (DFS) was agreed upon at 1.12, meaning that with a 95% probability a 12% detriment in DFS could be included if the study parameters were reached.

Editorial — Dr Grothey (continued)

A total of 12,834 patients were included in the analysis, of which 60% received FOLFOX, 40% CAPOX. No randomization was performed between the treatment regimens.

As expected, neurotoxicity, but also other side effects, was significantly reduced in the 3 months arm. In terms of efficacy, the study failed to prove non-inferiority of 3 vs 6 months of duration of therapy for the overall study cohort (upper limit of the 95% CI for DFS, HR: 1.15), even if the estimated difference in 3-year DFS rate was only 0.9%. However, in further analysis, 3 months of CAPOX were indeed non-inferior to 6 months treatment, whereas for FOLFOX 6 months were superior to 3 months.

Editorial — Dr Grothey (continued)

The different performance of the two regimens was a surprising finding of IDEA, but it was consistent across all presented substudies at ASCO 2017 (Italian TOSCA, UK SCOT, and French IDEA trials). In fact, the different outcomes in the individual studies could be completely explained by the variations in percentage of patients treated with either CAPOX (high in SCOT and TOSCA) or FOLFOX (90% of patients in IDEA France). In addition, IDEA showed a trend that high-risk cancers (T4 and/or N2) appeared to benefit from longer duration of therapy compared with low-risk cancers (T1-3 N1), in particular, when FOLFOX was used. In clinical practice, the duration of adjuvant therapy will depend on the treatment regimen used, the risk of recurrence, and patient preference.

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 Grothey

Over the last 3 years, the location of the primary tumor location has emerged as an important prognostic and predictive factor in mCRC. Right-sided cancers (cecum to splenic flexure) have poorer prognosis and a reduced (or absent) sensitivity to EGFR antibodies even when they are characterized as RAS/BRAF wild-type. The likely definitive analysis of sidedness as prognostic and predictive factor in the context of a prospectively conducted clinical trial was presented by Dr Venook at ASCO 2017. The US Intergroup study 80405 compared cetuximab and bevacizumab added to front-line chemotherapy (FOLFOX or FOLFIRI).

Editorial — Dr Grothey (continued)

Data on sidedness were available from more than 1,000 patients in this trial. For both treatment arms combined, right-sided cancers had much shorter OS compared with left-sided cancers (19.4 vs 33.3 months), confirming the prognostic implication of primary tumor location. More importantly, though, sidedness also carried predictive implications, with cetuximab outperforming bevacizumab in left-sided, RAS wild-type cancers and bevacizumab appearing to improve outcome over cetuximab in right-sided cancers. When additional factors (age, race, gender, synchronous vs metachronous, consensus molecular subtype, prior adjuvant therapy, MSI, BRAF, NRAS, KRAS, HRAS) were included in a multivariate analysis, right-sided cancers were still associated with poorer outcome compared with left-sided CRC.

Editorial — Dr Grothey (continued)

This indicates that at this point in time sidedness represents an independent prognostic factor which should be included as a stratification factor in clinical trials and should be taken into consideration for treatment planning.

Cost and reimbursement issues aside, for a patient with MSI-high metastatic CRC, in what line of therapy would you like to use an anti-PD-1/PD-L1 antibody?

a. First line
b. Second line
c. Third line
d. Beyond third line

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.

Cost and reimbursement issues aside, for a patient with BRAF-mutant metastatic CRC, would you likely administer anti-BRAF therapy outside of a clinical trial setting?

a. Yes (please specify regimen)
b. No

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

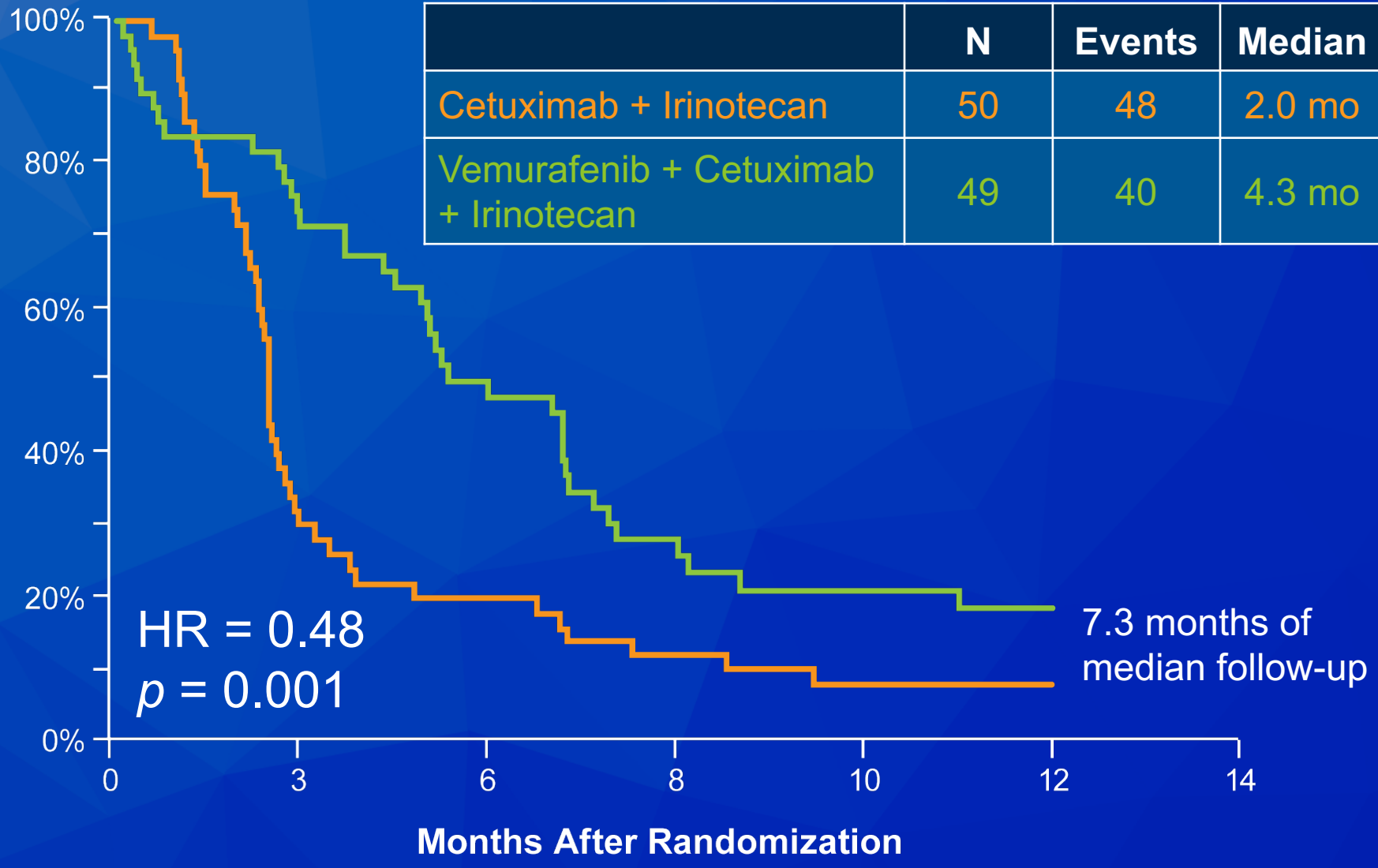
BEACON CRC: Safety lead-in (SLI) for the combination of binimetinib (BINI), encorafenib (ENCO), and cetuximab (CTX) in patients (Pts) with BRAF-V600E metastatic colorectal cancer (mCRC)

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



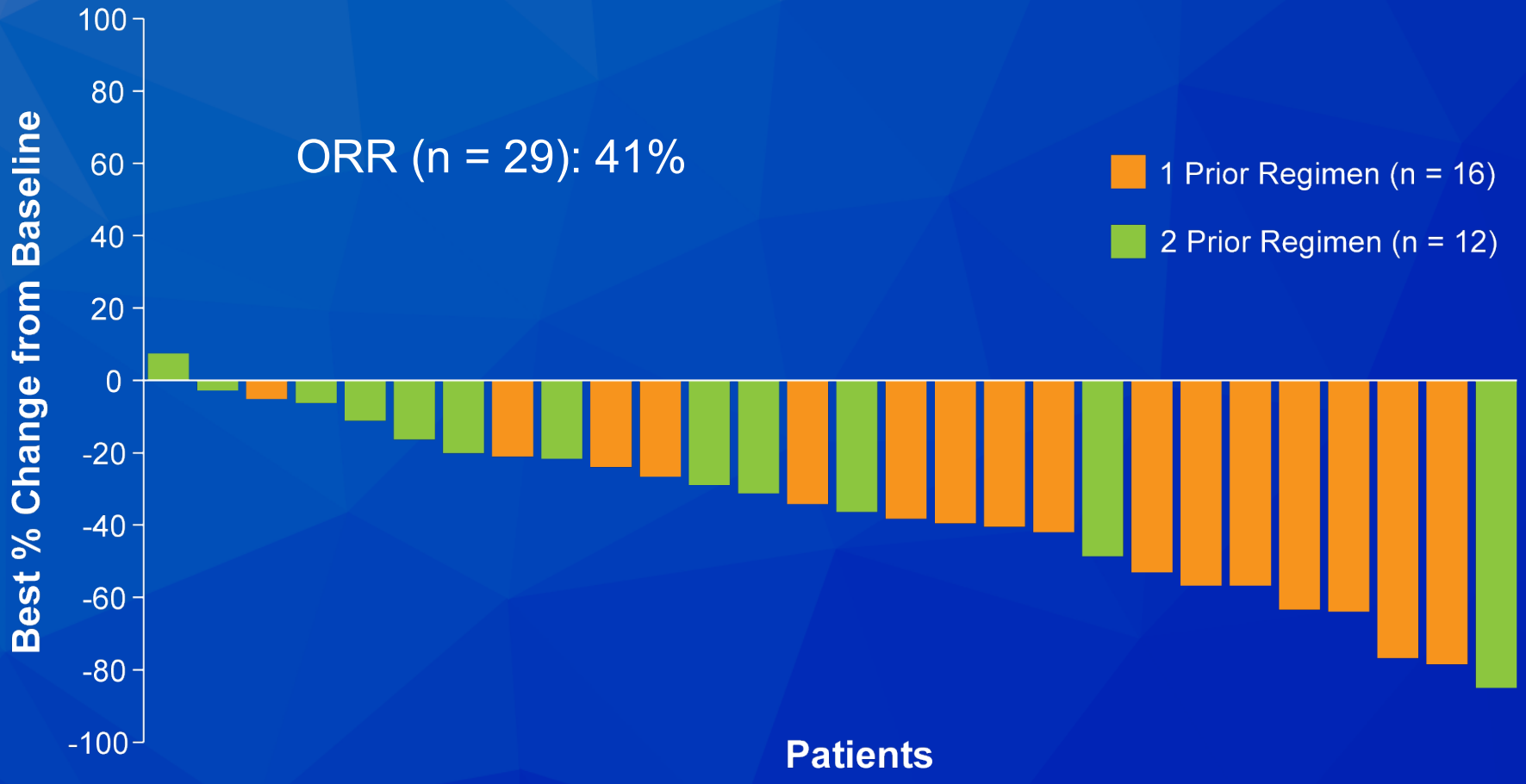
Kopetz S et al. *Proc ASCO* 2017;Abstract 3505.

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 Grothey

BRAF V600E mutated metastatic colorectal cancer (mCRC) is known to be associated with very poor prognosis compared with BRAF wild-type cancers. A recent pooled analysis of patients from Mayo Clinic and MD Anderson demonstrated median OS for BRAF V600E mutated mCRC of 11.5 months compared to around 40 months for patients with BRAF wild-type cancers. In addition to being a marker of poor prognosis, there is emerging evidence that a BRAF V600E mutation also leads to resistance to EGFR antibodies, even though this hypothesis has not yet been universally accepted. Thus, there is a strong need to optimize treatment approaches in patients with BRAF V600E mutated cancers.

Editorial — Dr Grothey (continued)

BRAF inhibitors have shown remarkable activity in BRAF V600E mutated melanoma, especially, in combination with MEK inhibitors. In mCRC, however, cancers harboring the exact same mutation are largely resistant to BRAF or MEK inhibitors. Preclinical studies have postulated that the reason for the lack of activity of this approach in mCRC is a feedback-loop activation of EGFR when BRAF is inhibited. Thus, combining a BRAF inhibitor with an EGFR inhibitor had a good preclinical and biological rationale.

This very idea was tested prospectively in a phase 2 trial in second-/third-line therapy of BRAF V600E mutated colorectal cancers in the US Intergroup study S1406, which randomized patients to cetuximab plus irinotecan with or without the BRAF inhibitor vemurafenib.

Editorial — Dr Grothey (continued)

The primary endpoint of the study, PFS, was easily reached with a HR of 0.48 in favor of the vemurafenib combination (median PFS 4.3 vs 2.0 months, *P* = 0.001). At the same time, a higher response rate was seen with the addition of the BRAF inhibitor (16% vs 4%). Conceivably due to the high percentage of patients crossing over to the experimental arm (48%), no statistically significant difference in OS was seen (HR 0.73, median OS 9.6 vs 5.9 months, *p* = 0.19).

Editorial — Dr Grothey (continued)

While S1406 still included conventional chemotherapy (irinotecan) as part of the treatment approach, the ongoing phase 3 BEACON study is currently testing the efficacy of combinations of targeted agents (BRAF inhibitor encorafenib plus cetuximab with or without MEK inhibitor binimetinib) against the standard irinotecan/cetuximab combination in second-/third-line therapy of BRAF V600E mutated mCRC. The data of the safety lead-in phase of the biologic triple combination was recently presented at ESMO 2017 and showed very encouraging results. None of the 29 patients treated with the triplet showed progression of disease at first response evaluation, and at the time of the data cut-off, median PFS exceeded 6 months (median not reached).

Editorial — Dr Grothey (continued)

These two studies demonstrate that the medical management of BRAF V600E mutated mCRC will likely move toward targeted approaches that will exploit the unique molecular biology associated with this aggressive form of cancer.

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.

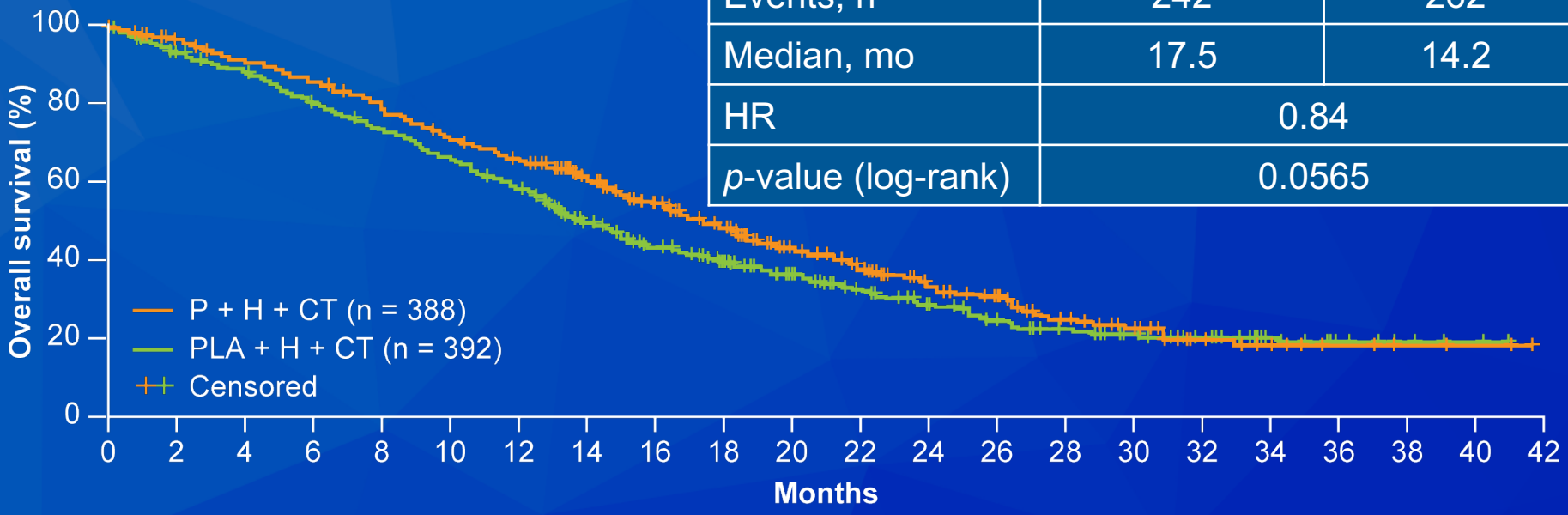
Case Report: Prolonged Response to HER2-Directed Therapy in a Patient with HER2-Amplified, Rapidly Progressive mCRC

- 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 Grothey

The role of HER2 as target for therapeutic interventions in gastrointestinal malignancies is highlighted by the pivotal data of the ToGA trial, which established the addition of trastuzumab to platinum/fluoropyrimidine first-line therapy in HER2-overexpressing gastro-esophageal (GE) cancer. About 20%-25% of patients with GE cancers show overexpression of HER2, but importantly, in contrast to breast cancer, HER2 overexpression in GE cancers is not associated with poor prognosis.

The recently presented JACOB trial tried to improve upon the efficacy of trastuzumab in HER2-positive GE cancers by adding pertuzumab, an antibody inhibiting dimerization of HER receptors, to first-line therapy in a placebo controlled trial.

Editorial — Dr Grothey (continued)

A total of 780 patients were included in the study, but even though the median OS (primary endpoint) was numerically improved (17.5 vs 14.2 months), the addition of pertuzumab to trastuzumab plus chemotherapy did not result in a statistically significant difference (HR 0.84, $p = 0.0565$). These findings are reminiscent of the GATSBY trial presented previously, which failed to demonstrate improved outcomes of HER2-positive GE cancers treated with T-DM1 compared with taxanes as second-line therapy.

These data indicate that regimens that have proved efficacy in HER2-positive breast cancer might not have the same activity in HER2-positive GE cancers.

Editorial — Dr Grothey (continued)

In mCRC, HER2 overexpression can be found in about 2.5% of all cancers but up to 10% in RAS/RAF/PIK3CA wild-type cancers, with a higher incidence in left-sided tumors. Two studies have shown that a combination of biologics targeting HER2 (trastuzumab plus lapatinib in the HERACLES study, trastuzumab plus pertuzumab in the MyPathway study) is effective in HER2-positive mCRC as last-line therapy, with response rates between 30% and 40%.

A recent case report in JNCCN highlights the potential activity of HER2 targeted agents in mCRC. A 48 yo man with HER2 positive, RAS/RAF wild-type mCRC experienced a long-lasting response on T-DM1 (10 months) with loss of HER2 expression upon progression on HER2 targeted therapy.

Editorial — Dr Grothey (continued)

Several clinical trials are ongoing to evaluate HER2-targeted agents in HER2-positive mCRC. HER2 testing is conceivably emerging as the next biomarker joining the portfolio of standard biomarkers tested for treatment decisions in mCRC.

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 Grothey

From the perspective of cancer biology, one of the most attractive treatment options would be the use of a stem cell inhibitor to target cells that are known to be largely resistant to conventional chemotherapy. Napabucasin (BBI-608) is an inhibitor of cancer cell stemness by inhibiting the STAT3 pathway. This agent is currently being investigated in various GI malignancies, including gastric, colorectal, and pancreas cancers.

At ESMO GI 2017, Dr Bendell presented data of a phase Ib/II study in which napabucasin was added to FOLFIRI with or without bevacizumab in patients with mCRC.

Editorial — Dr Grothey (continued)

The main side effects of this treatment combination were diarrhea and fatigue. Interestingly, the napabucasin combination yielded high disease control rates of over 80% (about 20% objective response), independent of whether or not the patients had been pretreated with FOLFIRI. The FOLFIRI (+/- BEV) plus napabucasin combination is currently being investigated in the CanStem303C phase 3 trial in second-line mCRC.

At the same time, napabucasin is being evaluated in a phase Ib/II study in pancreas cancer in combination with gemcitabine plus *nab*-paclitaxel.

Gastrointestinal Cancers — Drs Grothey and Berlin

Colorectal Cancer

Gastric Cancer

Hepatocellular Carcinoma

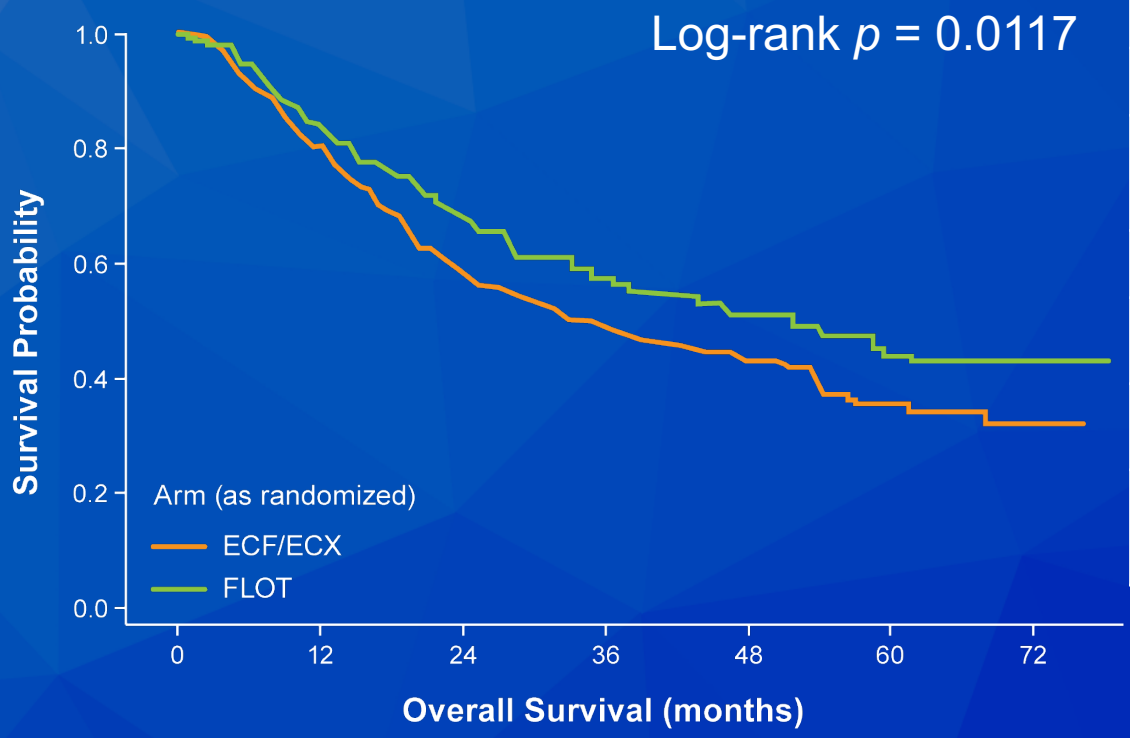
Pancreatic Cancer

GI Neuroendocrine Tumors (GI NET)

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 Berlin

FLOT4 is a randomized trial of perioperative chemotherapy for patients with gastric cancer or gastroesophageal cancer, Siewert type I-III, who were deemed medically potentially operable. A total of 716 patients were randomized to either FLOT (fluorouracil 2,600 mg/m^2 over 24 hours, folinic acid 200 mg/m^2, oxaliplatin 85 mg/m^2 and docetaxel 50 mg/m^2 given q2wk x 4 cycles preoperatively and 4 more cycles postoperatively) or standard EcX or ECF given x 3 cycles before and 3 cycles after surgery. Resection was D2 or 2 field and pathology and operative reports were centrally reviewed. Primary endpoint was overall survival with a co-primary endpoint of non-inferiority if superiority was not met.

Editorial — Dr Berlin (continued)

Arms were well-balanced for stage, baseline demographics and type of surgery performed. Progression-free survival was significantly improved with FLOT, HR 0.75, p-value 0.004. Overall survival was improved at 3 years, 57% vs 48% and HR 0.77, p-value 0.012. More patients in the FLOT arm were able to complete therapy.

Summary: This was a very well-conducted clinical trial that suggests FLOT is a new standard for gastric and gastroesophageal cancers based on improvements in OS and PFS. While some of this benefit may be due to improved tolerability and ability to deliver FLOT, these effects further support the benefit of FLOT as adjuvant therapy.

Editorial — Dr Berlin (continued)

Epirubicin has a diminishing to non-existent role in gastroesophageal cancers. This trial is strengthened by central review of pathology and operative reports.

RAINFALL: Phase III Trial of First-Line Capecitabine/ Cisplatin +/- Ramucirumab in Metastatic Gastric/GEJ Adenocarcinoma

Eligibility

- Metastatic gastric or GEJ adenocarcinoma
- No prior systemic chemoRx except for (neo)adjuvant
- ECOG PS: 0-1
- Measurable or nonmeasurable but evaluable disease

R

1:1 N ~616 (645 randomized)

A
- **Placebo** 8 mg/kg IV day 1 & day 8, q21d until PD
- **Cisplatin** 80 mg/m² IV day 1, q21d, 6 cycles
- **Capecitabine** 1,000 mg/m² BID, PO, d1-14 q21d, until PD

B
- **RAM** 8 mg/kg IV day 1 & day 8, q21d until PD
- **Cisplatin** 80 mg/m² IV day 1, q21d, 6 cycles
- **Capecitabine** 1,000 mg/m² BID, PO, d1-14 q21d, until PD

Primary endpoint: PFS (5.6 vs 8 mo, HR = 0.70, 95% power)
Secondary OS endpoint: 10 vs13 mo, HR = 0.77, 80% power)

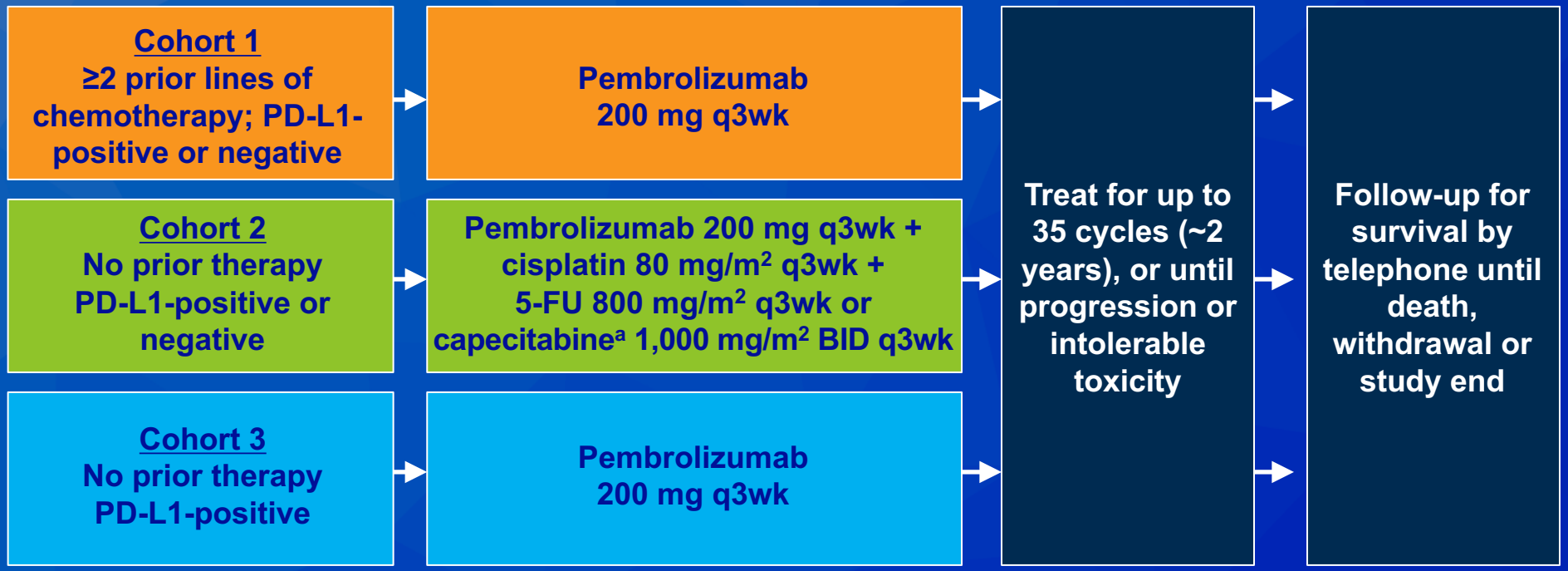
IDMC: RAINFALL met its primary endpoint of PFS in this analysis.
Allow the OS data to mature before unblinding and considering a regulatory submission. Final OS data expected in 2018.

Courtesy of Charles S Fuchs, MD, MPH.

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 Grothey

Checkpoint inhibitors are rapidly making inroads into the standard of care in the management of GI malignancies. In gastric cancer, both pembrolizumab and nivolumab are undergoing rigorous evaluation in various clinical settings.

KEYNOTE-059 consisted of three cohorts, one of which investigated the efficacy of pembrolizumab in patients with pretreated advanced gastric cancer. A total of 259 patients received single-agent pembrolizumab independent of PD-L1 expression status. In the overall patient population, a response rate of about 12% was observed, with higher response rates (up to 16%) in PD-L1-positive cancers and in 3rd (compared with 4th) line of therapy.

Editorial — Dr Grothey (continued)

The durability of responses was remarkable with a median duration of 14.2 months. In the small cohort of MSI-H gastric cancers, 4 of 7 patients demonstrated an objective response. Based on these data, the FDA granted accelerated approval for pembrolizumab in PD-L1-positive, pretreated gastric cancers on September 22, 2017.

A second cohort of KEYNOTE-059 added pembrolizumab to standard cisplatin/5-FU therapy in 25 patients in the first-line setting. A response rate of 60% was achieved, which compared favorably with historic controls for chemotherapy alone. In this small cohort, a median PFS of 6.6 months and a median OS of 13.8 months do not allow far reaching conclusions about potential efficacy of the combination.

Editorial — Dr Grothey (continued)

The third cohort of KEYNOTE-059 evaluated pembrolizumab as single agent in first-line PD-L1-positive cancers. In 31 patients a response rate of 26% was achieved, with some of the responses lasting for more than 12 months.

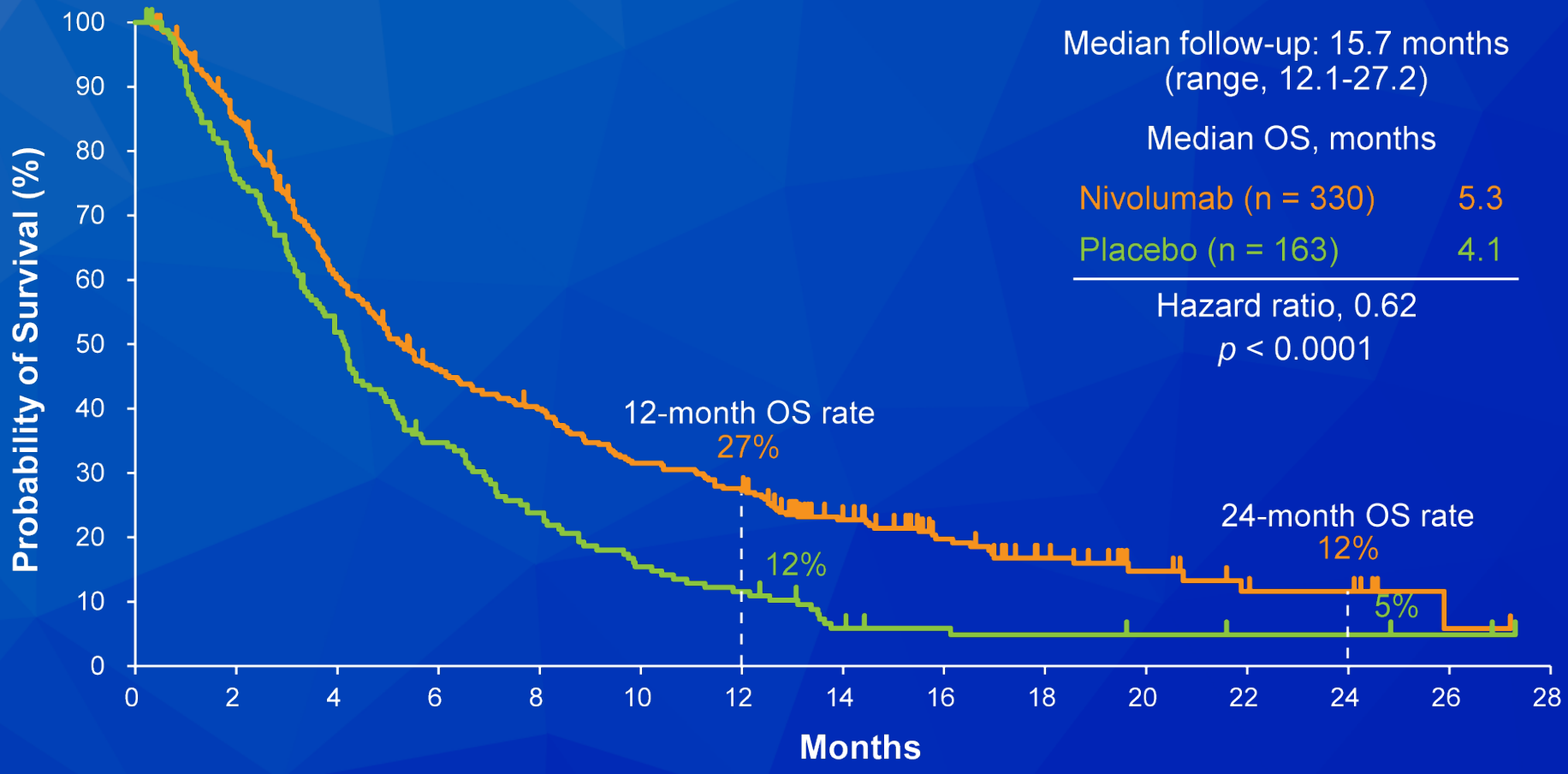
In conclusion, pembrolizumab has already become an FDA-approved standard of care in patients with pretreated, PD-L1 positive gastric cancers. It is conceivable that this agent will see an expansion of its labelled use in earlier lines of therapy, in particular in combination with standard chemotherapy regimens.

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.

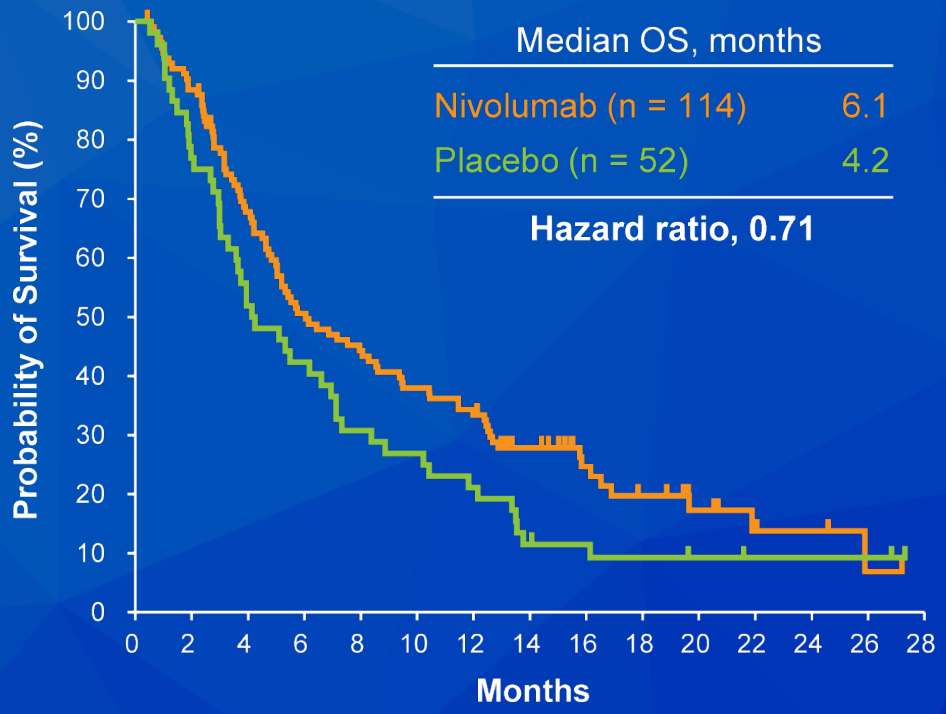
ATTRACTION-02: Updated Overall Survival (OS)



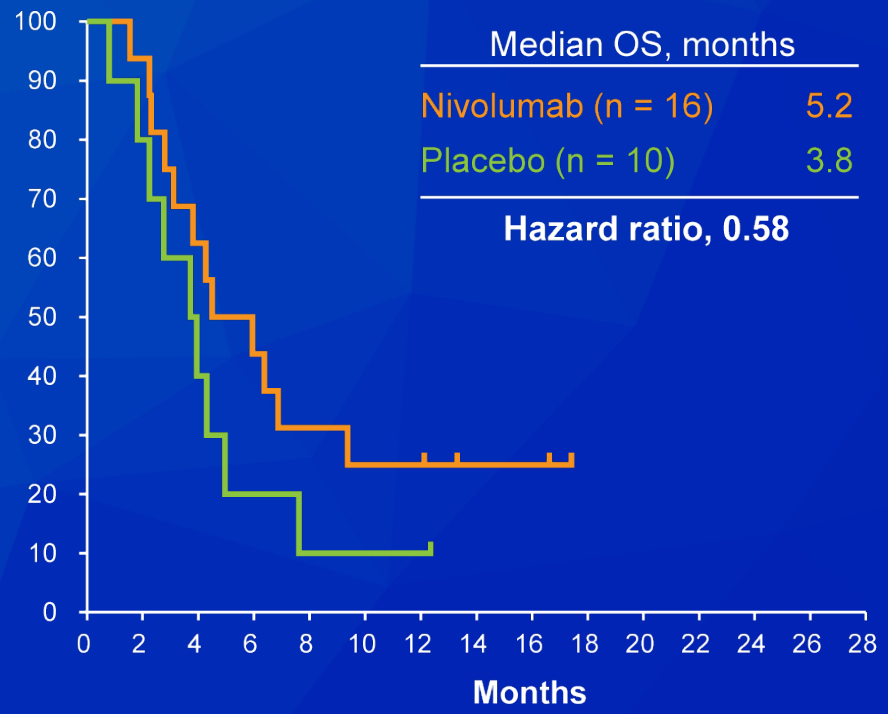
Boku N et al. *Proc ESMO* 2017;Abstract 617O.

ATTRACTION-02: OS by PD-L1 Expression

PD-L1 <1%



PD-L1 ≥1%



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

Editorial — Dr Grothey

The development of PD-1 antibodies in oncology and their approval in various malignancies initially depended on nonrandomized, single-arm studies, which showed response rates and survival outcomes that compared favorably with historic controls. Especially in gastrointestinal malignancies, randomized trials comparing PD-1 antibodies with standard of care or placebo/best supportive care have been lacking. ATTRACTION-2 is the first randomized trial of the PD-1 antibody nivolumab compared with placebo in later-line advanced gastroesophageal cancer that has reported final results. Nivolumab improved overall survival significantly and will emerge as a new standard of care in this setting.

Editorial — Dr Grothey (continued)

Several points of this trial are noteworthy. No biomarker selection was performed to identify patients for the study. It has been shown in other studies that patients who have cancers with a higher expression level of PD-L1 might benefit more from PD-1 antibodies than low- or non-expressors. In 40% of patients on the trial, data on PD-L1 expression were available and the survival benefit noted with nivolumab was independent of PD-L1 expression levels.

Secondly, while the difference in median overall survival was only moderate (5.3 vs 4.1 months, HR 0.61, $P < 0.001$), the percentage of patients alive at 1 year more than doubled with nivolumab (26% vs 11%), which points to the known long-term benefit that responders to PD-1 antibodies might enjoy.

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 Grothey

Nivolumab is a PD-1 antibody with proven efficacy in various malignancies. In melanoma and in other cancers, the addition of the CTLA-4 antibody ipilimumab has been shown to enhance the efficacy of nivolumab, but at a cost of more severe adverse events.

In the CheckMate 032 study, patients with pretreated advanced gastro-esophageal (GE) cancers received either nivolumab (59 patients) or nivolumab plus ipilimumab (101 patients — two different dosing schedules: N1+I3 and N3+I1) in a nonrandomized study. Both regimens, single agent nivolumab or the combination, demonstrated objective responses (Nivo alone: 12%, N1+I3: 24%, N3+I1: 8%).

Editorial — Dr Grothey (continued)

Median OS was similar for nivolumab single agent and N1+I3 (6.22 and 6.9 months, respectively), whereas the N3+I1 combination had numerically shorter OS (4.8 months). The N1+I3 combination arm had a higher rate of immune-related adverse events compared to single agent nivolumab or the N3+I1 combination, in particular with regard to diarrhea.

These data confirm the activity of nivolumab as a single agent in GE cancers. It is unclear if the addition of ipilimumab will further enhance the efficacy of checkpoint inhibitor therapy in advanced GE cancers.

Gastrointestinal Cancers — Drs Grothey and Berlin

Colorectal Cancer

Gastric Cancer

Hepatocellular Carcinoma

Pancreatic Cancer

GI Neuroendocrine Tumors (GI NET)

Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC)

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

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.

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 Berlin

This is a randomized non-inferiority trial for patients with untreated hepatocellular carcinoma and Child-Pugh A cirrhosis comparing lenvatinib to sorafenib. The primary endpoint is overall survival (OS).

Results: In 954 patients randomized 1:1, the arms appeared well-balanced. Non-inferiority of OS was achieved with a hazard ratio of 0.92 (0.79-1.06) with the 95% confidence interval staying below 1.08. Lenvatinib was superior to sorafenib for secondary endpoints, including progression-free survival (PFS) (HR 0.66, $p < 0.00001$), time to tumor progression (TTP) (HR 0.63, $p < 0.00001$), and response rate (24.1% vs 9.2%, $p < 0.00001$).

Editorial — Dr Berlin (continued)

Some quality of life measures also favored lenvatinib, although both drugs had substantial numbers of adverse events. An analysis correcting for differences in alpha fetoprotein levels suggested a borderline benefit in survival for lenvatinib (HR 0.856, $p = 0.0342$).

Summary: Sorafenib is a minimally effective agent available for healthy patients with HCC. Lenvatinib is not inferior to sorafenib in OS but has intriguing apparent near-doubling of PFS and TTP times with possible quality of life improvements. However, the benefits with lenvatinib occurred in secondary endpoints and an unplanned secondary analysis and not for the primary endpoint of survival.

Editorial — Dr Berlin (continued)

It is unclear if this data will support or warrant the approval of lenvatinib as a new treatment for HCC. Concern exists that this is also minimally effective and will also be expensive. Analyses for value of this agent would be helpful.

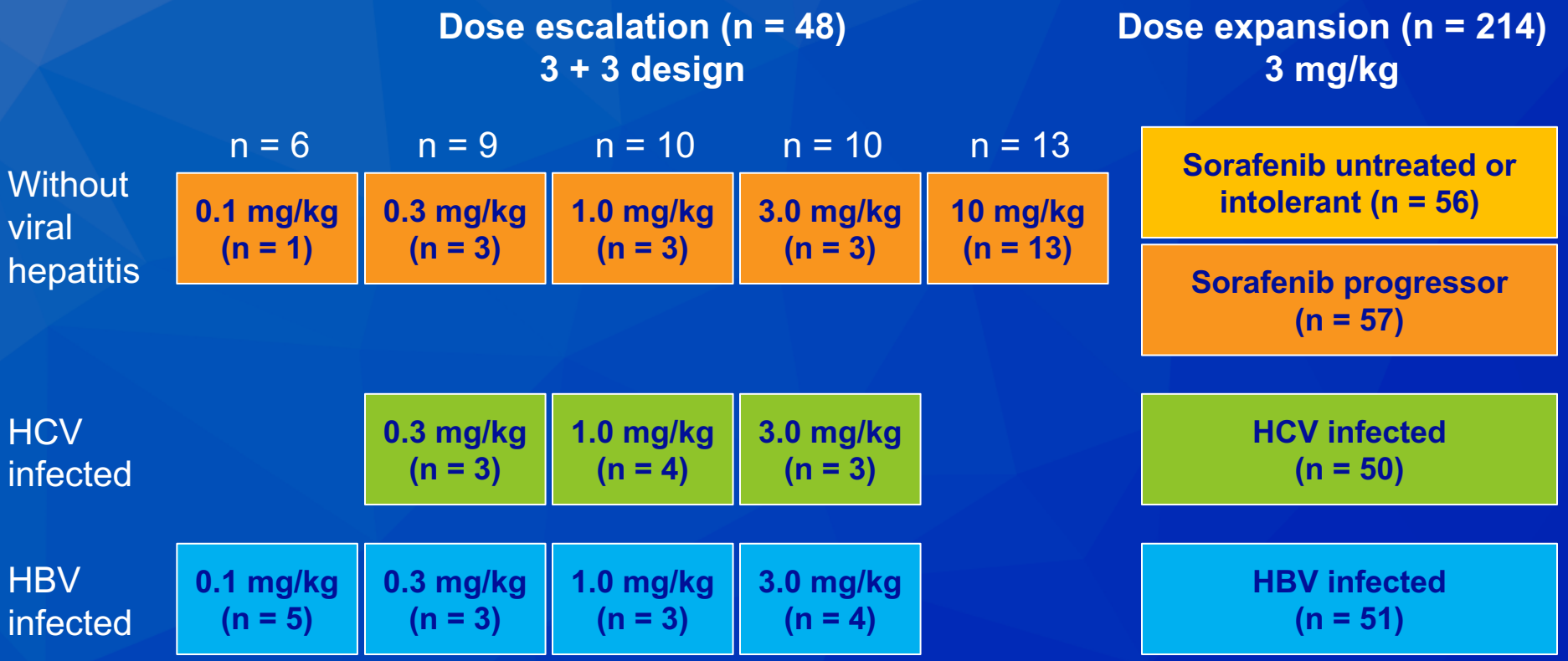
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial

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 Berlin

CheckMate 040 is a phase I/II trial for patients with hepatocellular cancer (HCC), with 48 patients in dose escalation and 214 in dose expansion. Data was collected on viral infection status.

Based on dose escalation, 3 mg/kg every other week was chosen for dose expansion. In the 216 patients on the dose expansion phase, objective response was seen in 20% with a median duration of response of 9.9 months. Response rates were slightly lower in the escalation phase. The overall disease control rate was 64% with 37% having disease control of 6 months or more. At 9 months, 74% were still alive, and at time of the *Lancet* paper, median OS was not reached.

Editorial — Dr Berlin (continued)

Overall, there were no apparent differences based on viral status. Prior sorafenib exposure appeared to play no role in likelihood of benefit. Safety profile appeared similar to other reports of nivolumab. The investigators also analyzed the data by age group. The response rate and the safety profile appeared similar across age groups.

Summary: In patients with HCC with Child-Pugh scores of 7 or less, nivolumab appears to have antitumor activity with a significant minority experiencing prolonged disease control. These effects appear to occur regardless of prior sorafenib, age, or viral infection status, meaning that the cohort that receives greatest benefit is as yet undefined. These data support CheckMate 469, randomizing nivolumab versus sorafenib in untreated patients.

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 cut-off for primary analysis: February 29, 2016
- Data cut-off 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 Berlin

RESORCE was designed to randomize Child-Pugh A hepatocellular carcinoma (HCC) patients refractory to sorafenib in a 2:1 fashion to either regorafenib or placebo.

Results: The treatment arms appeared well-balanced with a notable median time on sorafenib for both groups of 7.8 months. Responses were seen in 11% of patients on regorafenib. The primary analysis was for overall survival (OS), and hazard ratio was 0.63 at initial report and 0.61 ($p < 0.0001$ both times) at update with medians of 10.6 and 7.8 months for regorafenib and placebo, respectively. Safety profile was typical of regorafenib, and health-related quality of life was not significantly different between the two arms. Grade 3 or 4 fatigue occurred in 9% of regorafenib patients versus 5% of placebo patients.

Editorial — Dr Berlin (continued)

Summary: While this trial is positive for survival and offers a new option, there is still no biomarker for this class of agents, although tolerance and benefit from sorafenib may be a marker for benefit from regorafenib. As with most modern trials of chronically administered oral agents, this trial focuses on grade 3 and 4 adverse events when chronic low grade toxicities may be very important. Regorafenib should probably be considered only for those patients who still have Child A cirrhosis, tolerated sorafenib and received benefit from sorafenib. It remains to be seen if regorafenib is truly tolerable in this cohort of patients as oncologists have run into significant difficulties administering this agent in colorectal cancer patients.

Phase III CELESTIAL Trial of Cabozantinib Meets Primary Endpoint of Overall Survival for Patients with Advanced Hepatocellular Carcinoma

"[The] global phase 3 CELESTIAL trial met its primary endpoint of overall survival (OS), with cabozantinib providing a statistically significant and clinically meaningful improvement in median OS compared to placebo in patients with advanced hepatocellular carcinoma (HCC)… CELESTIAL is a randomized, global phase 3 trial of cabozantinib versus placebo in patients with advanced HCC who have been previously treated with sorafenib. The safety data in the study were consistent with the established profile of cabozantinib."

https://www.ipsen.com/press_release/ipsen-announces-phase-3-celestial-trial-cabozantinib-meets-primary-endpoint-overall-survival-patients-advanced-hepatocellular-carcinoma/

Gastrointestinal Cancers — Drs Grothey and Berlin

Colorectal Cancer

Gastric Cancer

Hepatocellular Carcinoma

Pancreatic Cancer

GI Neuroendocrine Tumors (GI NET)

Which neoadjuvant regimen would you likely recommend for a 78-year-old otherwise healthy patient who has unresectable pancreatic cancer that according to the surgeon may become resectable with tumor shrinkage?

a. FOLFIRINOX (or modified FOLFIRINOX)
b. *Nab* paclitaxel/gemcitabine
c. Other

A 60-year-old patient is s/p surgical removal of a T3N1 pancreatic cancer with 2 of 12 positive peripancreatic lymph nodes. What adjuvant systemic therapy, if any, would you most likely recommend?

a. Gemcitabine
b. Gemcitabine/capecitabine
c. Gemcitabine/*nab* paclitaxel
d. 5-FU
e. 5-FU + radiation therapy
f. Modified FOLFIRINOX
g. Other

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.

Biology of Human Tumors

Clinical Cancer Research

Desmoplasia in Primary Tumors and Metastatic Lesions of Pancreatic Cancer

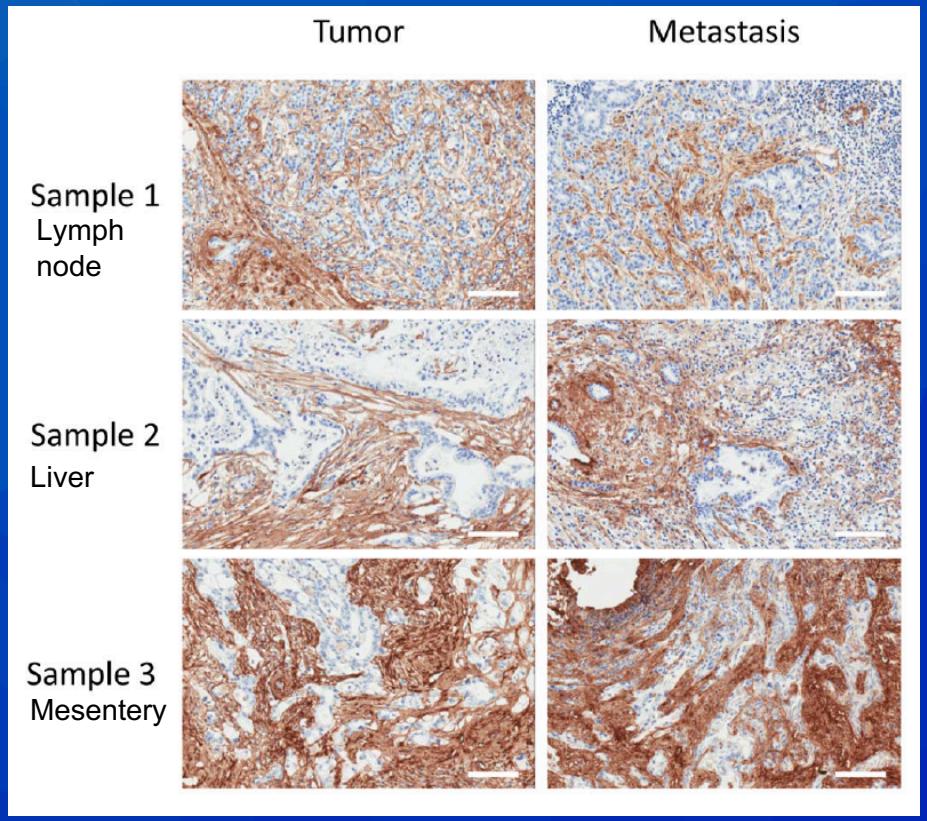
Clifford J. Whatcott, Caroline H. Diep, Ping Jiang, Aprill Watanabe, Janine LoBello, Chao Sima, Galen Hostetter, H. Michael Shepard, Daniel D. Von Hoff, and Haiyong Han

Clin Cancer Res 2015;21(15):3561-8.

Desmoplasia in Primary and Metastatic Pancreatic Ductal Adenocarcinoma (PDAC)

- Primary tumors and metastatic lesions were analyzed for extracellular matrix protein (collagen I) expression in matched patient samples (N = 7) and unmatched tissue microarray.

Patient Samples – Collagen I



- **Metastatic lesions of multiple sites display significant levels of desmoplasia, including high levels of collagens I, III and IV, comparable to those found in primary pancreatic tumors.**

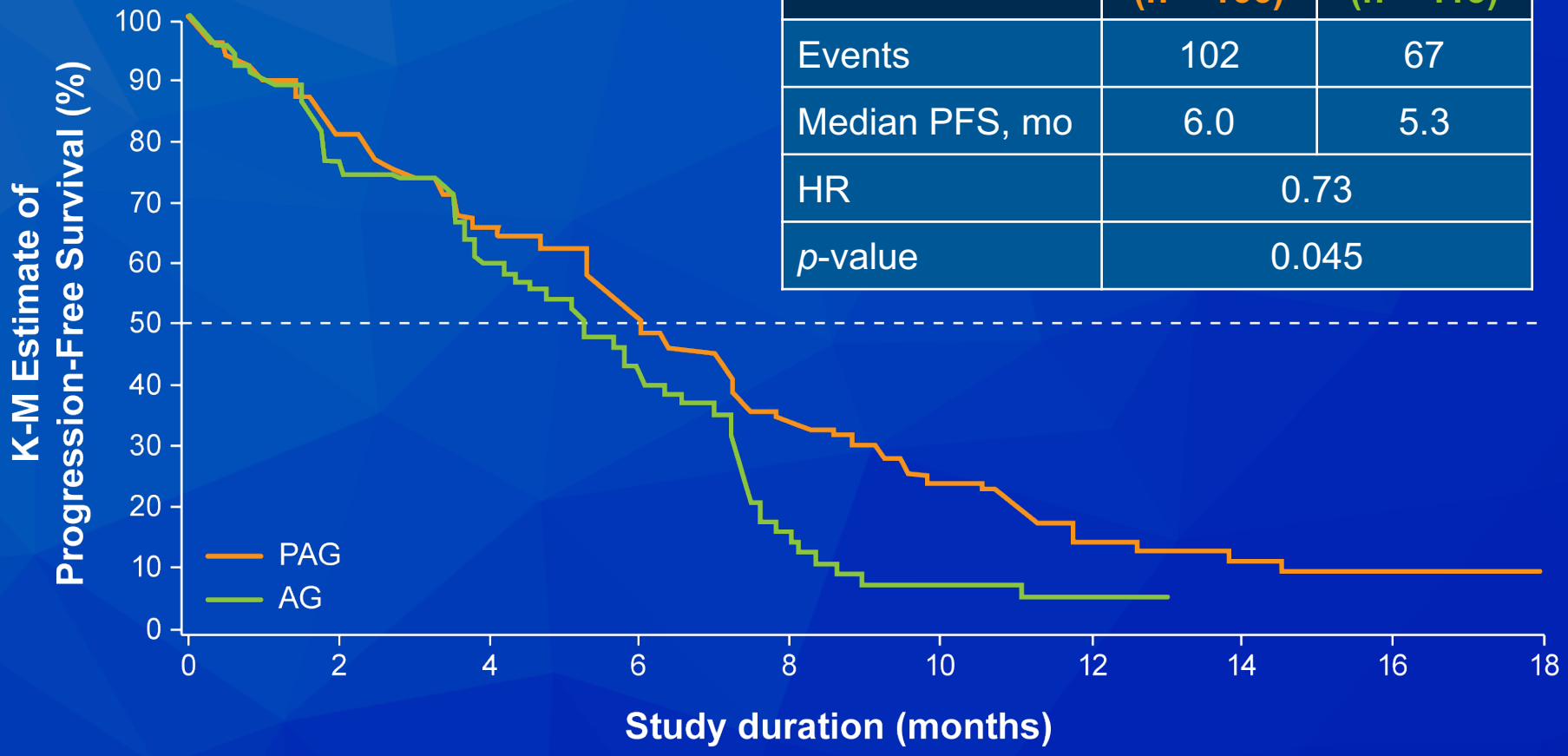
Whatcott CJ et al. *Clin Cancer Res* 2015;21(15):3561-8.

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)

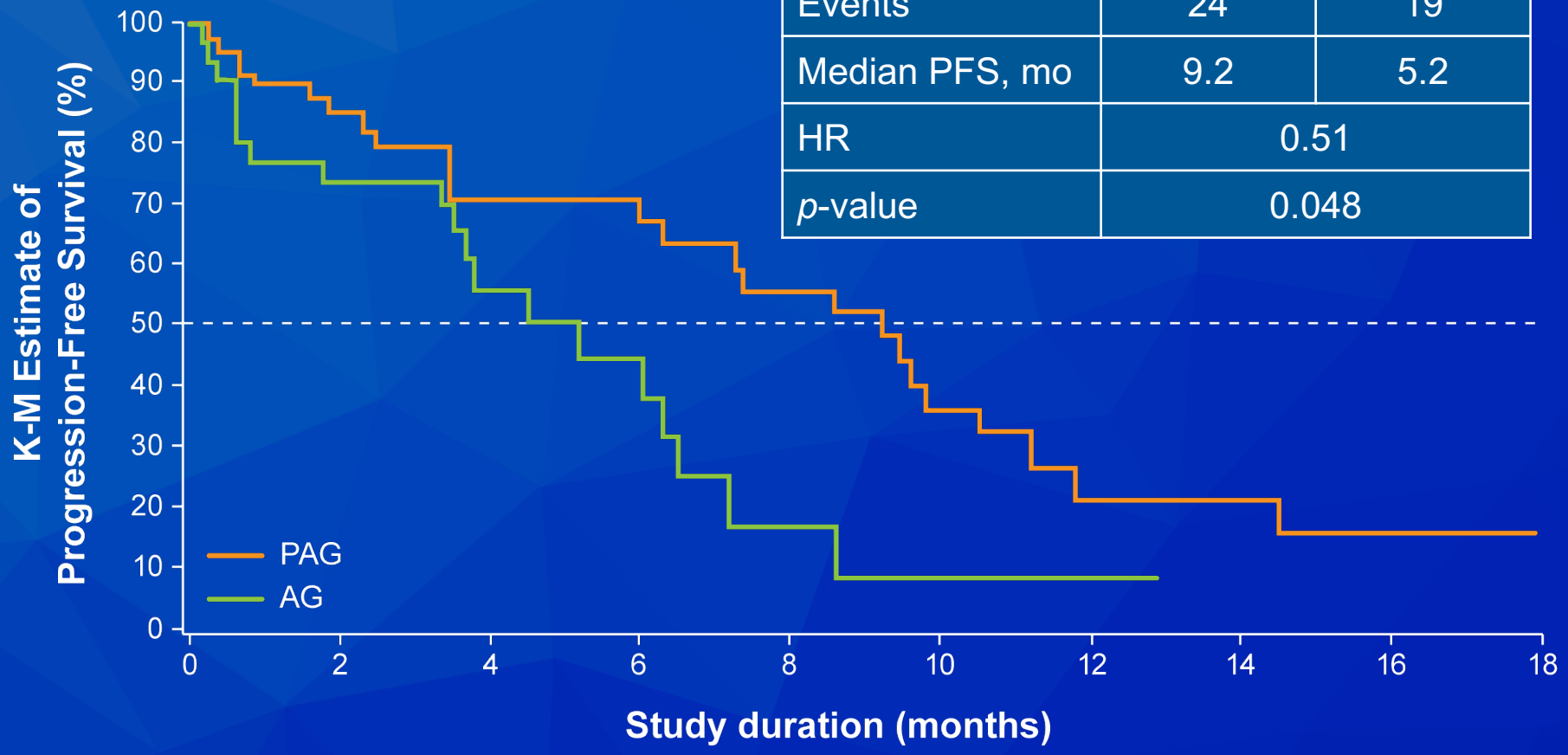
	PAG (n = 166)	AG (n = 113)
Events	102	67
Median PFS, mo	6.0	5.3
HR	0.73	
p-value	0.045	



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 Berlin

PEGPH20 degrades hyaluronan (HA) deposition in cancer stroma, and administration may lead to decreased intratumoral pressure. HALO-202 randomized 279 metastatic pancreas cancer patients to gemcitabine plus *nab*-paclitaxel with or without PEGPH20 (initially 1:1 and later 2:1 randomization). Primary endpoint was progression-free survival (PFS) with a co-primary endpoint added of thromboembolic events (TE) after TEs started occurring on the trial. The key secondary endpoint was PFS by HA level.

Editorial — Dr Berlin (continued)

Of treated patients, 49 in the experimental arm were HA high and 35 in the control arm were HA high. In the intent-to-treat analysis, the PFS was improved for the PEGPH20 arm (HR 0.73, *p*-value 0.045), which was more substantial for the HA-high subset (HR for OS 0.51, *p*-value 0.048). Initially there were more TEs in the PEGPH20 arm (43% vs 25%) but this appears to have been ameliorated with prophylactic enoxaparin. Median OS in the HA-high group did not appear different, though numbers were small (HR 0.96, *p* NS).

This randomized trial showed encouraging PFS data for patients with HA-high metastatic pancreas cancer and suggested the ongoing 420-patient phase III trial with co-primary endpoints of OS and PFS.

Editorial — Dr Berlin (continued)

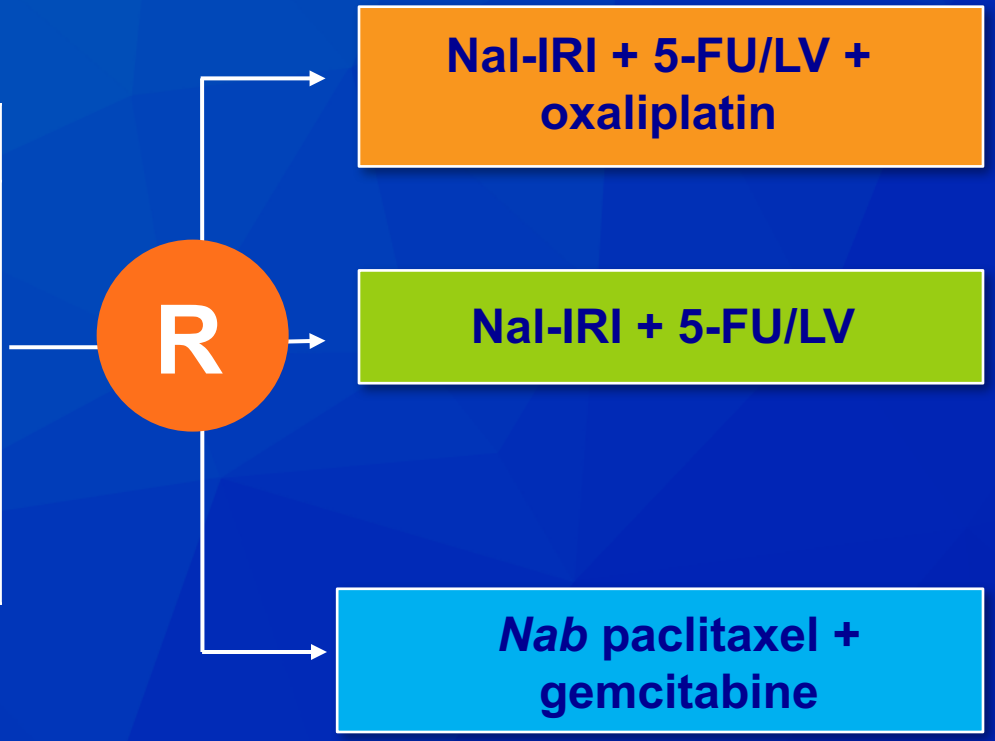
However, caution about these results includes: small subset analysis is informing a large trial, and survival is not better for the HA-high group treated with PEGPH20, though this subset is small. Additionally, a second unselected randomized phase II trial, SWOG-S1313 comparing FOLFIRINOX with or without PEGPH20, was stopped after meeting a futility endpoint (press release only).

Phase II Trial of Nanoliposomal Irinotecan (nal-IRI)-Containing Regimens in Patients with Previously Untreated Metastatic Pancreatic Adenocarcinoma

Trial Identifier: NCT02551991 (Open)
Estimated Enrollment: 168

Eligibility

- Part 1: Unresectable, locally advanced or metastatic pathologically confirmed pancreatic adenocarcinoma
- Part 2: Metastatic pancreatic adenocarcinoma diagnosed ≤6 weeks prior



Primary endpoint: Progression-free survival

www.clinicaltrials.gov; Accessed October 2017.

Personalized Medicine and Imaging

Clinical Cancer Research

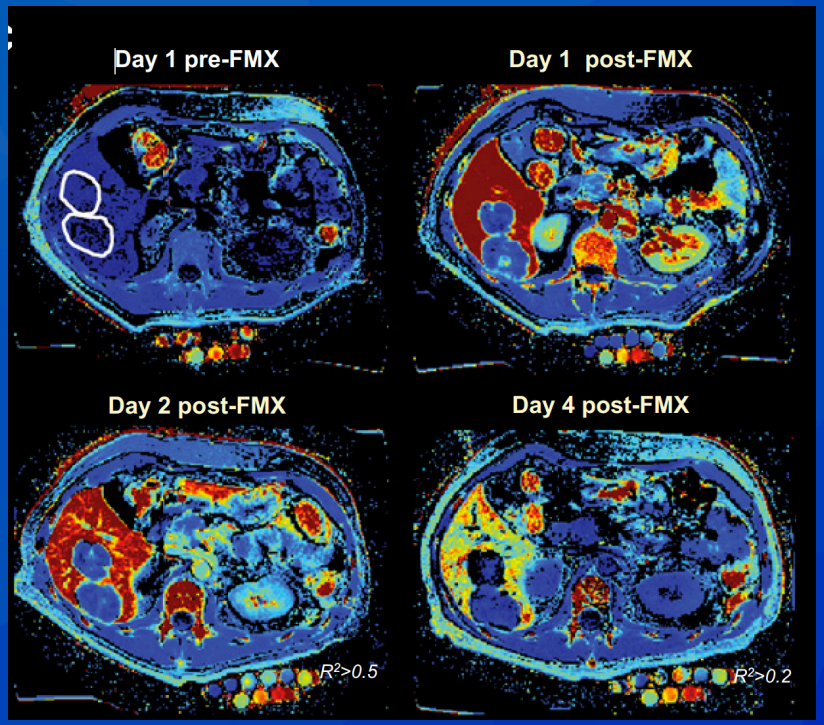
Correlation between Ferumoxytol Uptake in Tumor Lesions by MRI and Response to Nanoliposomal Irinotecan in Patients with Advanced Solid Tumors: A Pilot Study

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.

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;[Epub ahead of print].

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;[Epub ahead of print].

Editorial — Dr Berlin

Little is known about second-line therapies after first-line gemcitabine-based chemotherapy. This study was a “meta-analysis” of 5 studies using published data, not primary data. In the end, after extensive searching, the investigators found 5 studies that met their criteria, 2 involving a form of irinotecan in combination with fluoropyrimidine and 3 that included oxaliplatin in combination with a fluoropyrimidine. The total number of patients was only 895 in the 5 trials.

The authors noted that the “meta-analysis” of fluoropyrimidine plus oxaliplatin improved progression-free survival (PFS), with a hazard ratio (HR) of 0.81 compared to fluoropyrimidine, $p = 0.02$, but not overall survival (OS), with HR of 1.03, $p = 0.90$.

Editorial — Dr Berlin (continued)

However, fluoropyrimidine plus irinotecan did result in improvement in both PFS (HR of 0.64, $p = 0.005$) and OS (HR of 0.70, $p = 0.004$). Risk-bias assessments were done to minimize error in this data.

Summary: While this is called a meta-analysis, only 5 trials exist that qualified, making this more of a combined analysis with good statistical design. With few trials, flaws and biases in any individual trial can have a big impact in the results. The PANCREOX trial has an almost inexplicable improvement in OS for the control arm, and that led to the negative OS result for oxaliplatin-based regimens.

Editorial — Dr Berlin (continued)

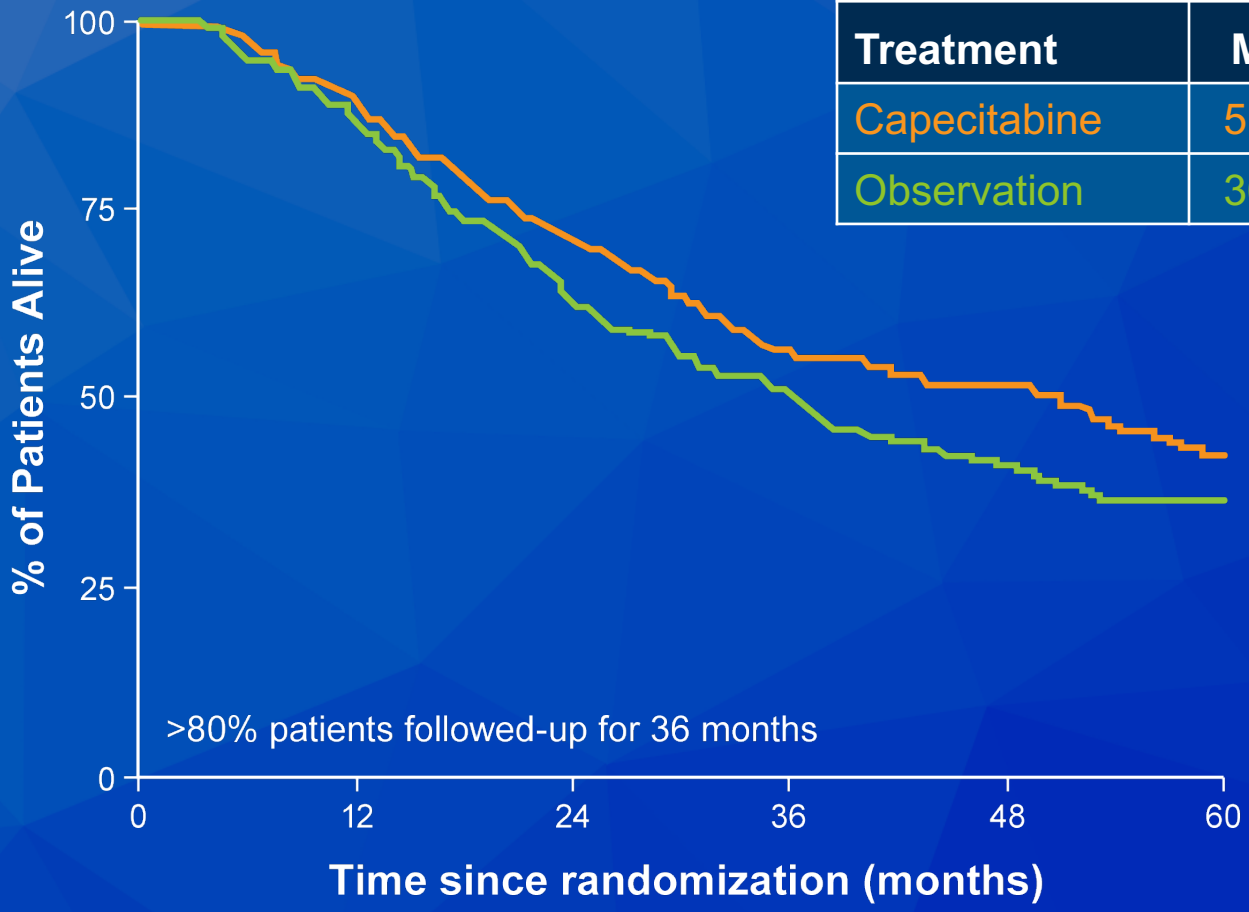
Therefore, limited conclusions can be safely drawn from this analysis. Couplets are likely better than single agents. They improve PFS, which is important in this very symptomatic disease, and at least irinotecan adds to survival.

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 Berlin

BILCAP is a randomized study of capecitabine for 6 months versus observation after surgical resection of biliary tract and gallbladder cancers. Primary endpoint was overall survival (OS).

Results: Overall, 447 patients who had undergone resection of biliary tract and gallbladder cancer were randomized to either capecitabine (8 cycles) or observation. Arms appear well-balanced with 38% in both arms having had R1 resection and 46%-48% having node+ disease. Hazard ratio (HR) for OS was 0.81 (p = 0.097) for the intent-to-treat group, but the protocol planned analysis eliminated patients who did not start capecitabine and had a HR for OS of 0.75 (p = 0.028) with medians of 52.7 and 36.1 months for capecitabine and observation, respectively.

Editorial — Dr Berlin (continued)

Secondary endpoint of relapse-free survival had a HR of 0.71 (p = 0.11) in the protocol planned group. Subset analysis did not show an identified group that received more of the benefit.

Summary: This is the first study to demonstrate benefit of any adjuvant therapy in biliary tract cancer. On the other hand, the PRODIGE 12-ACCORD 18 adjuvant trial of gemcitabine and oxaliplatin did not demonstrate benefit as adjuvant therapy for the same diseases. The two studies differed significantly in patient population, with BILCAP having more patients with R1 resection and node positive disease.

Editorial — Dr Berlin (continued)

It is unclear if this is why the results differed substantially or if the PRODIGE 12-ACCORD 18 was too small to see improvements. Capecitabine is a new standard for adjuvant therapy of biliary tract and gallbladder cancers.

Gastrointestinal Cancers — Drs Grothey and Berlin

Colorectal Cancer

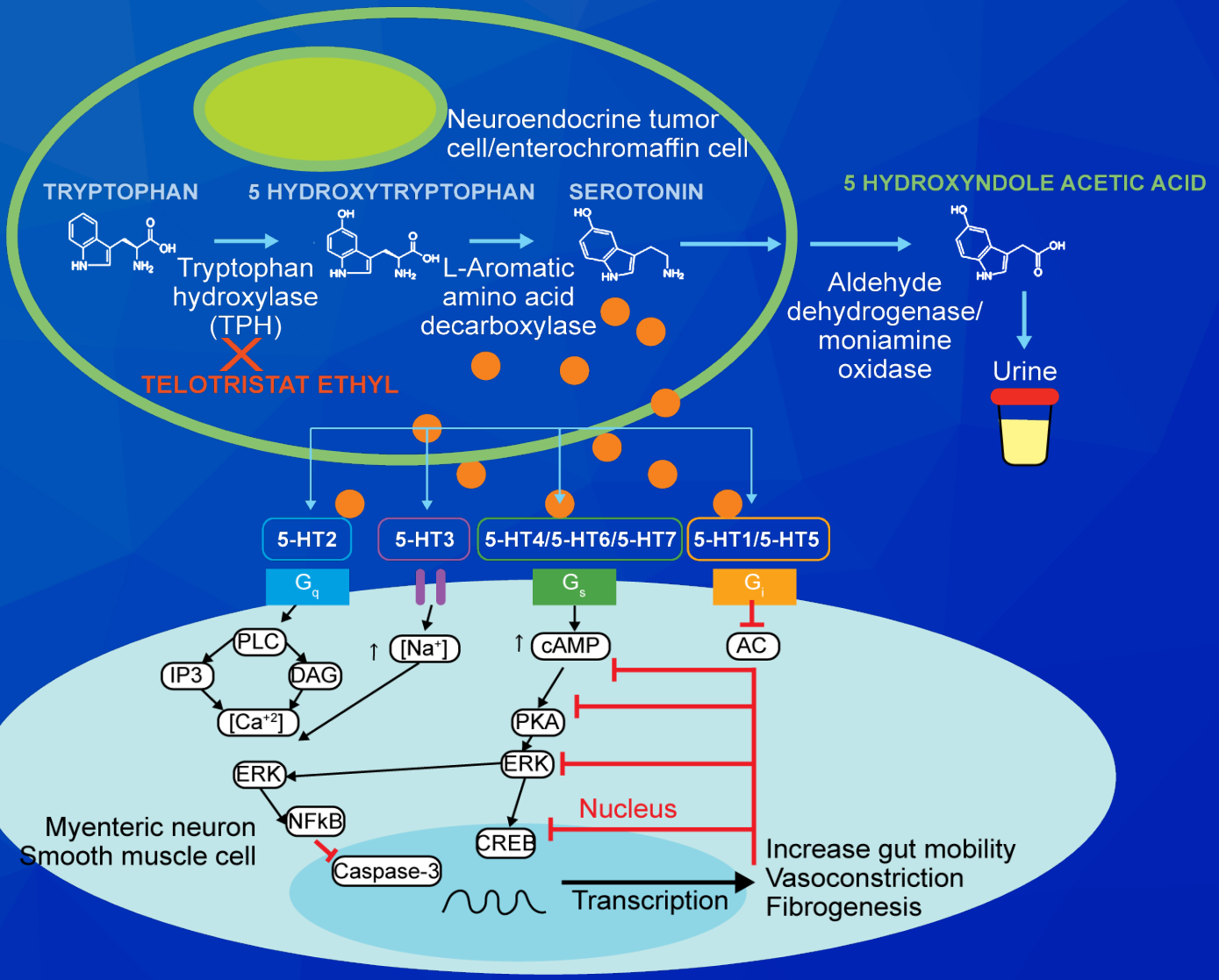
Gastric Cancer

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.

VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

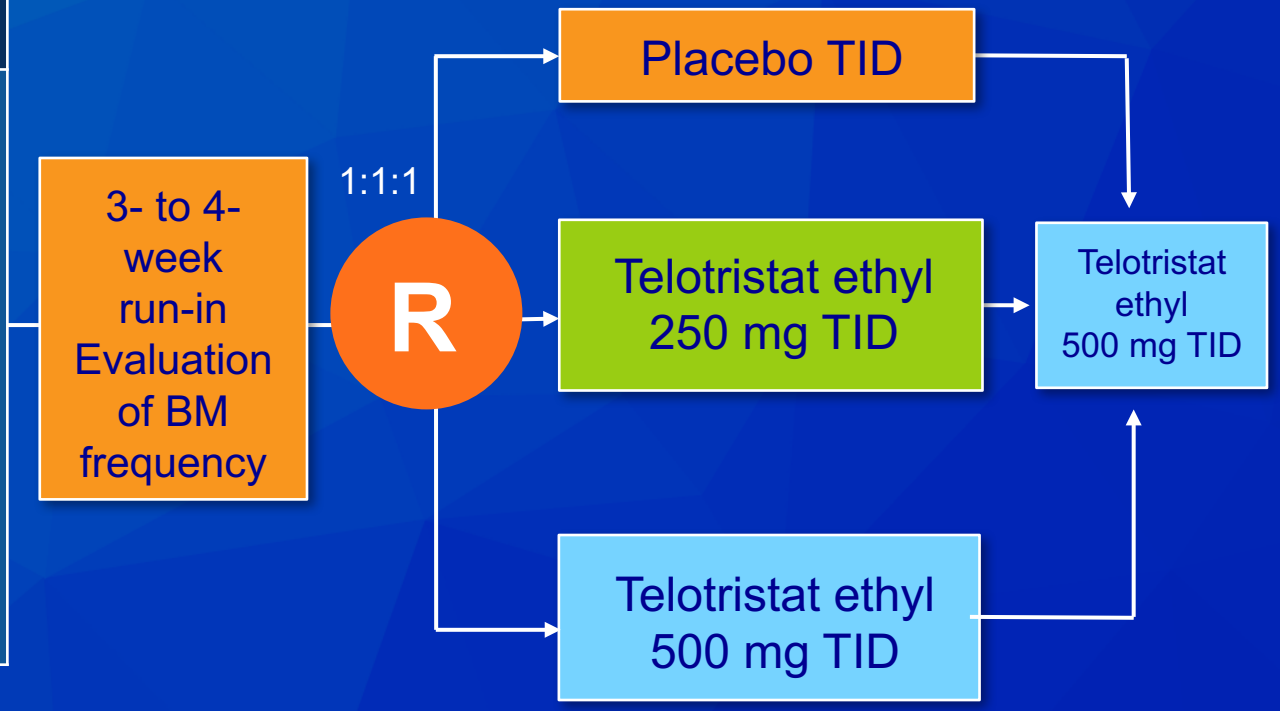
Matthew H. Kulke, Dieter Hörsch, Martyn E. Caplin, Lowell B. Anthony, Emily Bergsland, Kjell Öberg, Staffan Welin, Richard R.P. Warner, Catherine Lombard-Bohas, Pamela L. Kunz, Enrique Grande, Juan W. Valle, Douglas Fleming, Pablo Lapuerta, Phillip Banks, Shanna Jackson, Brian Zambrowicz, Arthur T. Sands,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

TELESTAR: Phase III Trial Schema

Trial Identifier: NCT01677910
Enrollment: 135

Eligibility

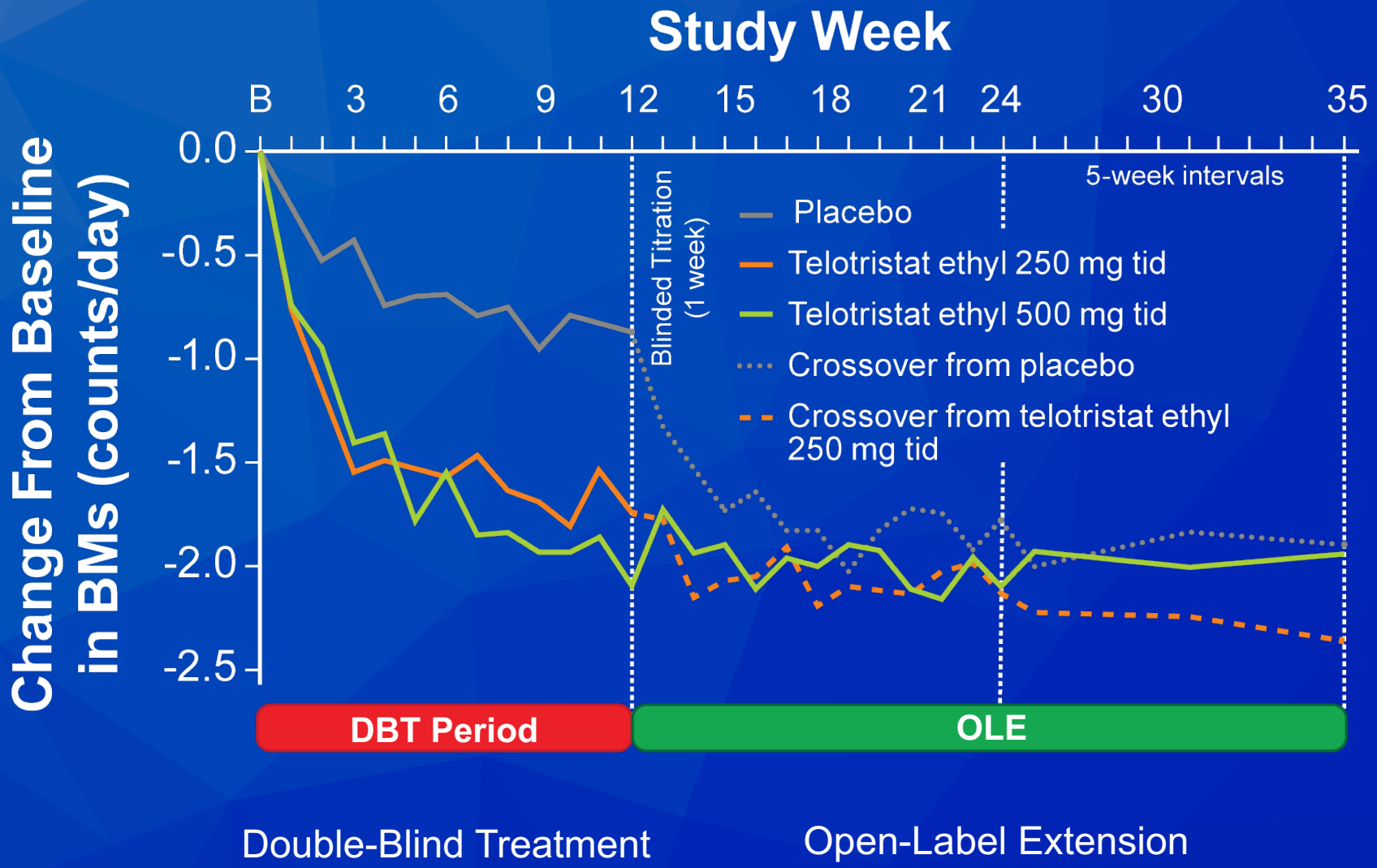
- Carcinoid syndrome
- Experiencing ≥4 bowel movements (BMs) per day despite stable-dose somatostatin analogue (SSA) therapy
- Continue SSA throughout study period



Primary endpoint: Change from baseline in BM frequency

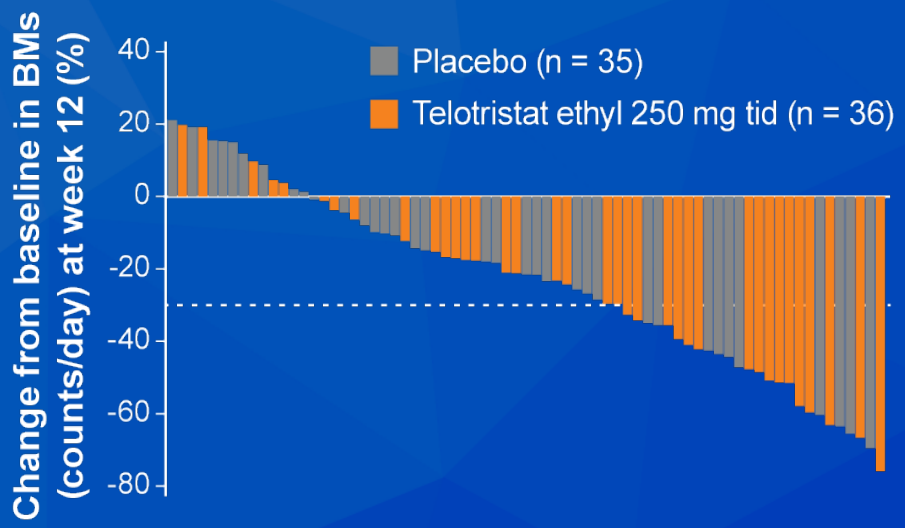
Kulke MH et al. *J Clin Oncol* 2017;35(1):14-23.

TELESTAR: Change from Baseline in BMs Per Day

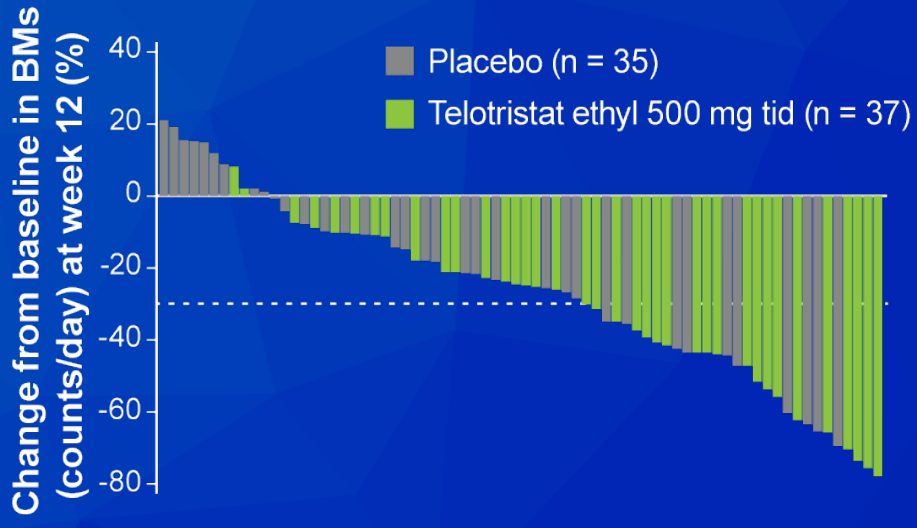


Kulke MH et al. *J Clin Oncol* 2017;35(1):14-23.

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



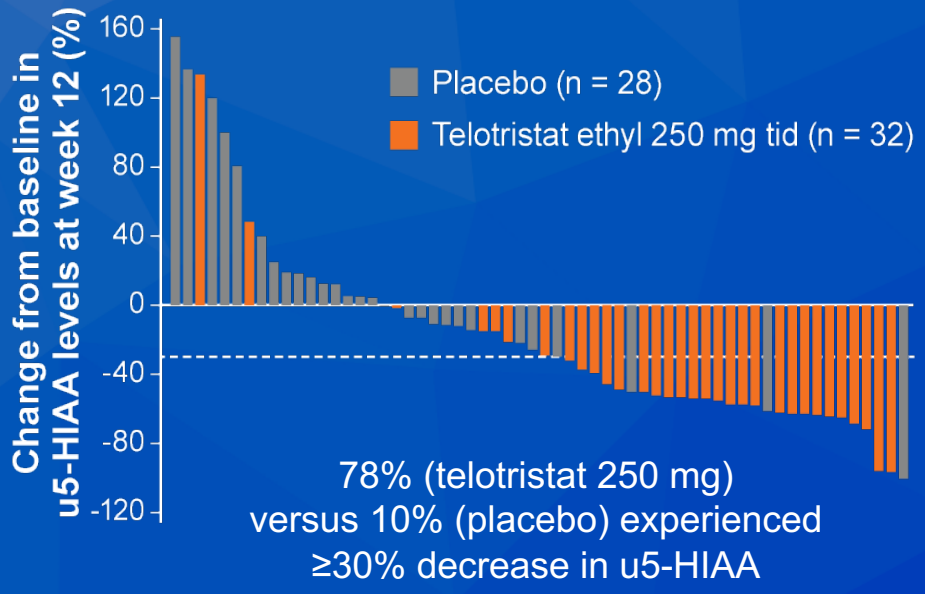
Mean reduction in daily BM frequency from baseline to week 12
250 mg three times per day: -1.7
Placebo: -0.9

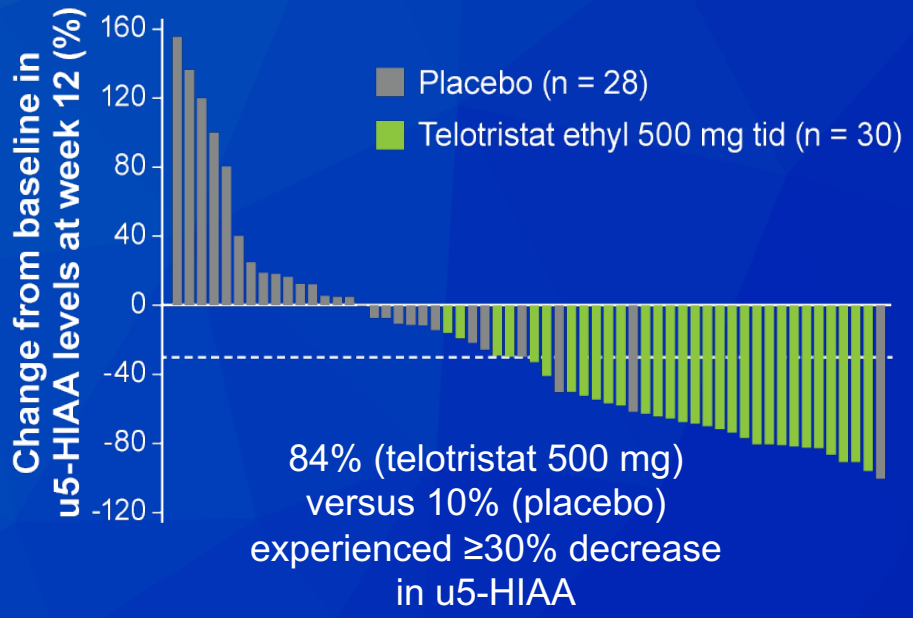


Mean reduction in daily BM frequency from baseline to week 12
500 mg three times per day: -2.1
Placebo: -0.9

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 Berlin

Telotristat ethyl is an inhibitor of tryptophan hydroxylase, a key enzyme in the conversion of tryptophan to serotonin, which should, in theory, ameliorate the serotonin-induced carcinoid syndrome symptoms, such as flushing and diarrhea. TELESTAR was a randomized trial comparing telotristat to placebo in reducing diarrhea in patients with continued diarrhea despite adequate and stable doses of octreotide. The study evaluated diarrhea frequency over 12 weeks. Patients were randomized to placebo versus one of two doses of telotristat.

In the 135 patients randomized, both doses of telotristat reduced bowel movement frequency by 1.7-2.1 bowel movements per day compared to only a 0.9 bowel movement per day reduction for placebo.

Editorial — Dr Berlin (continued)

Additionally, 78% and 87% of patients on the telotristat arms had a >30% reduction in 24-hour urinary 5-HIAA compared with 10% of the placebo arm. Toxicity was minimal, but more nausea was observed with the higher telotristat dose.

Summary: Telotristat was effective in reducing serotonin production in patients with carcinoid syndrome, subsequently reducing diarrhea. While this appears on the surface to be a minimal decrease in diarrhea, bringing up questions of the value in prescribing this very expensive medicine, subsequent reports are questioning if this agent could impact the development of carcinoid heart, one of the most dangerous effects of carcinoid syndrome. Better understanding of this potential impact will be important.

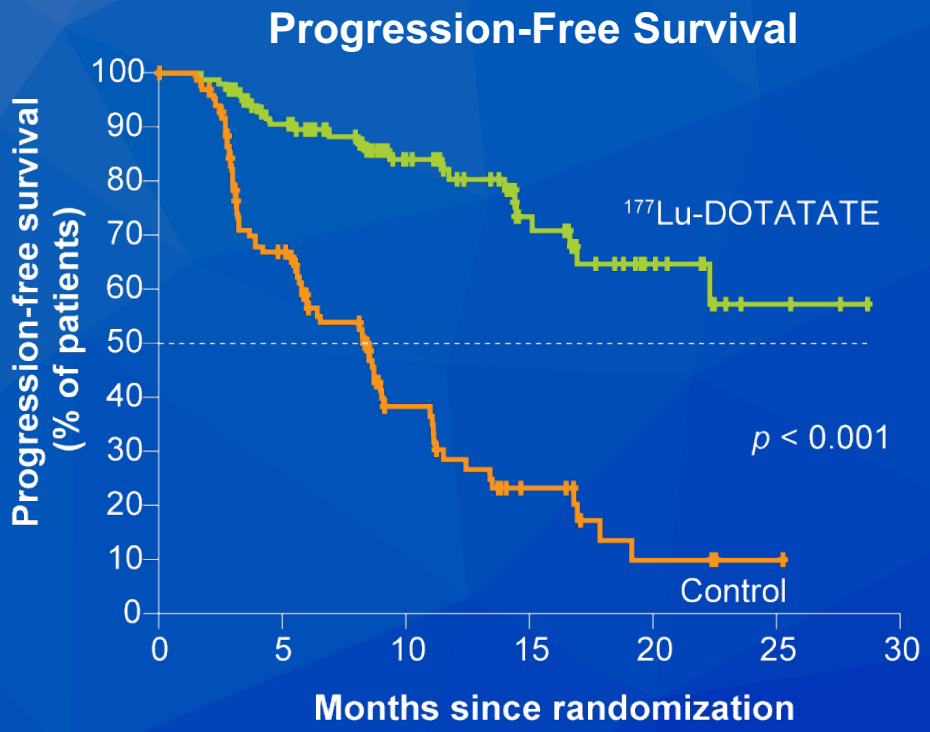
ORIGINAL ARTICLE

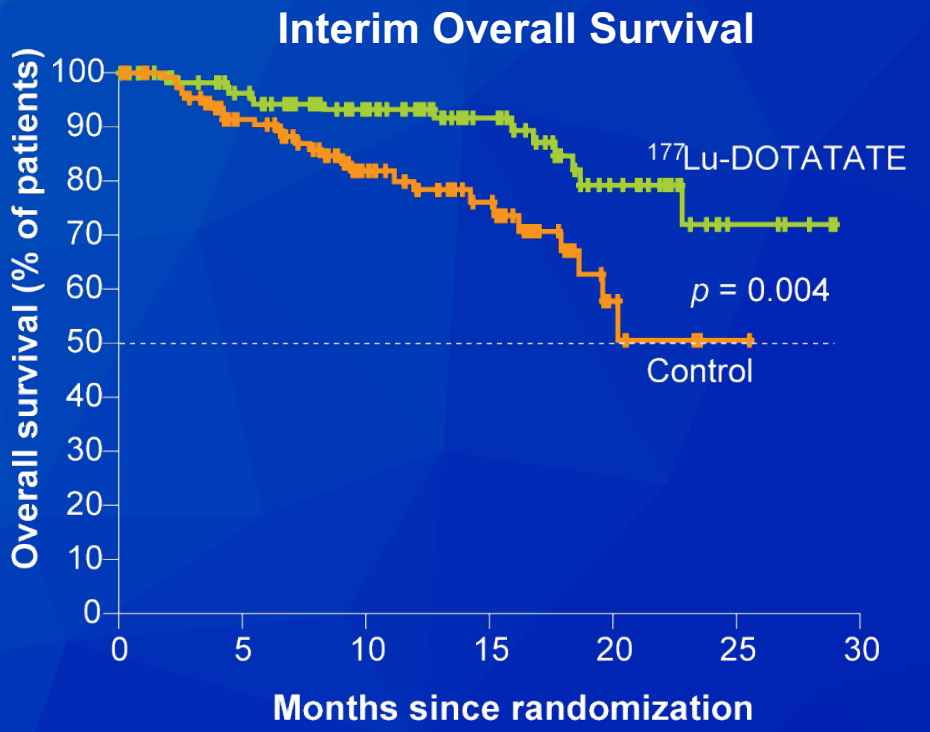
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

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 Berlin

177-Lutetium-Dotatate (PRRT) has been used therapeutically to treat low grade neuroendocrine tumors for several years in limited sites in Europe, without definitive data. The NETTER-1 trial is the first randomized trial to evaluate PRRT prospectively for benefit. Patients had midgut neuroendocrine tumors with radiographic (centrally reviewed) disease progression within the prior 3 years while on somatostatin analogue therapy, well-differentiated histology, and Ki-67 of <20% (stratified by WHO grade 1 versus 2). Patients were randomly assigned to either octreotide 60 mg every 4 weeks or PRRT for 4 doses with co-administered amino acid solution to prevent kidney failure.

Editorial — Dr Berlin (continued)

The 229 patients randomized had well-balanced baseline characteristics. For the primary endpoint of progression free survival (PFS), the hazard ratio was 0.21 ($p < 0.001$) with median PFS unreached on the PRRT arm compared to 8.4 months on the control arm. Overall survival was early. Response rate to PRRT was 18%. Only 5% of patients withdrew from PRRT due to treatment-related adverse events. Toxicities were manageable.

Summary: 177-Lutetium Dotatate is highly effective in preventing progression of well-differentiated WHO grade 1 or 2 midgut neuroendocrine tumors. Survival data is pending.

Editorial — Dr Berlin (continued)

Although we suspect this will work for other forms of somatostatin receptor-positive neuroendocrine tumors, this is not proven by NETTER-1. Approval is expected, but people should be cautious to administer this as in the trial because the amino acid solution is crucial to prevent renal failure.