Colorectal Cancer

VOLUME 36 · NUMBER 8 · MARCH 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

J Clin Oncol 2018;36(8):773-9.

CheckMate 142: Phase II Multicohort Trial Design

NCT02060188

Eligibility (N = 340)

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H positive by local laboratory
- ≥1 prior line of therapy

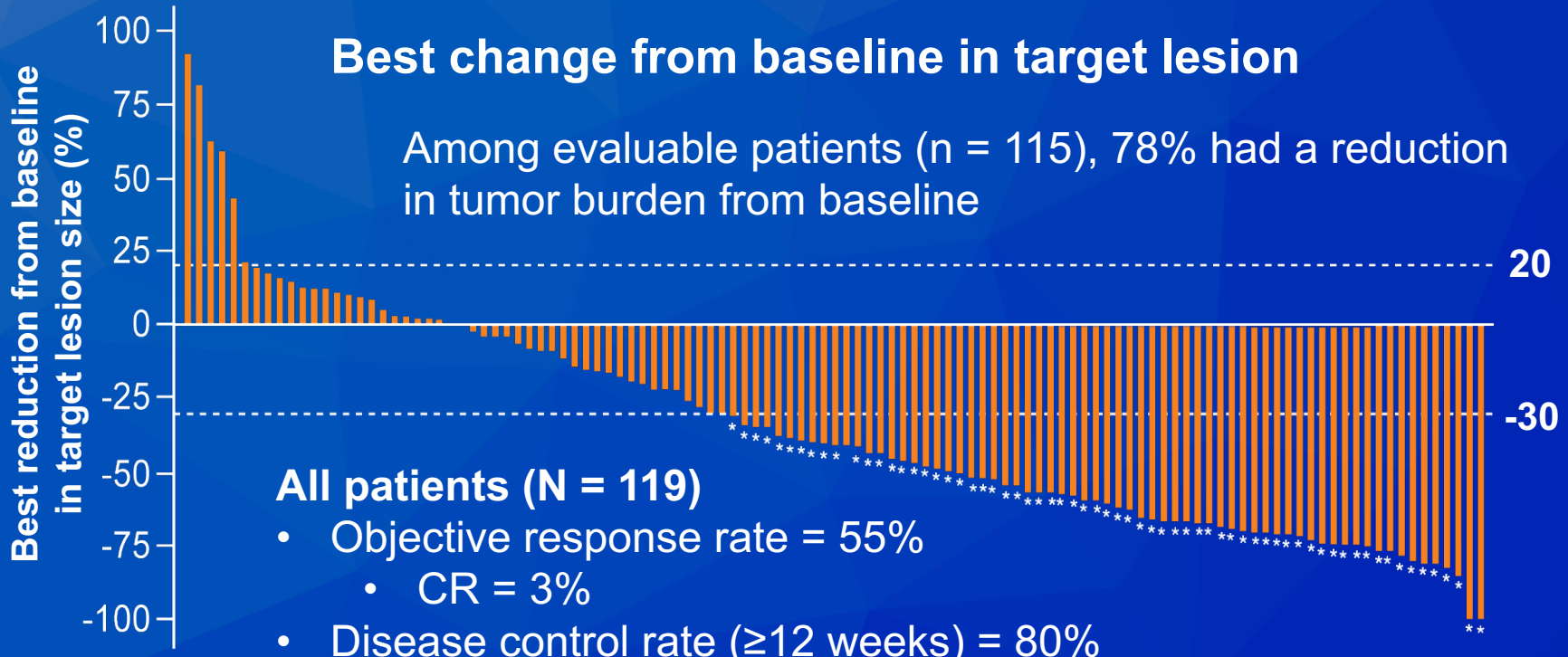
→

- **Nivolumab Monotherapy (Cohort 1)**
- **Nivolumab + Ipilimumab (Cohorts 2 & 3)**
- **Nivolumab + Ipilimumab + Cobimetinib (Cohort 4)**
- **Nivolumab + Relatlimab (BMS-986016) (Cohort 5)**
- **Nivolumab + Daratumumab (Cohort 6)**

- **Primary endpoint:** Objective response rate
- Cohort 2: Dose-escalation phase (0.3 mg/kg – 3 mg/kg Nivo + 1 – 3 mg/kg Ipi every 2 or 3 weeks until disease progression)
- Cohort 3: Nivo dosed every 2 weeks + Ipi dosed every 6 weeks
- This study reports the efficacy and safety results of patients who received 3 mg/kg Nivo + 1 mg/kg Ipi once every 3 weeks (4 doses) → 3 mg/kg Nivo once every 2 weeks

Overman MJ et al. *J Clin Oncol* 2018;36(8):773-9; Clinicaltrials.gov.

CheckMate 142: Response and Survival by Investigator Assessment



- Responses were durable; 94% of responders with ongoing responses
- The median duration of response = not reached
- Median PFS and OS = not reached
  - 12-mo PFS = 71%
  - 12-mo OS = 85%

Overman MJ et al. *J Clin Oncol* 2018;36(8):773-9.

CheckMate 142: Nivolumab + Ipilimumab: Select AEs in >10% of Patients

Treatment-related AE (N = 119)	Grade 1-2	Grade 3	Grade 4
Diarrhea	20%	2%	0
Fatigue	16%	2%	0
Pruritus	15%	2%	0
Increased AST	7%	8%	0
Hypothyroidism	13%	1%	0
Nausea	12%	1%	0
Increased ALT	5%	7%	0
Rash	9%	2%	0
Hyperthyroidism	11%	0	0

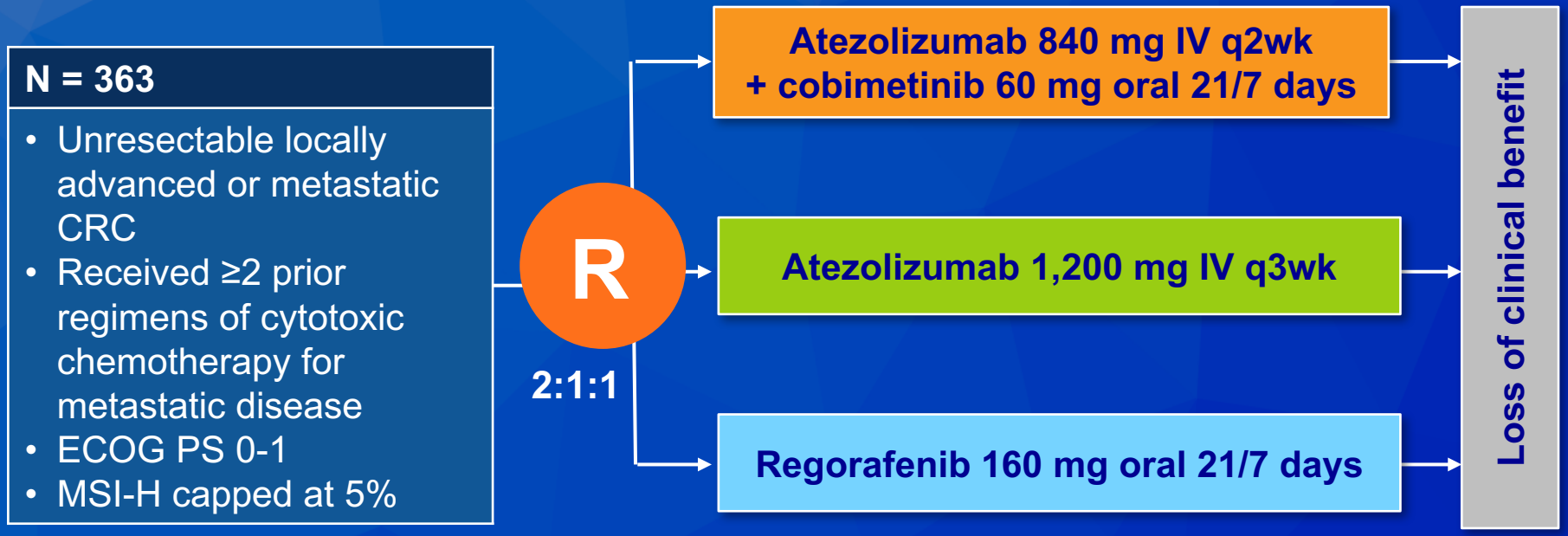
Overman MJ et al. *J Clin Oncol* 2018;36(8):773-9.

Efficacy and Safety Results from IMblaze370, a Randomised Phase III Study Comparing Atezolizumab + Cobimetinib and Atezolizumab Monotherapy vs Regorafenib in Chemotherapy Refractory Metastatic Colorectal Cancer

Bendell J et al.

Proc ESMO 2018;Abstract LBA-004.

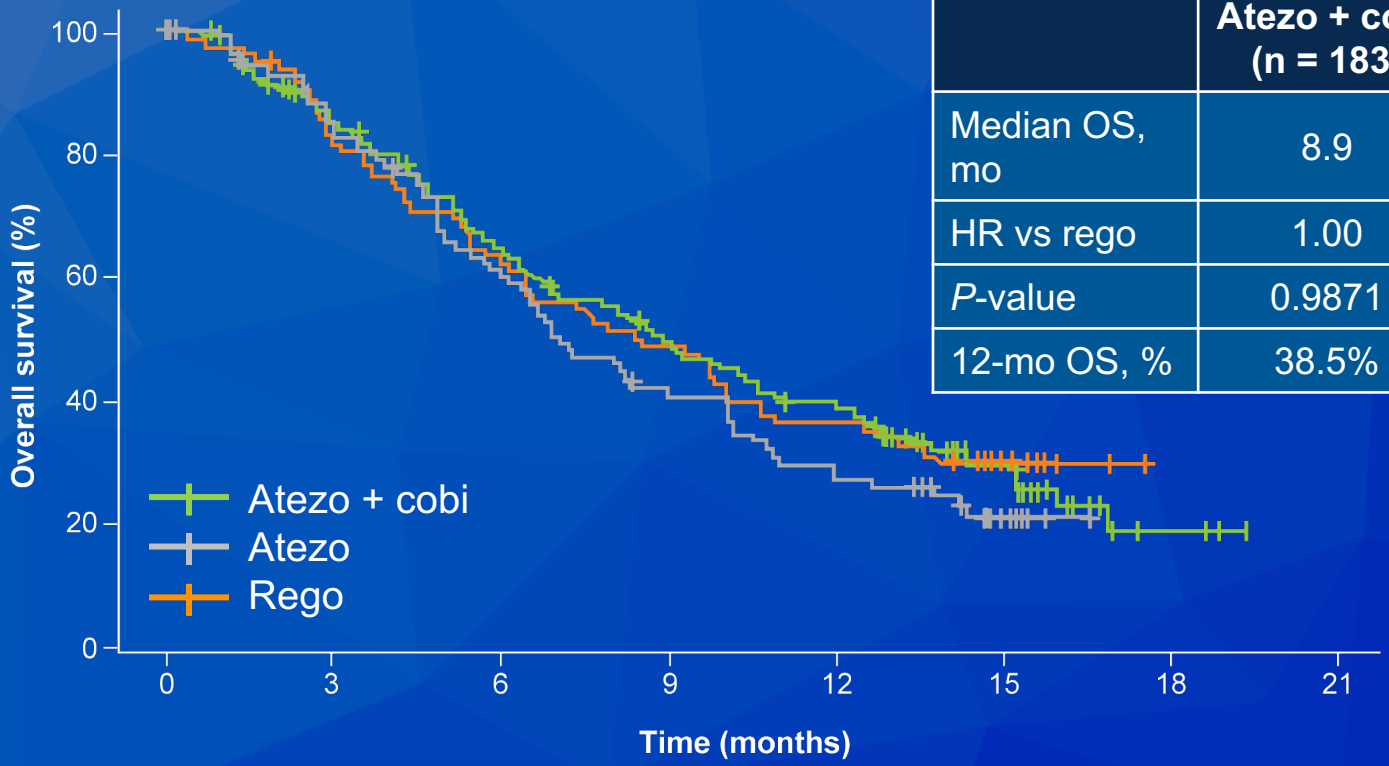
IMblaze370: Phase III Trial Design



- **Primary endpoint:** OS (versus regorafenib)
- Stratification by:
  - Extended RAS mutation status (≥50% of patients in each arm)
  - Time since diagnosis of first metastasis (<18 mo vs ≥18 mo)

Bendell J et al. *Proc ESMO* 2017;Abstract LBA-004.

IMblaze370: Survival and Response Results



	Atezo + cobi (n = 183)	Atezo (n = 90)	Rego (n = 90)
Median OS, mo	8.9	7.1	8.5
HR vs rego	1.00	1.19	N/A
P-value	0.9871	0.3360	N/A
12-mo OS, %	38.5%	27.2%	36.6%

Outcome	Atezo + cobi (n = 183)	Atezo (n = 90)	Rego (n = 90)
Median PFS	1.9 mo	1.9 mo	2.0 mo
HR (PFS) vs regorafenib	1.25	1.39	Not applicable
ORR	2.7%	2.2%	2.2%
Median duration of response	11.4 mo	4.8 mo	9.2 mo

Bendell J et al. *Proc ESMO* 2017;Abstract LBA-004.

IMblaze370: Select AEs Occurring in ≥20% of Patients

All Grade AE	Atezo + cobi (n = 179)	Atezo (n = 90)	Rego (n = 80)
Diarrhea	117 (65%)	17 (19%)	30 (38%)
Rash	83 (46%)	8 (9%)	19 (24%)
Nausea	66 (37%)	19 (21%)	11 (14%)
Fatigue	64 (36%)	23 (26%)	37 (46%)
Pyrexia	59 (33%)	14 (16%)	20 (25%)
Decreased appetite	48 (27%)	22 (24%)	33 (41%)
Hypertension	9 (5%)	4 (4%)	25 (31%)
Palmar-plantar erythrodysesthesia	3 (2%)	1 (1%)	42 (53%)

- Safety in the atezolizumab + cobimetinib arm was consistent with the known safety profiles of the individual agents.

Bendell J et al. *Proc ESMO* 2017;Abstract LBA-004.

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

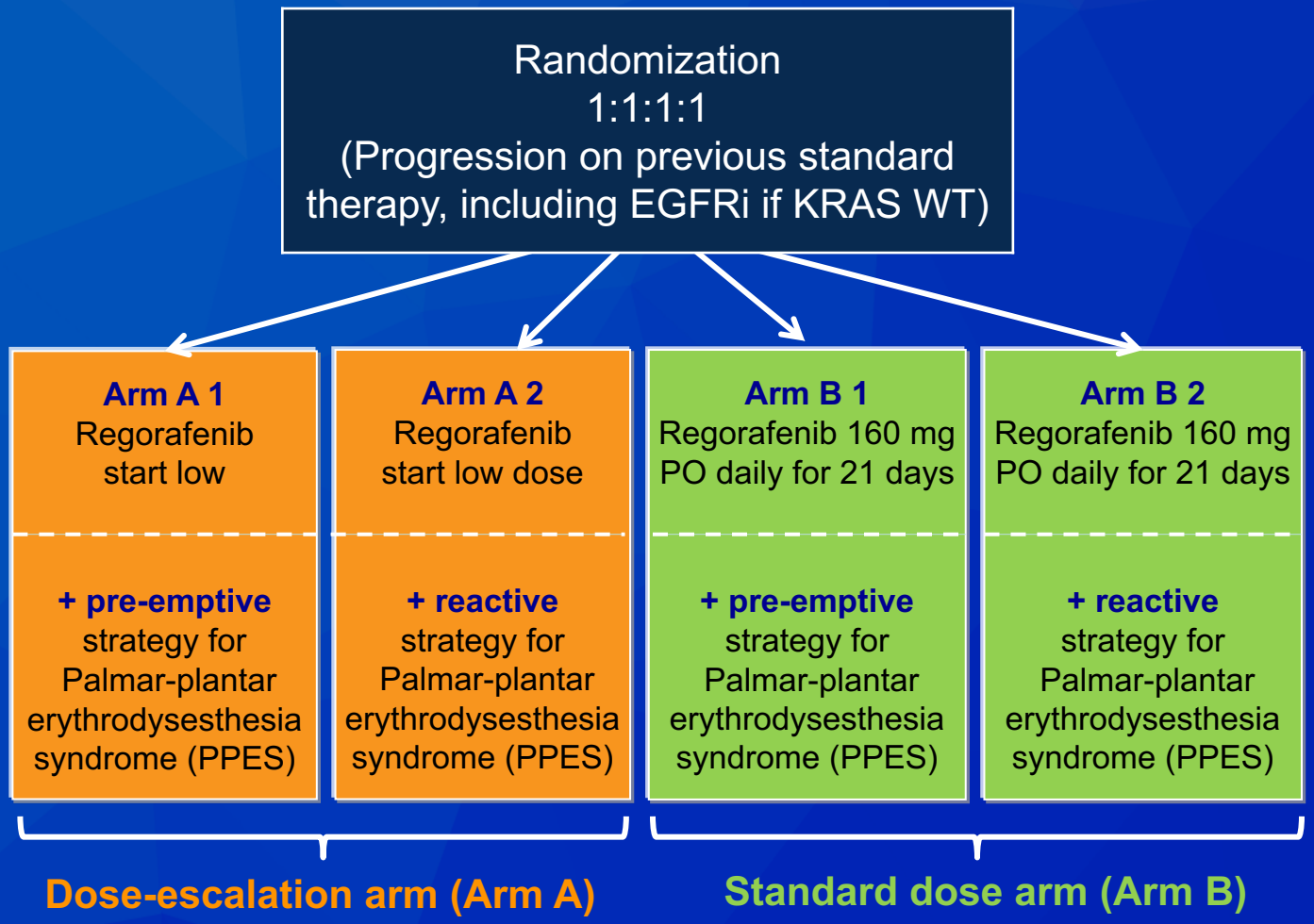
Regorafenib Dose Optimization Study (ReDOS): Randomized Phase II Trial to Evaluate Escalating Dosing Strategy and Pre-Emptive Topical Steroids for Regorafenib in Refractory Metastatic Colorectal Cancer (mCRC) — An ACCRU Network Study

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

Bekaii-Saab TS et al. *Proc ESMO* 2018;Abstract O-014.

ReDOS: Phase II Trial Design

WEEK of C1		DOSE
1	Starting dose C1	80 mg
2	⬇	120 mg
3	End dose C1	160 mg
4		off
WEEK of C2+		**DOSE**
1		Dose from C1

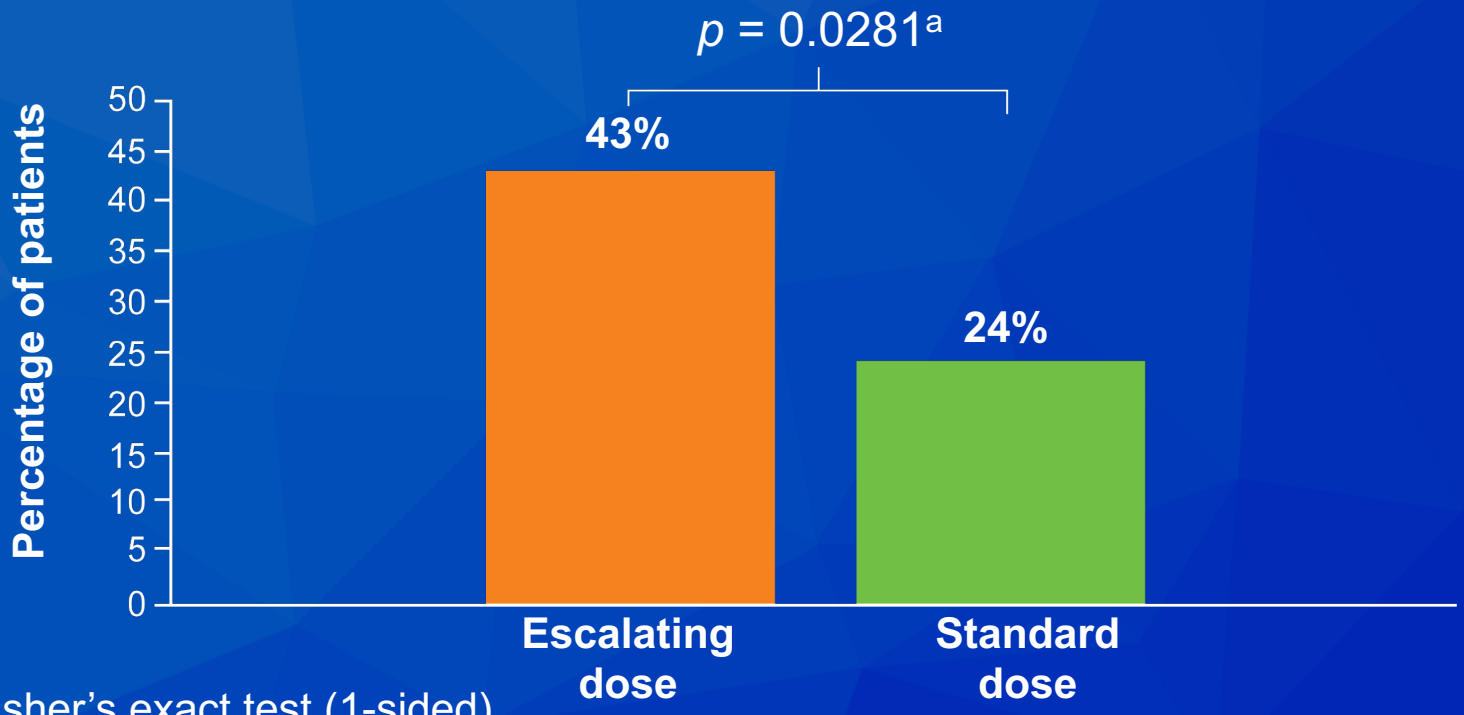


- **Primary endpoint:** Proportion of patients who complete 2 cycles of treatment and initiate cycle 3 in both arms

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

ReDOS: Clinical Outcomes

Proportion of patients starting cycle 3 (N = 116)



[a] Fisher's exact test (1-sided)

Survival	Esc dose (n = 54)	Std 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

Bekaii-Saab TS et al. Gastrointestinal Cancers Symposium 2018;Abstract 611;
Bekaii-Saab TS et al. *Proc ESMO* 2018;Abstract O-014.

ReDOS: Select AEs

Grade 3/4 AE	Escalating dose (n = 54)		Standard dose (n = 62)	
	Grade 3	Grade 4	Grade 3	Grade 4
HFSR	8 (14.8%)	0	10 (16.1%)	0
Abdominal pain	9 (16.7%)	0	4 (6.5%)	0
Hypertension	4 (7.4%)	0	9 (14.5%)	0
Hyponatremia	2 (3.7%)	1 (1.9%)	4 (6.5%)	1 (1.6%)
Dehydration	0	0	5 (8.1%)	0
Dyspnea	1 (1.9%)	1 (1.9%)	3 (4.8%)	0
Lymphopenia	4 (7.4%)	0	0	0
Maculopapular rash	0	0	3 (4.8%)	0

HFSR = hand-foot skin reaction

- Multiple quality of life (QoL) parameters were favorable with the escalating dose vs standard dose strategy primarily at week 2 of cycle 1

Bekaii-Saab TS et al. Gastrointestinal Cancers Symposium 2018;Abstract 611; Bekaii-Saab TS et al. *Proc ESMO* 2018;Abstract O-014.

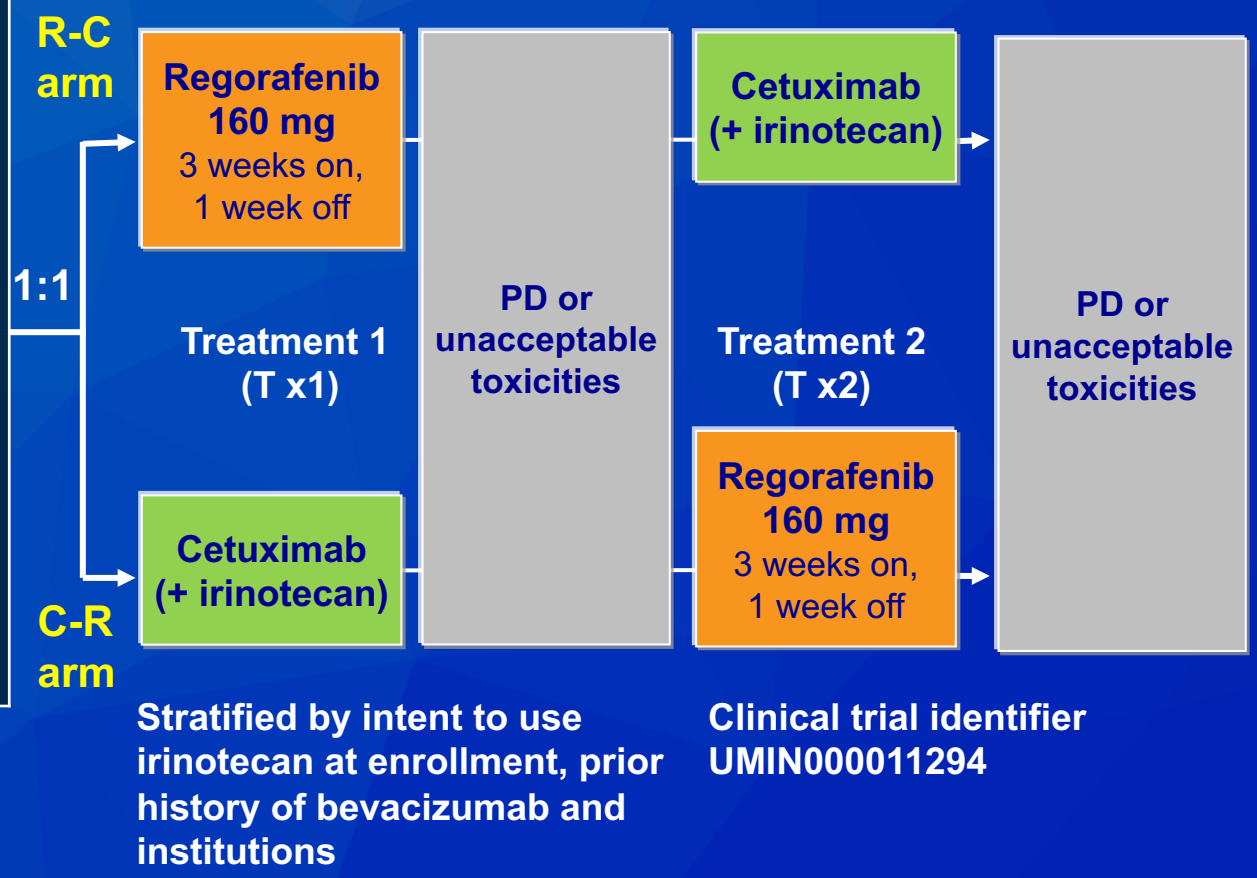
REVERCE: Randomized Phase II Study of Regorafenib Followed by Cetuximab versus the Reverse Sequence for mCRC Patients Previously Treated with Fluoropyrimidine, Oxaliplatin, and Irinotecan

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

REVERCE: Phase II Trial Design

- Metastatic CRC
- Treatment failure with fluoropyrimidines, oxaliplatin and irinotecan
- Anti-EGFR naïve
- *KRAS* exon 2 WT
- Patients with minor *RAS* mutations* are excluded since March 2015

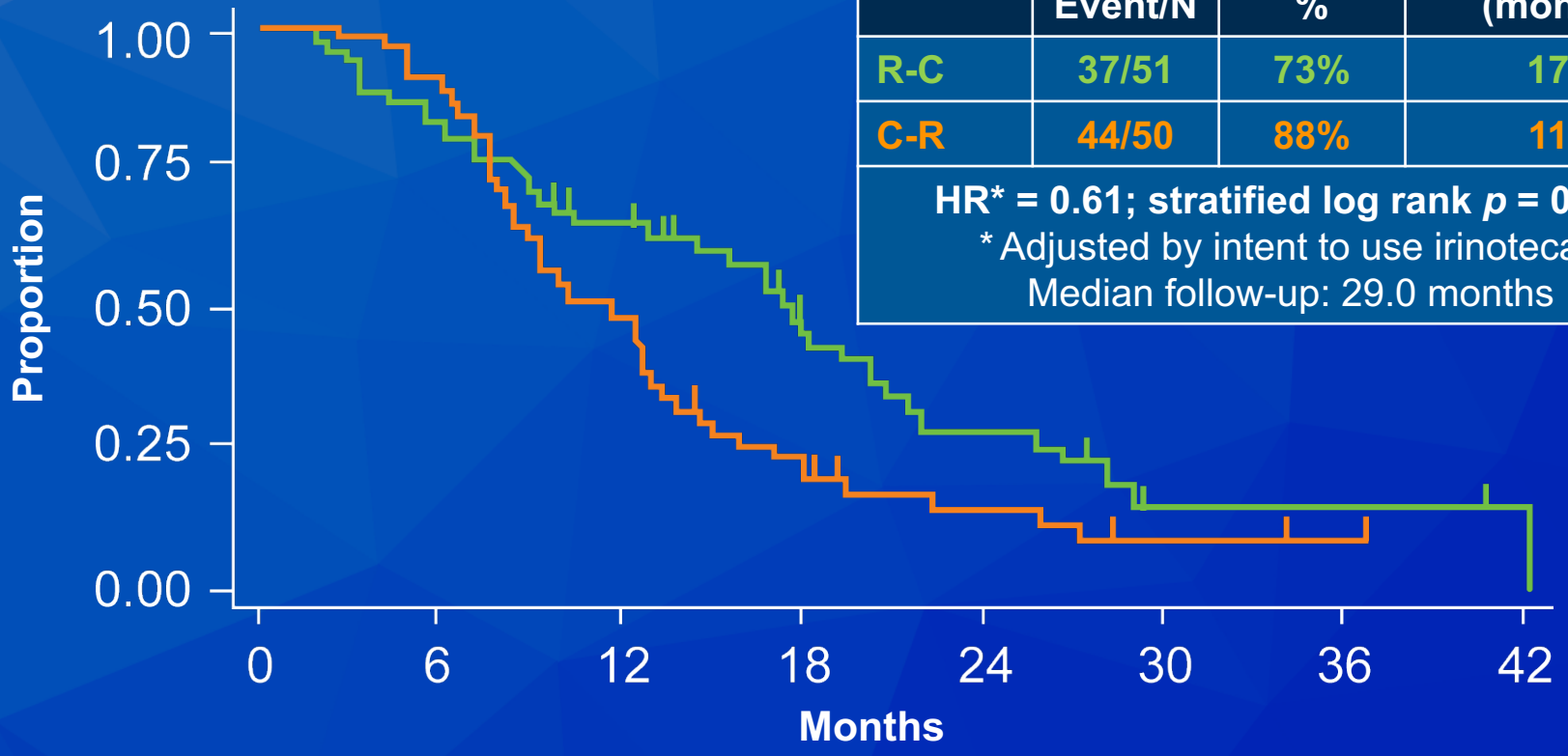
  * *KRAS* exon 3 (codon 59/61), exon 4 (codon 117/146), *NRAS* exon 2 (codon 12/13), exon 3 (codon 59/61) and exon 4 (codon 117/146)



- Primary endpoint: OS
- Secondary endpoints include: TTF, PFS, ORR, DCR, toxicities and QoL
- Enrollment was discontinued in September 2016 due to slow accrual

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

REVERCE: Primary Endpoint (OS)



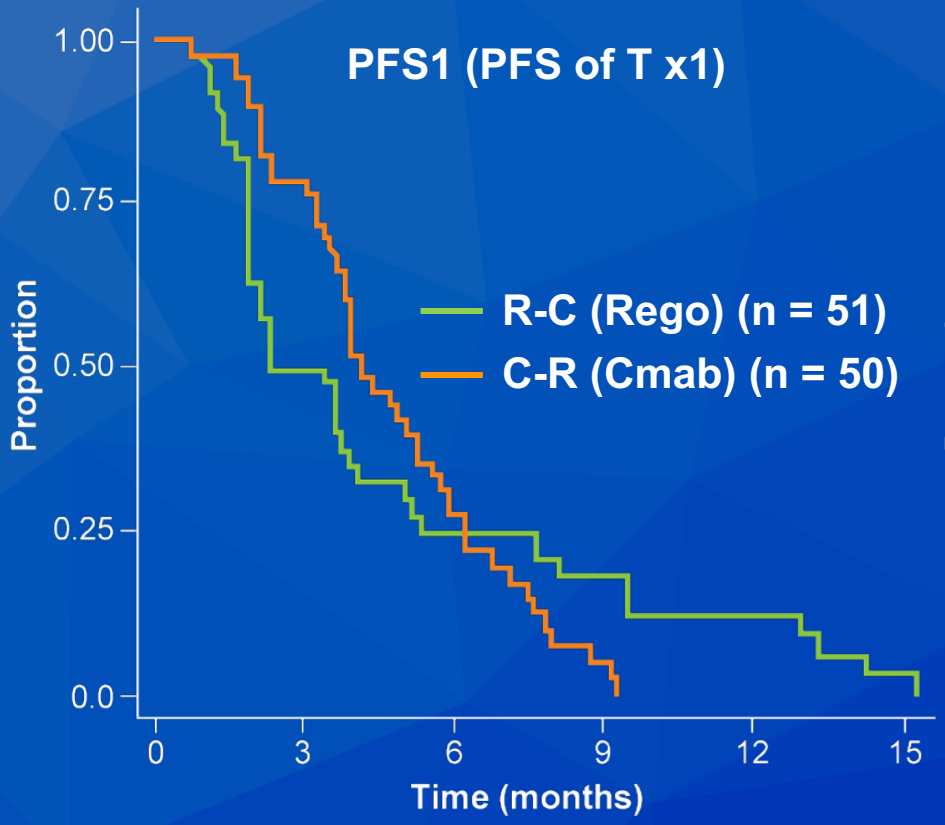
	Event/N	%	Median (months)
R-C	37/51	73%	17.4
C-R	44/50	88%	11.6

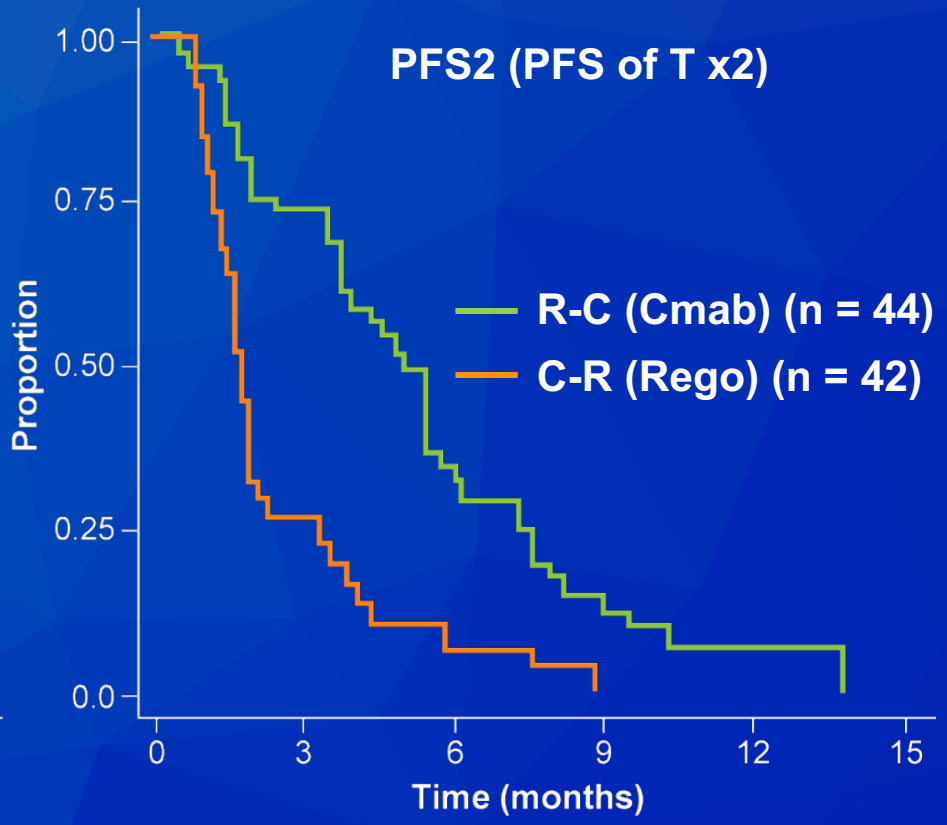
HR* = 0.61; stratified log rank *p* = 0.029
* Adjusted by intent to use irinotecan
Median follow-up: 29.0 months

- OS was longer in the R → C arm compared to the C → R arm and this was consistent across all subgroups:
  - Median OS in left-sided primary (n = 81): 20.5 mo vs 11.9 mo (*p* = 0.011)
  - Median OS in RAS/RAF wild-type dx (n = 86): 18.2 mo vs 12.7 mo (*p* = 0.036)

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

REVERCE: Secondary Endpoints



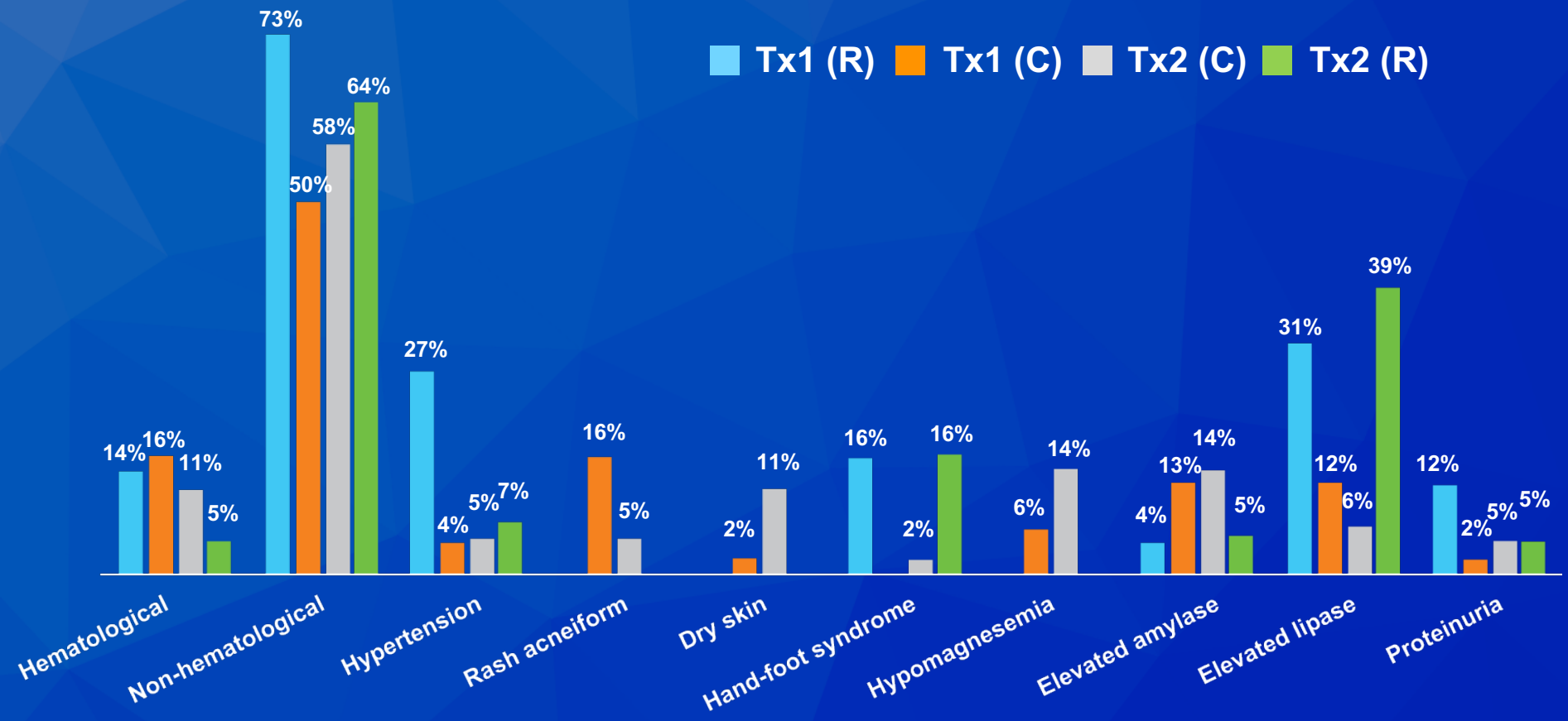


	Event/N	Median (months)
R-C (Rego)	39/51	2.4
C-R (Cmab)	47/50	4.2
HR = 0.97 Stratified log rank *p* = 0.91		

	Event/N	Median (months)
R-C (Cmab)	38/44	5.2
C-R (Rego)	37/43	1.8
HR = 0.29 Stratified log rank *p* < 0.0001		

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

REVERCE: Safety (Grade ≥3 AEs in ≥10% of Patients)



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

- No unexpected safety signals
- Safety and QoL were comparable between the two arms

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

VOLUME 36 · NUMBER 4 · FEBRUARY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

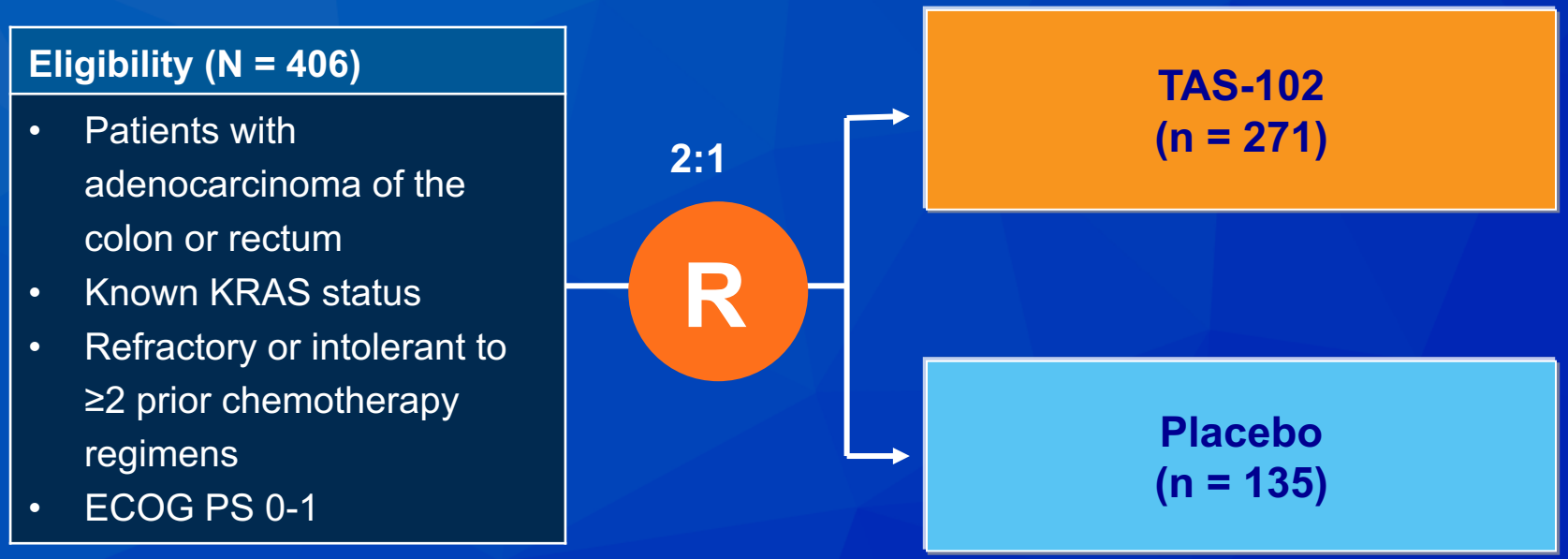
Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study

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

J Clin Oncol 2018;36(4):350-8.

TERRA: Phase III Trial Design

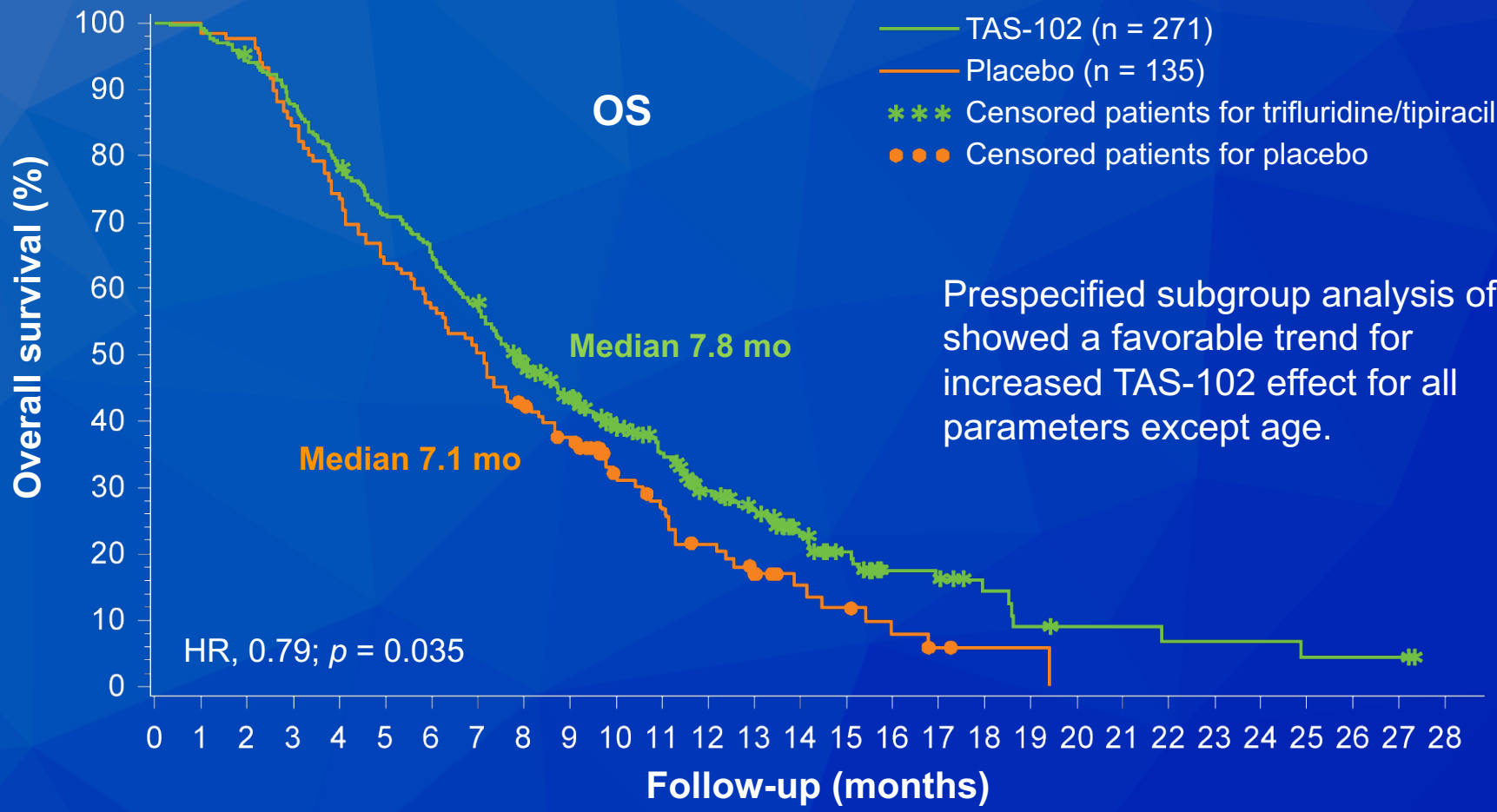
NCT01955837



- **Primary endpoint: OS**

Xu J et al. *J Clin Oncol* 2018;36(4):350-8; Clinicaltrials.gov.

TERRA: Survival and Response in ITT Population



Prespecified subgroup analysis of OS showed a favorable trend for increased TAS-102 effect for all parameters except age.

Survival	TAS-102	Placebo	HR	*p*-value
Median PFS (n = 271, 135)	2.0 mo	1.8 mo	0.43	<0.001
DCR (n = 261, 130)	44.1%	14.6%	—	<0.001

Xu J et al. *J Clin Oncol* 2018;36(4):350-8.

TERRA: Select AEs

Event	TAS-102 (n = 271)		Placebo (n = 135)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	77.1%	17.7%	38.5%	5.9%
Leukopenia	70.1%	20.7%	3.0%	0
Neutropenia	67.2%	33.2%	0.7%	0
Lymphopenia	53.9%	14.4%	25.2%	2.2%
Increased total bilirubin	36.5%	7.0%	20.7%	7.4%
Thrombocytopenia	35.4%	3.0%	7.4%	1.5%
Fatigue	20.3%	1.5%	6.7%	0
Bone marrow failure	1.8%	1.1%	0	0

No treatment-related deaths were reported.

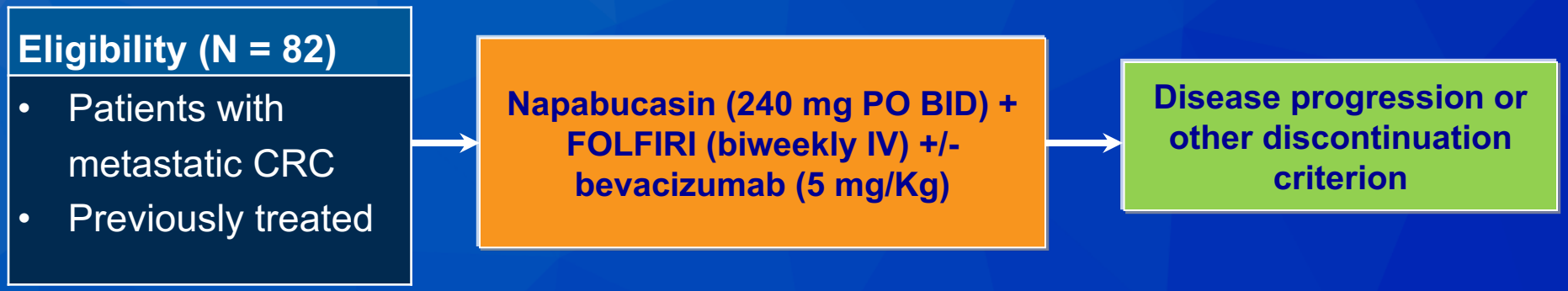
Xu J et al. *J Clin Oncol* 2018;36(4):350-8.

Phase Ib/II Study of Cancer Stemness Inhibitor Napabucasin in Combination with FOLFIRI ± Bevacizumab in mCRC Patients

Bendell J et al.

Proc ESMO 2017;Abstract LBA-003.

Phase Ib/II Trial Design



- **Endpoints:** Recommended Phase II dose (R2PD) and activity
- There was no dose-limiting or unexpected toxicity or significant PK interactions.

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

Phase Ib/II Trial: Response

All patients	ORR	DCR
ITT (n = 82)	14 (17%)	55 (67%)
Evaluable (n = 66)	14 (21%)	55 (83%)
≥Second-line FOLFIRI-naïve	**ORR**	**DCR**
ITT (n = 50)	8 (16%)	33 (66%)
Evaluable (n = 39)	8 (21%)	33 (85%)
≥Second-line FOLFIRI-pretreated	**ORR**	**DCR**
ITT (n = 82)	6 (19%)	22 (69%)
Evaluable (n = 66)	6 (22%)	22 (81%)

Napabucasin with or without bevacizumab showed encouraging signs of efficacy in patients with pretreated mCRC including those pretreated with FOLFIRI +/- bevacizumab

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

Phase Ib/II Trial: Treatment-Emergent AEs

Event (n = 82)	Grade 3
Diarrhea	15 (18%)
Fatigue	6 (7%)
Hypokalemia	2 (2%)
Hyponatremia	1 (1%)
Hypophosphatemia	1 (1%)
Dehydration	1 (1%)
Abdominal pain	1 (1%)
Vomiting	1 (1%)
Weight loss	1 (1%)

- The most common AEs included Grade 1/2 diarrhea, cramping, nausea, vomiting, fatigue and anorexia.
- Grade 4 diarrhea was observed in 1 patient.
- All AEs resolved with dose reduction and supportive care.

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

The NEW ENGLAND JOURNAL of MEDICINE

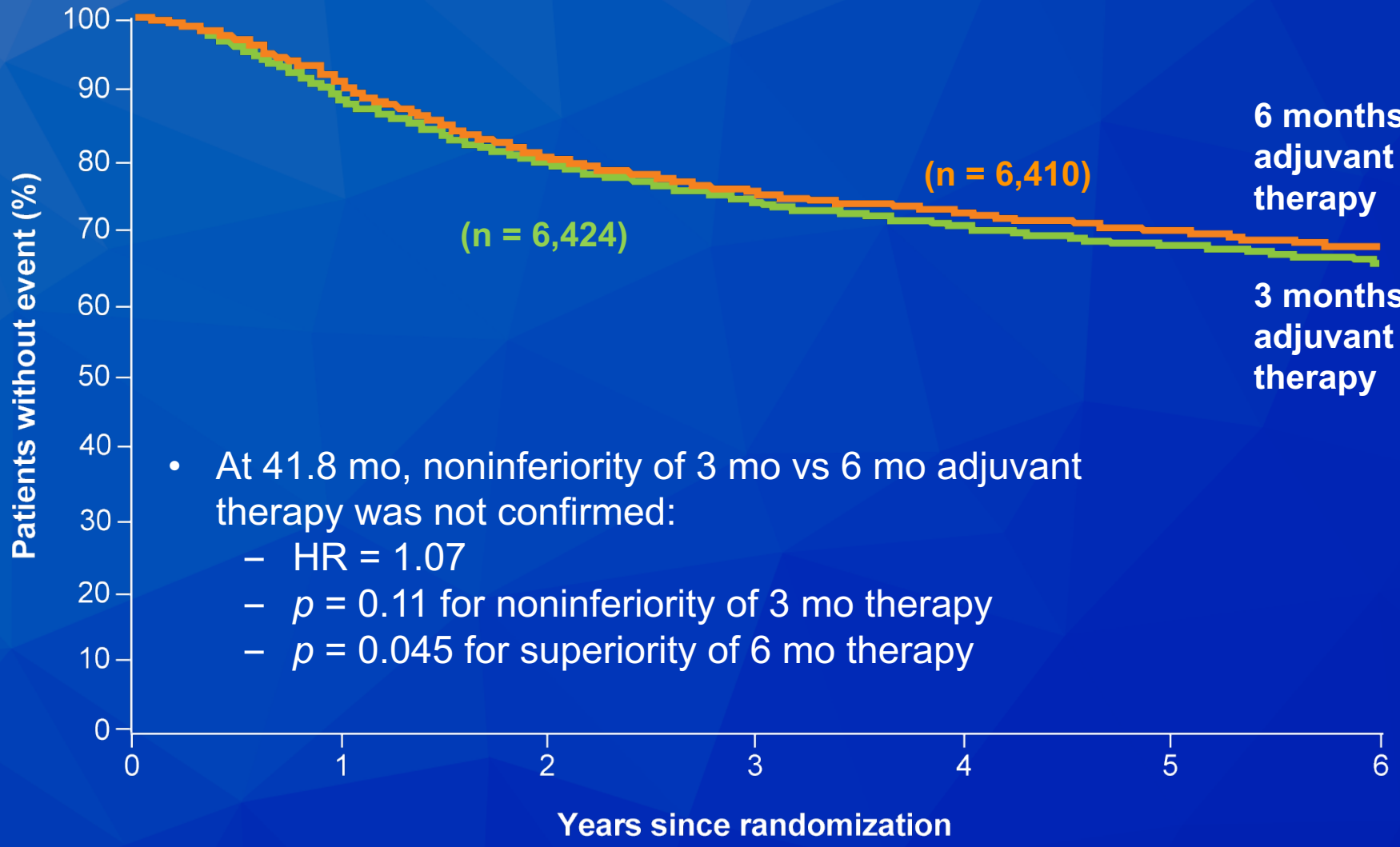
ESTABLISHED IN 1812 MARCH 29, 2018 VOL. 378 NO. 13

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

A. Grothey, A.F. Sobrero, A.F. Shields, T. Yoshino, J. Paul, J. Taieb, J. Souglakos, Q. Shi, R. Kerr, R. Labianca, J.A. Meyerhardt, D. Vernerey, T. Yamanaka, I. Boukovinas, J.P. Meyers, L.A. Renfro, D. Niedzwiecki, T. Watanabe,* V. Torri, M. Saunders, D.J. Sargent,* T. Andre, and T. Iveson

N Engl J Med 2018;378(13):1177-88.

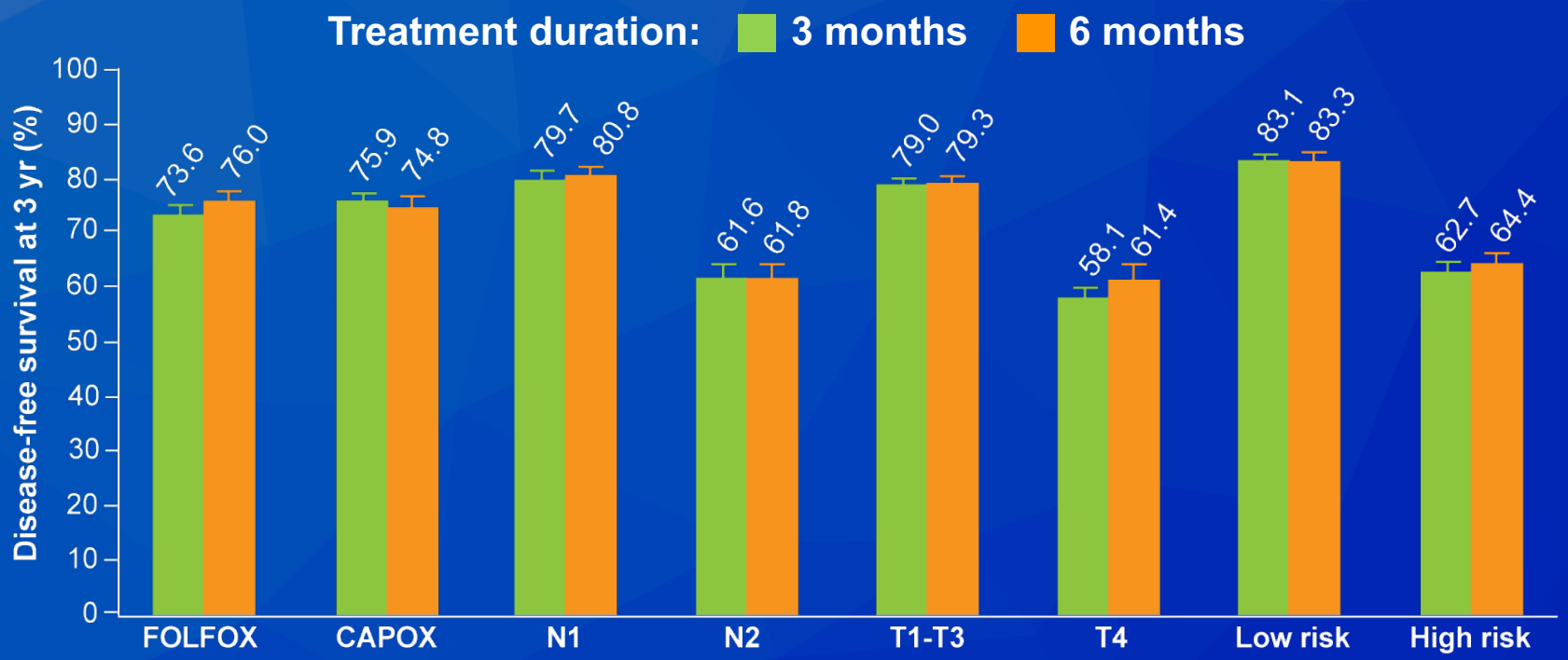
Pooled Analysis of 6 Randomized Phase III Trials: Disease-Free Survival (DFS) in Overall Population



- At 41.8 mo, noninferiority of 3 mo vs 6 mo adjuvant therapy was not confirmed:
  - HR = 1.07
  - *p* = 0.11 for noninferiority of 3 mo therapy
  - *p* = 0.045 for superiority of 6 mo therapy

Grothey A et al. *N Engl J Med* 2018;378(13):1177-88.

3-Year DFS in the Overall Population and By Subgroup



	FOLFOX	CAPOX	N1	N2	T1-T3	T4	Low risk	High risk
No. of patients	7,763	5,071	9,168	3,567	10,090	2,655	7,471	5,256
Hazard ratio 3 vs 6 mo	1.16	0.95	1.07	1.07	1.04	1.16	1.01	1.12

3-year DFS	3 mo (n = 6,424)	6 mo (n = 6,410)	HR	*p*-value
Overall population	74.6%	75.5%	Not reported	Not reported

Grothey A et al. *N Engl J Med* 2018;378(13):1177-88.

Select Adverse Events (AEs) According to Treatment and Duration of Therapy

Grade 3/4 AEs	FOLFOX		CAPOX	
	3 mo	6 mo	3 mo	6 mo
Peripheral sensory neurotoxicity	2.5%	15.9%	2.6%	8.9%
Diarrhea	4.7%	7.2%	7.4%	8.8%
Neutropenia	20.3%	26.6%	7.7%	11.9%
Thrombocytopenia	1.0%	1.8%	2.1%	4.2%
Nausea	1.6%	2.2%	3.0%	3.1%
Mucositis	0.7%	1.6%	0.3%	0.9%
Hand-foot syndrome	0	0.3%	0.7%	2.6%

Grothey A et al. *N Engl J Med* 2018;378(13):1177-88.

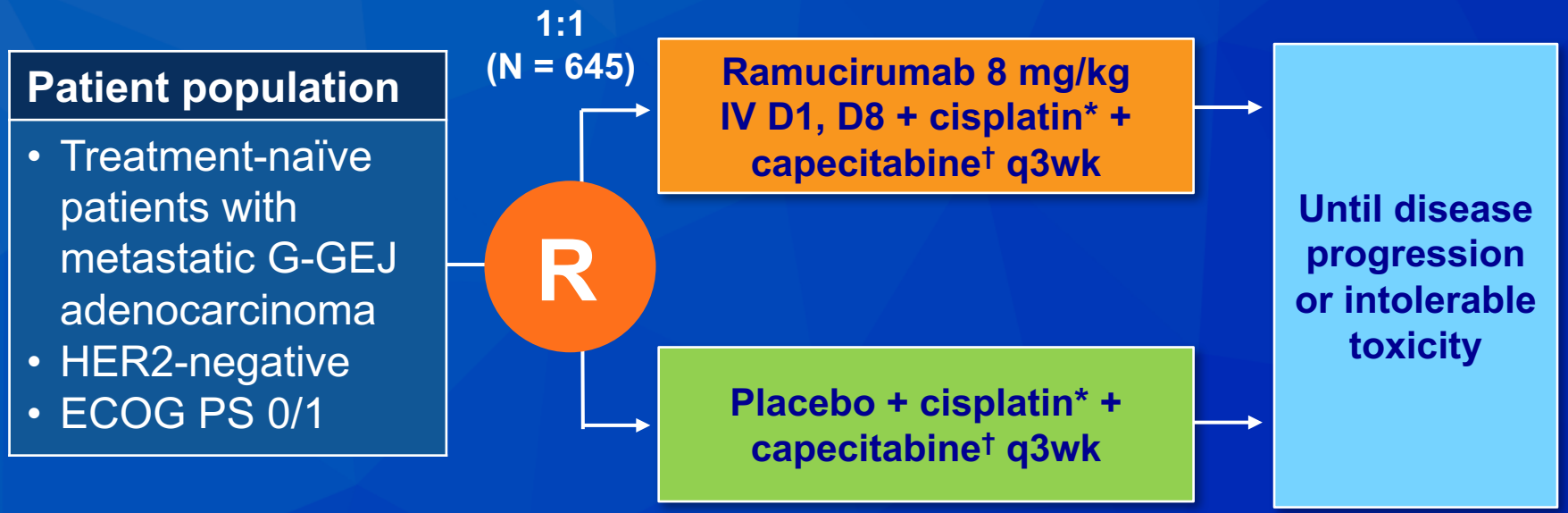
Gastric Cancer

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: Phase III Trial Design

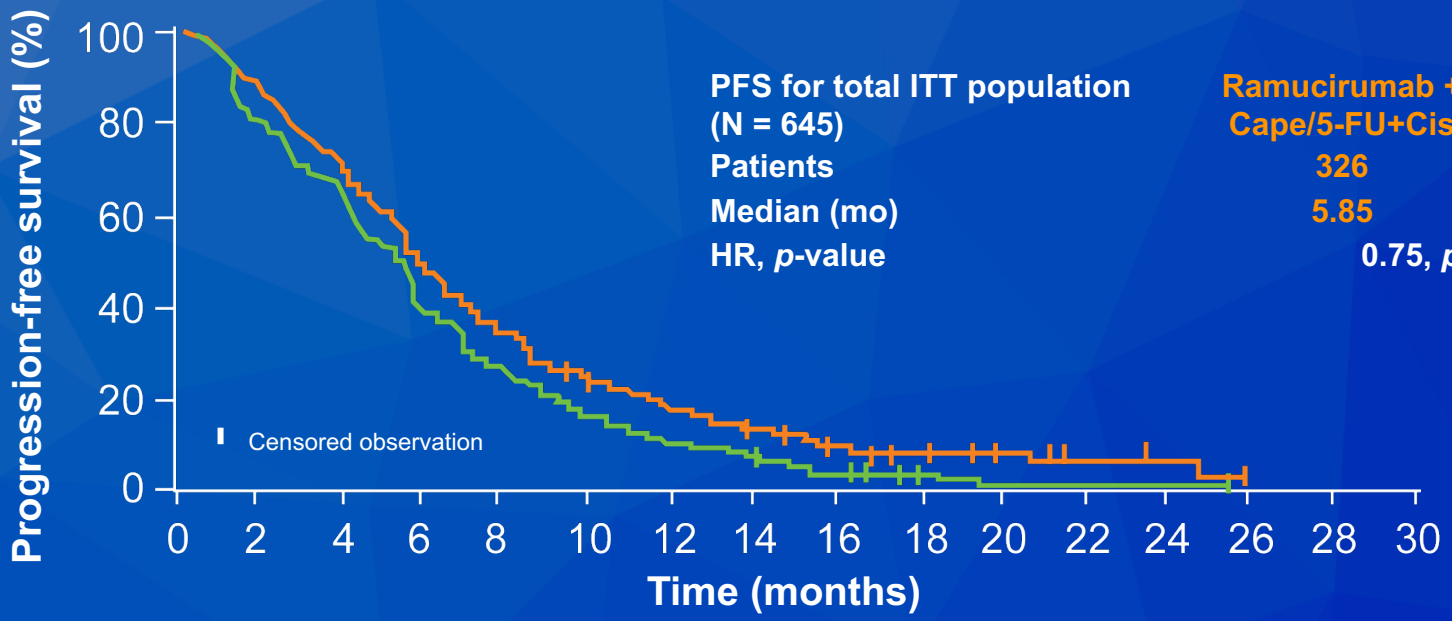


* Cisplatin 80 mg/m^2 d1 (IV), maximum of 6 cycles
† Capecitabine 1,000 mg/m^2 BID (PO)
† 5-FU 800 mg/m^2 d1-5 (IV) was allowed for patients unable to swallow capecitabine

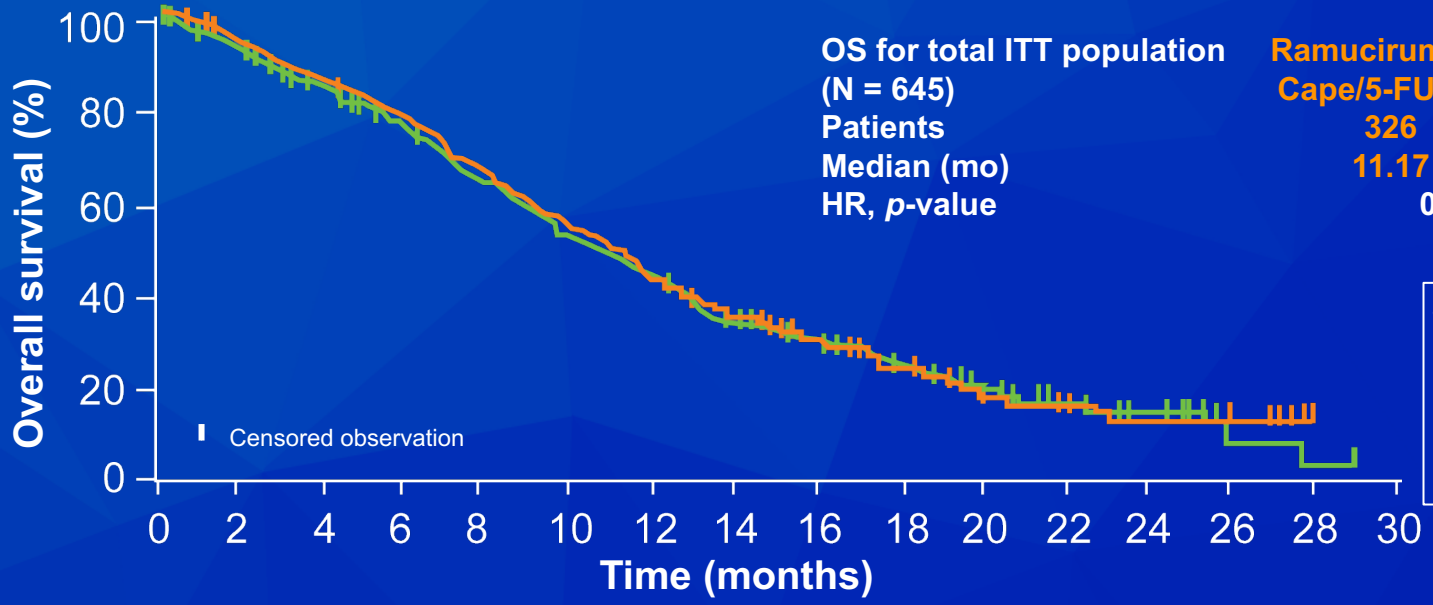
- **Primary endpoint:** PFS

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

RAINFALL: Survival and Response in ITT Population



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	

- Best overall response rate = 41% (ramucirumab) vs 36% (placebo), *p* = 0.1696

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

RAINFALL: Select AEs in ≥5% of Patients

Event	Ramucirumab/Cape/5-FU/Cis (n = 323)		Placebo/Cape/5-FU/Cis (n = 315)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	54%	26%	53%	27%
Decreased appetite	41%	6.5%	32%	3.2%
Anemia	34%	12%	37%	14%
Thrombocytopenia	34%	7.7%	19%	3.5%
Hand-foot syndrome	31%	8.7%	20%	3.8%
Bleeding events*	25%	3.4%	14%	4.1%
Hypertension	22%	9.9%	7.3%	1.6%
Proteinuria	19%	2.5%	11%	0.6%

* Includes hemorrhagic events

No new or unexpected safety findings emerged.

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

Safety and Efficacy of Pembrolizumab Monotherapy in Patients with Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial

Pembrolizumab (Pembro) vs Paclitaxel (PTX) for Previously Treated Advanced Gastric or Gastroesophageal Junction (G/GEJ) Cancer: Phase 3 KEYNOTE-061 Trial

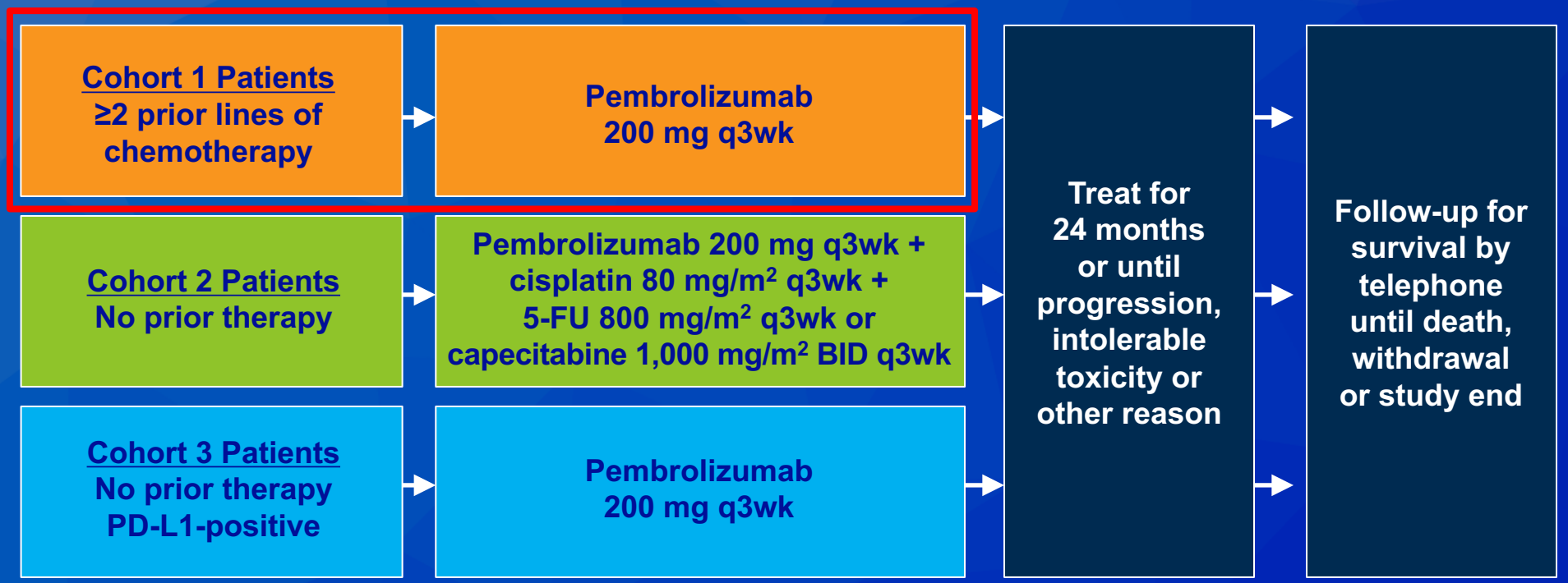
Pembrolizumab versus Paclitaxel for Previously Treated, Advanced Gastric or Gastro-Oesophageal Junction Cancer (KEYNOTE-061): A Randomised, Open-Label, Controlled, Phase 3 Trial

Fuchs CS et al.
JAMA Oncol 2018;[Epub ahead of print].

Fuchs CS et al.
Proc ASCO 2018;Abstract 4062.

Shitara K et al.
Lancet 2018;[Epub ahead of print].

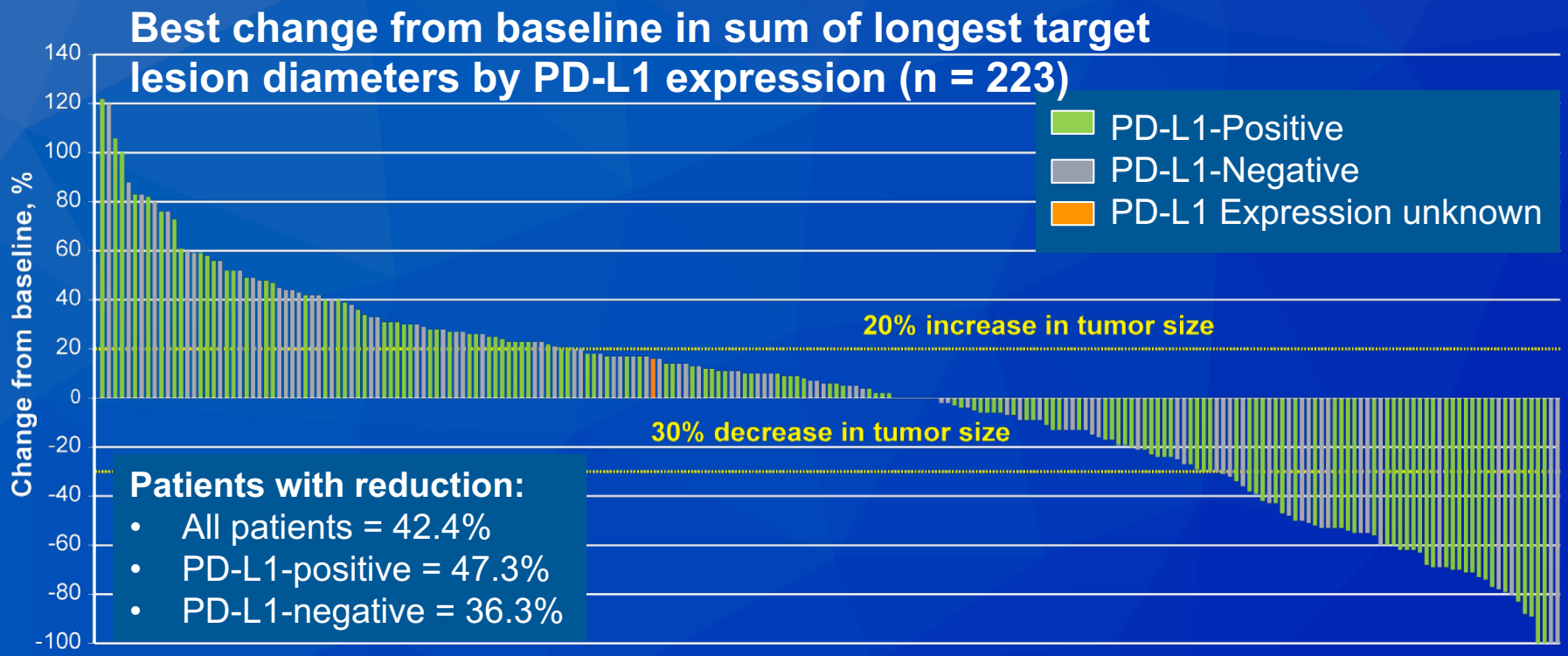
KEYNOTE-059: Phase II Multicohort Trial Design



- **Endpoints:** Response, survival and safety
- Response assessments by RECISTv1.1: First scan at 9 weeks after cycle 1, then every 6 weeks for the first year, followed by every 9 weeks

Fuchs CS et al. *JAMA Oncol* 2018;[Epub ahead of print]; Fuchs CS et al. *Proc ASCO* 2017;Abstract 4003.

KEYNOTE-059 (Cohort 1): Survival and Response



Clinical outcome	N = 259
Objective response rate	30 (11.6%)
Disease control rate	70 (27.0%)
Median PFS	2.0 mo
Median OS	5.6 mo

Fuchs CS et al. *JAMA Oncol* 2018;[Epub ahead of print]; Fuchs CS et al. *Proc ASCO* 2017;Abstract 4003.

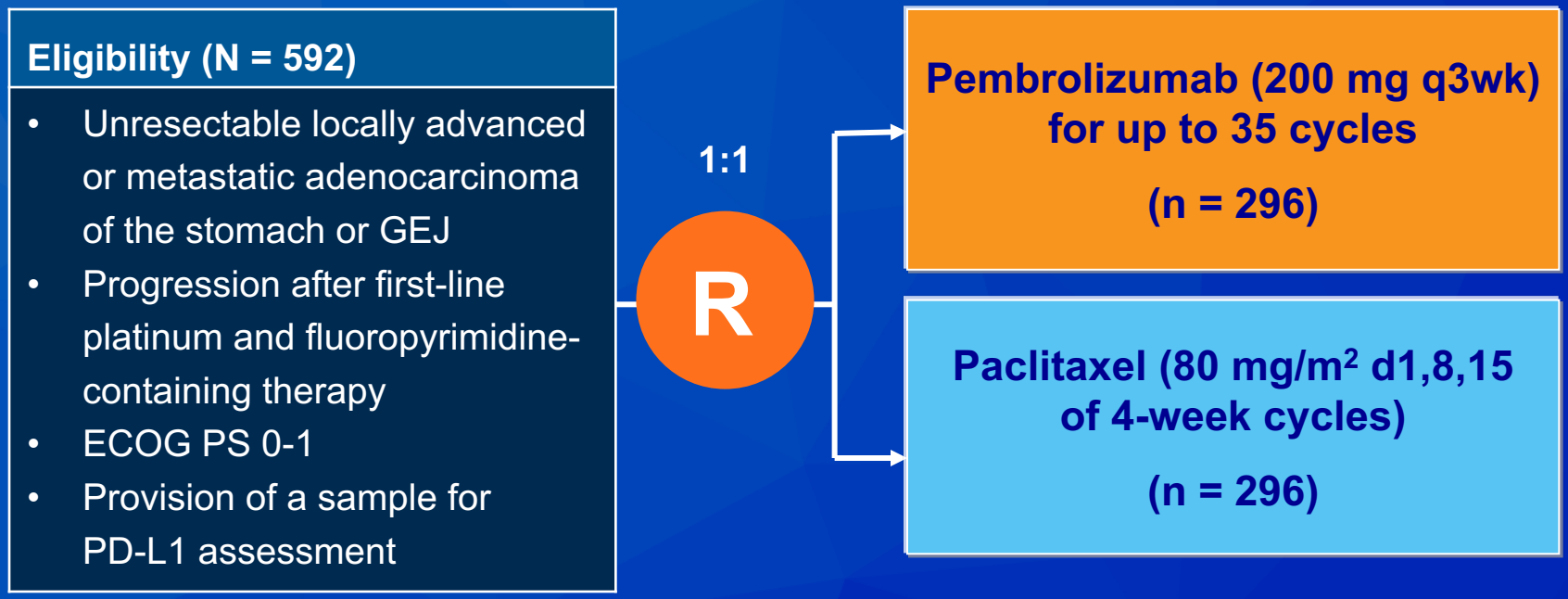
KEYNOTE-059 (Cohort 1): Select AEs (N = 259)

Treatment-related AEs	Any grade	Grade 3/4
Fatigue	18.9%	2.3%
Rash	8.5%	0.8%
Anemia	6.9%	2.7%
Nausea	6.9%	0.8%
Diarrhea	6.6%	1.2%
Immune-mediated AEs	**Any grade**	**Grade 3/4**
Hypothyroidism	8.9%	0.4%
Colitis	2.3%	1.2%
Pneumonitis	1.9%	0.8%
Severe skin reactions	1.5%	1.5%

- Patients who received corticosteroids for immune-mediated AEs: 13
- Patients who experienced drug interruption due to immune-mediated AEs: 10

Fuchs CS et al. *JAMA Oncol* 2018;[Epub ahead of print]; Fuchs CS et al. *Proc ASCO* 2017;Abstract 4003.

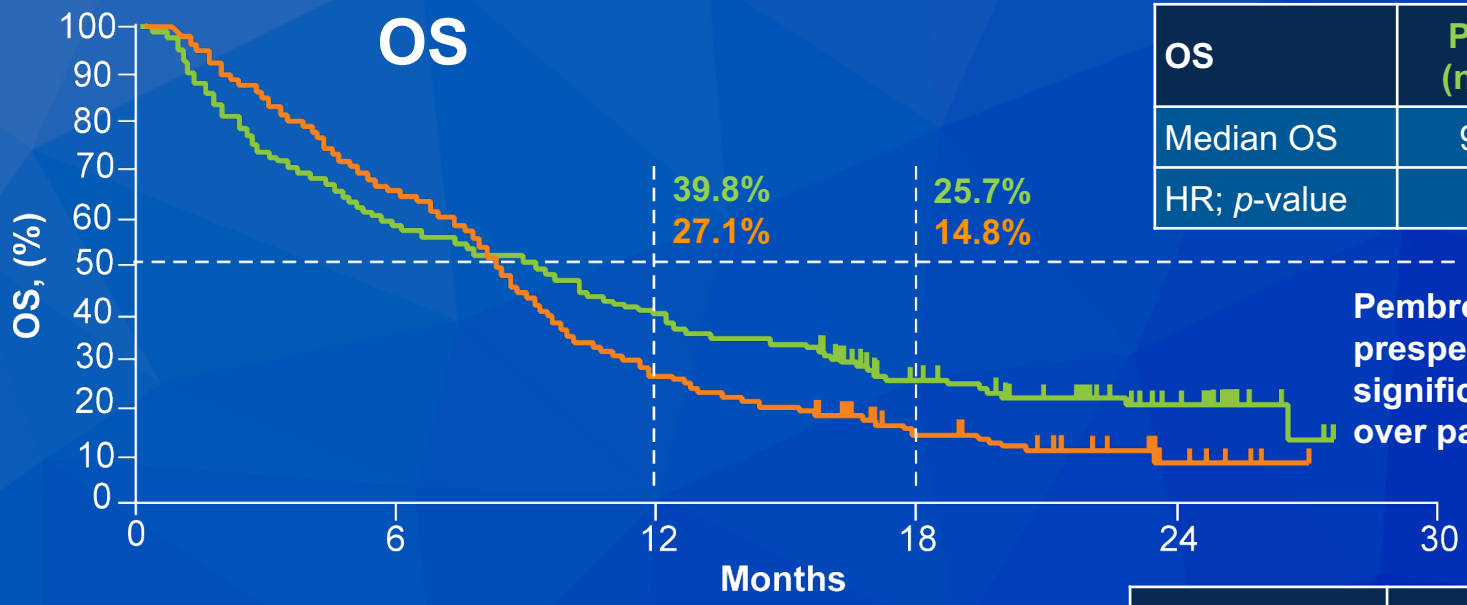
KEYNOTE-061: Phase III Trial Design



- **Primary endpoints: OS and PFS in the CPS ≥1 population**
- Prior to randomization, patients were stratified by geographic location, ECOG PS, time to progression on first-line therapy and PD-L1 CPS.

Fuchs CS et al. *Proc ASCO* 2018;Abstract 4062; Shitara K et al. *Lancet* 2018;[Epub ahead of print].

KEYNOTE-061: Survival and Response (CPS ≥1)



OS	Pembro (n = 196)	Paclitaxel (n = 199)
Median OS	9.1 mo	8.3 mo
HR; *p*-value	0.82; 0.0421	

Pembro did not reach the prespecified level of statistical significance for improving OS over paclitaxel.

PFS	Pembro (n = 196)	Paclitaxel (n = 199)
Median PFS	1.5 mo	4.1 mo
HR; *p*-value	1.27; NR	

Response rate:

- Pembro = 15.8%
- Paclitaxel = 13.6%

Fuchs CS et al. *Proc ASCO* 2018;Abstract 4062; Shitara K et al. *Lancet* 2018;[Epub ahead of print].

KEYNOTE-061: Select AEs in the Overall Population

Event	Pembrolizumab (n = 294)		Paclitaxel (n = 276)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	35 (12%)	7 (2%)	64 (23%)	13 (5%)
Decreased appetite	24 (8%)	2 (<1%)	43 (16%)	0
Hypothyroidism	23 (8%)	0	1 (<1%)	0
Nausea	17 (6%)	1 (<1%)	50 (18%)	2 (<1%)
Hyperthyroidism	12 (4%)	0	1 (<1%)	0
Anemia	10 (3%)	7 (2%)	39 (14%)	12 (4%)
Pneumonitis	8 (3%)	2 (<1%)	0	0
Colitis	3 (1%)	1 (<1%)	4 (1%)	3 (1%)
Peripheral neuropathy	1 (<1%)	0	40 (14%)	6 (2%)
Alopecia	1 (<1%)	0	111 (40%)	3 (1%)

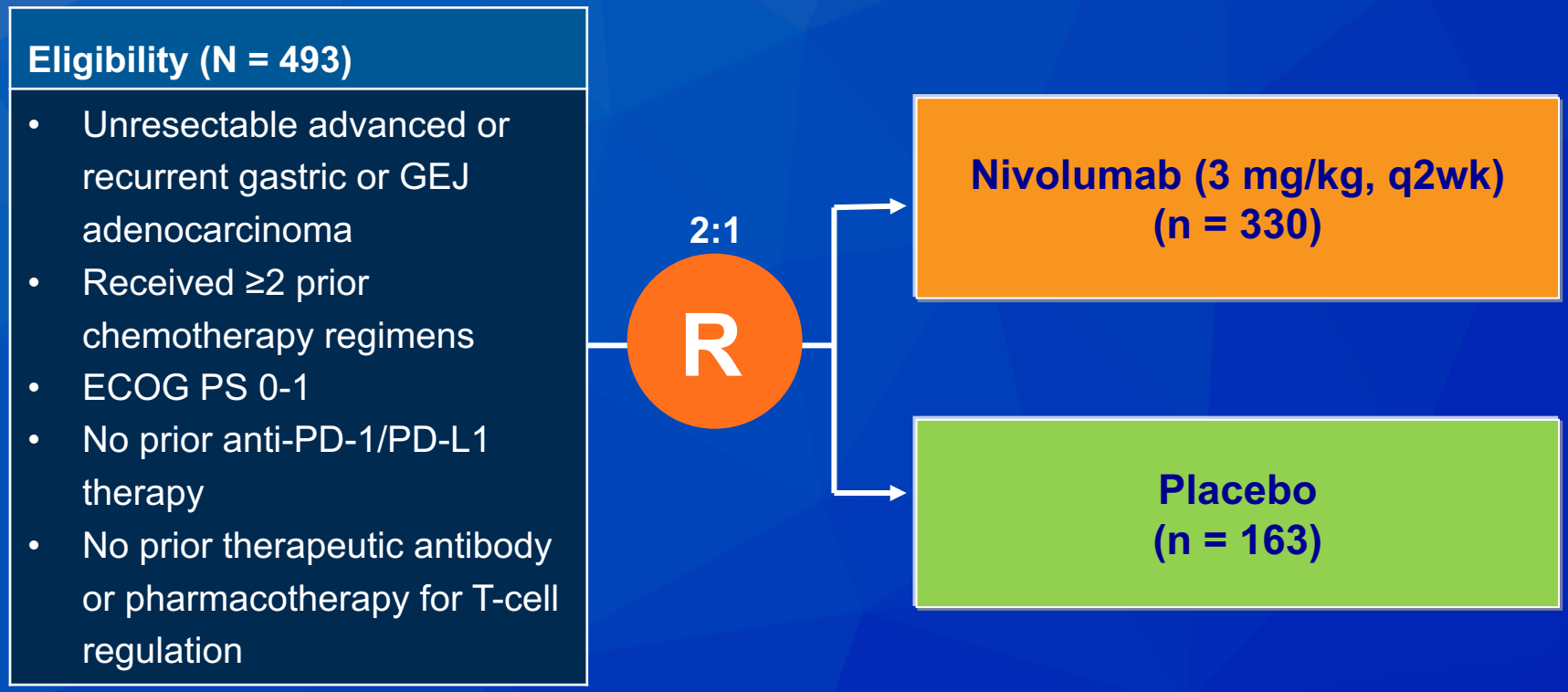
Shitara K et al. *Lancet* 2018;[Epub ahead of print].

Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial

Yoon-Koo Kang, Narikazu Boku, Taroh Satoh, Min-Hee Ryu, Yee Chao, Ken Kato, Hyun Cheol Chung, Jen-Shi Chen, Kei Muro, Won Ki Kang, Kun-Huei Yeh, Takaki Yoshikawa, Sang Cheul Oh, Li-Yuan Bai, Takao Tamura, Keun-Wook Lee, Yasuo Hamamoto, Jong Gwang Kim, Keisho Chin, Do-Youn Oh, Keiko Minashi, Jae Yong Cho, Masahiro Tsuda, Li-Tzong Chen

Lancet 2017;390(10111):2461-71.

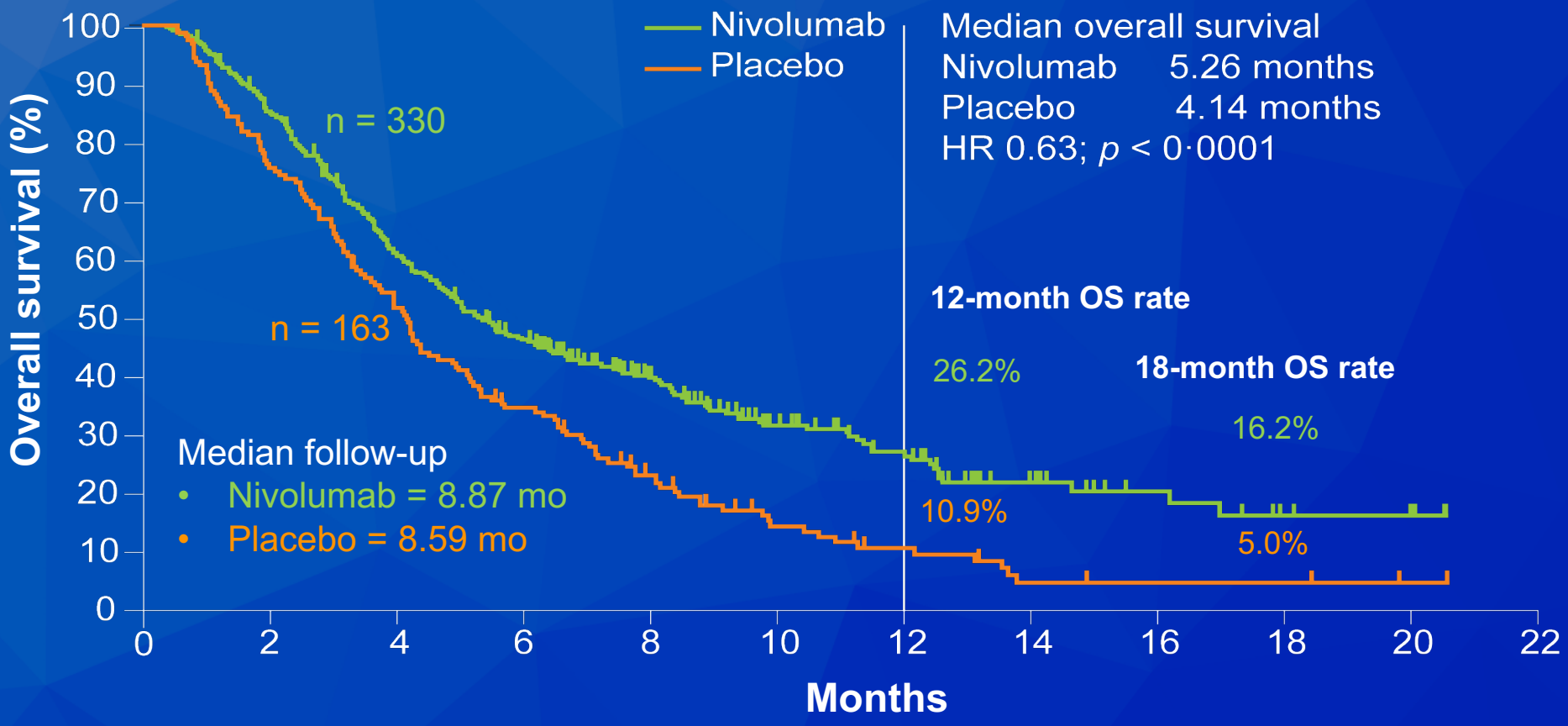
ATTRACTION-02: Phase III Trial Design



- **Primary endpoint: OS in the ITT population**
- Prior to randomization, patients were stratified by country, ECOG PS and the number of organs with metastases.

Kang YK et al. *Lancet* 2017;390(10111):2461-71.

ATTRACTION-02: Survival and Response



Outcome	Nivolumab	Placebo	HR	*p*-value
Median PFS (n = 330, 163)	1.61 mo	1.45 mo	0.60	<0.0001
Objective response (n = 268, 131)	30 (11.2%)	0	—	NR

Kang YK et al. *Lancet* 2017;390(10111):2461-71.

ATTRACTION-02: Select Treatment-Related AEs

Event	Nivolumab (n = 330)		Placebo (n = 161)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Pruritus	30 (9%)	0	9 (6%)	0
Diarrhea	23 (7%)	2 (1%)	3 (2%)	0
Decreased appetite	16 (5%)	4 (1%)	7 (4%)	1 (1%)
ILD	6 (2%)	1 (<1%)	0	0
Maculopapular rash	4 (1%)	0	1 (<1%)	0
Colitis	2 (1%)	1 (<1%)	0	0
Hypothyroidism	2 (1%)	0	0	0
Pneumonitis	1 (<1%)	1 (<1%)	0	0

ILD = interstitial lung disease

- Treatment-related AEs leading to death: Nivolumab (2%) vs placebo (1%).
- No new safety signals were observed.

Kang YK et al. *Lancet* 2017;390(10111):2461-71.

Overall Survival Results from a Phase III Trial of Trifluridine/Tipiracil versus Placebo in Patients with Metastatic Gastric Cancer Refractory to Standard Therapies (TAGS)

Tabernero J et al.

Proc ESMO GI 2018;Abstract LBA-002.

TAGS: Phase III Trial Design

NCT02500043

- **Primary endpoint: OS in the ITT population**
- Prior to randomization, patients were stratified by geographic region (Japan vs rest of the world), ECOG PS (0 vs 1) and prior treatment with ramucirumab.

Tabernero J et al. *Proc ESMO GI* 2018;Abstract LBA-002; Clinicaltrials.gov.

TAGS: Survival and Safety Outcomes

Outcome*	TAS-102 (n = 337)	Placebo (n = 170)	HR	*p*-value
Median OS	5.7 mo	3.6 mo	0.69	0.0003
12-mo OS	21.2%	13.0%		
Median PFS	2.0 mo	1.8 mo	0.57	<0.0001
4-mo PFS	26.8%	7.7%		
6-mo PFS	14.6%	6.4%		

* At data cutoff (31 March 2018)

- Grade ≥3 AEs occurred in 266 (79.4%) for TAS-102 vs 97 (57.7%) for placebo
- Grade 3/4 hematologic AEs with TAS-102 include: Neutropenia (38.1%), leukopenia (21.0%), anemia (18.6%) and lymphopenia (18.9%).
  - Of the 38.1% who experienced Grade 3/4 neutropenia, 6 (1.8%) experienced febrile neutropenia.
- No new safety signals were observed.

Tabernero J et al. *Proc ESMO GI* 2018;Abstract LBA-002.

Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial

Annemieke Cats*, Edwin P M Jansen*, Nicole C T van Grieken, Karolina Sikorska, Pehr Lind, Marianne Nordsmark, Elma Meershoek-Klein Kranenbarg, Henk Boot, Anouk K Trip, H A Maurits Swellengrebel, Hanneke W M van Laarhoven, Hein Putter, Johanna W van Sandick, Mark I van Berge Henegouwen, Henk H Hartgrink, Harm van Tinteren, Cornelis J H van de Velde†, Marcel Verheij†, for the CRITICS investigators‡

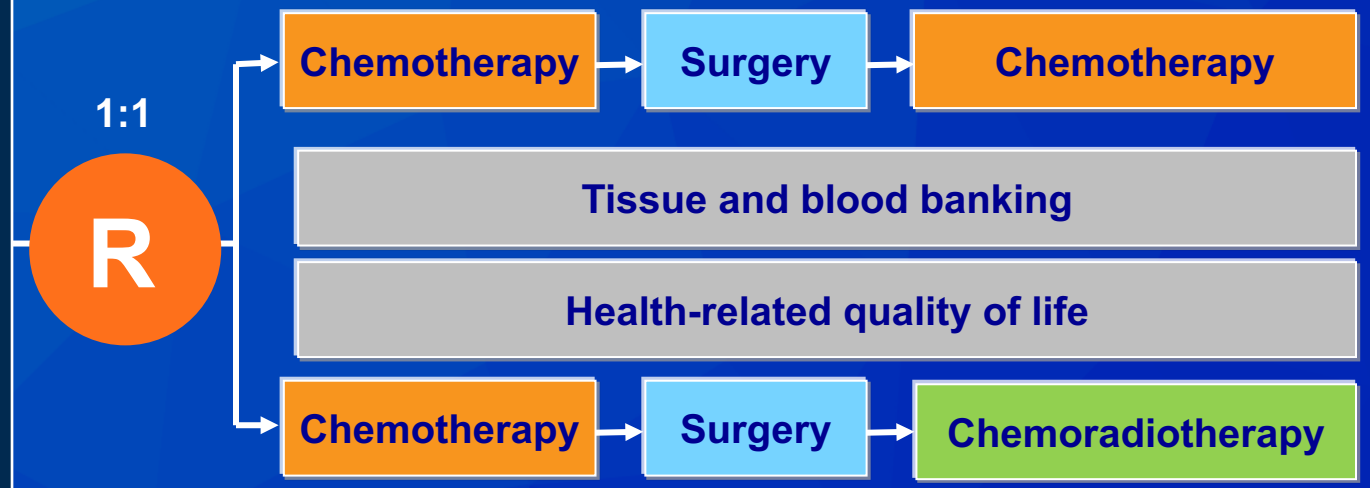
Lancet Oncol 2018;19(5):616-28.

CRITICS: Phase III Adjuvant Trial Design

NCT00407186

Eligibility (N = 788)

- Stage Ib-IVa resectable gastric adenocarcinoma
- No distant metastases
- Localized disease in the stomach or GEJ with the tumor bulk in the stomach
- Performance status WHO 0-1

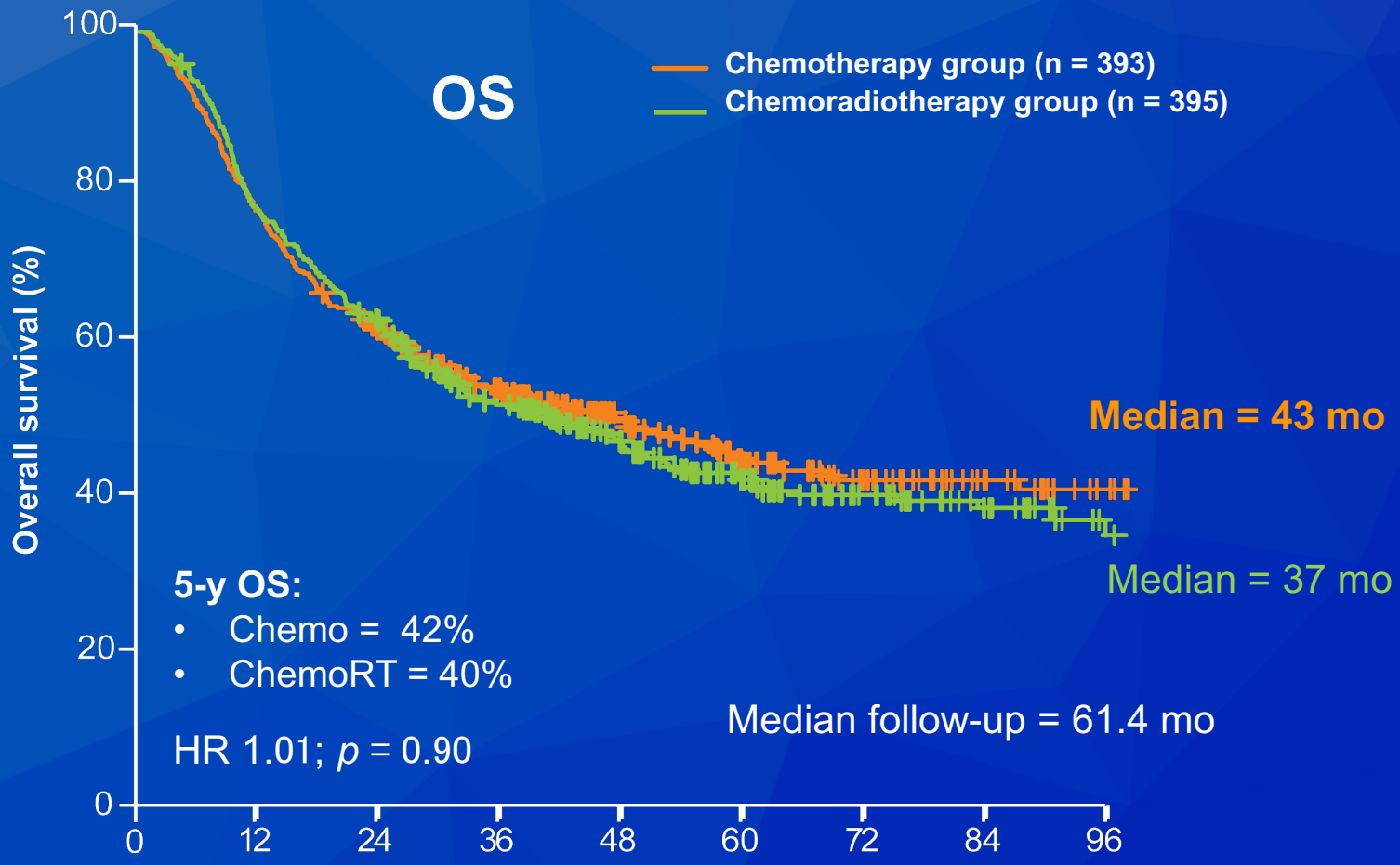


Chemotherapy includes: Epirubicin, cisplatin, oxaliplatin and capecitabine

- **Primary endpoint: OS in the ITT population**

Cats A et al. *Lancet Oncol* 2018;19(5):616-28; Verheij M et al. *Proc ASCO* 2016;Abstract 4000.

CRITICS: Survival Outcomes



Outcome	Chemo (n = 393)	ChemoRT (n = 395)	HR	*p*-value
Median EFS	28 mo	25 mo	0.99	0.92
5-y EFS	39%	38%		

Cats A et al. *Lancet Oncol* 2018;19(5):616-28.

CRITICS: Select Treatment-Related AEs

Grade 3-5 AE	Preop chemo* (n = 781)	Postop chemo (n = 233)	Postop chemoRT (n = 245)
Neutropenia	250 (32%)	79 (34%)	11 (4%)
Diarrhea*	102 (13%)	13 (6%)	8 (3%)
Infection without neutropenia*	67 (9%)	10 (4%)	14 (6%)
Thromboembolic event	65 (8%)	5 (2%)	3 (1%)
Mucositis/stomatitis	32 (4%)	6 (3%)	2 (<1%)
Anemia	24 (3%)	1 (<1%)	2 (<1%)
GI obstruction*	10 (1%)	2 (<1%)	2 (<1%)
Cardiac arrhythmia*	6 (<1%)	0	0
Thrombocytopenia	5 (<1%)	1 (<1%)	4 (2%)
Sudden death*	1 (<1%)	0	0

* Includes Grade 5 AEs

Cats A et al. *Lancet Oncol* 2018;19(5):616-28.

Pancreatic Cancer

Unicancer GI PRODIGE 24/CCTG PA.6 Trial: A Multicenter International Randomized Phase III Trial of Adjuvant mFOLFIRINOX versus Gemcitabine (gem) in Patients with Resected Pancreatic Ductal Adenocarcinomas

Conroy T et al.

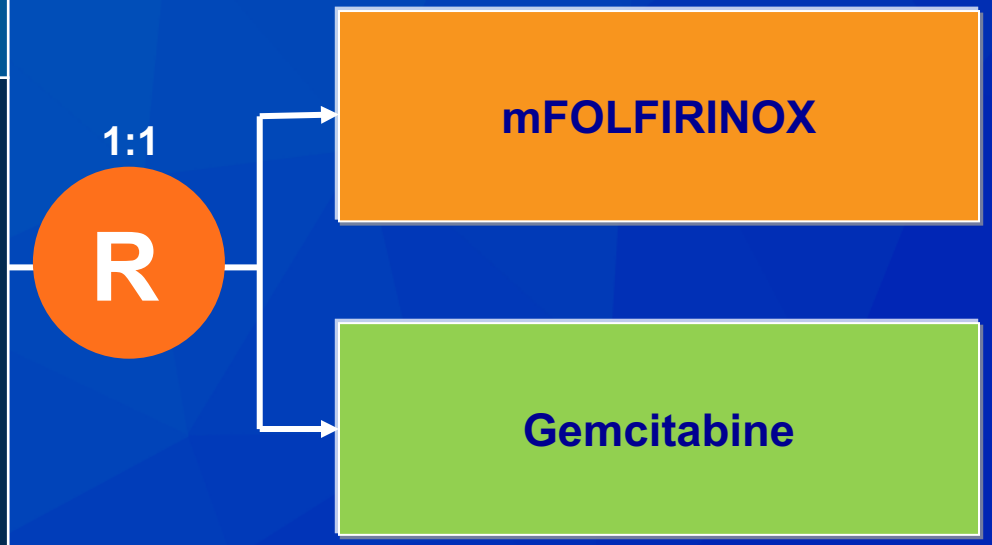
Proc ASCO 2018;Abstract LBA4001.

PRODIGE 24/CCTG PA.6: Phase III Trial Design

NCT01526135

Eligibility (N = 493)

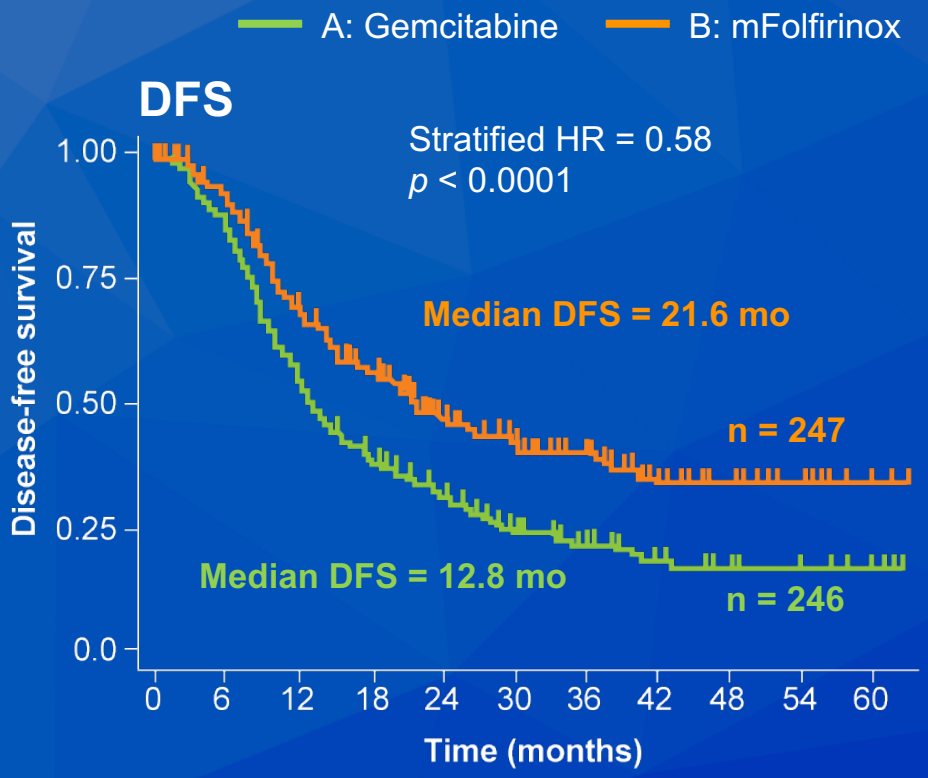
- R0/R1 resected PDAC
- Able to receive chemotherapy within 12 weeks of resection
- ECOG PS 0-1
- No prior radiotherapy or chemotherapy
- No metastatic disease

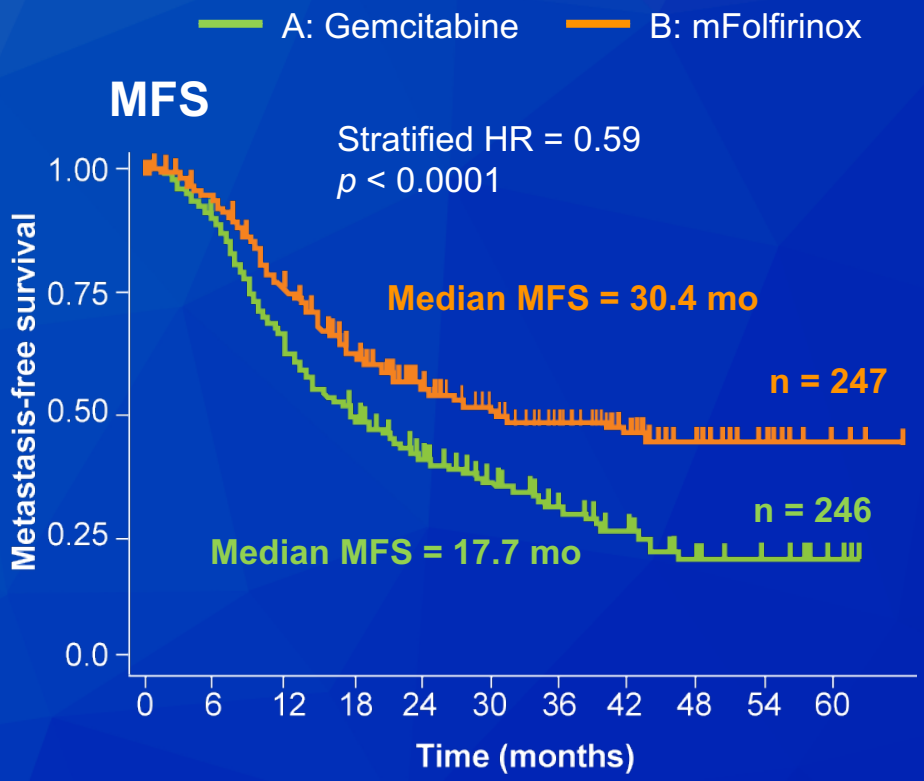


- **Primary endpoint: Disease-free survival (DFS)**
- Prior to randomization, patients were stratified by center, resection margin (R0 vs R1), CA19-9 level (≤90 vs 91-179 U/mL) and pN0 (<12 vs ≥examined nodes) vs pN1.

Conroy T et al. *Proc ASCO* 2018;Abstract LBA4001; Clinicaltrials.gov.

PRODIGE 24/CCTG PA.6: Survival Outcomes





DFS = disease-free survival; MFS = metastasis-free survival; DSS = disease-specific survival

Outcome	mFOLFIRINOX (n = 247)	Gem (n = 246)	HR	*p*-value
Median OS	54.4 mo	35.0 mo	0.64	0.003
3-year DSS	66.2%	51.2%	0.63	0.003

Conroy T et al. *Proc ASCO* 2018;Abstract LBA4001.

PRODIGE 24/CCTG PA.6: Select AEs

Grade 3/4 AE	mFOLFIRINOX (n = 238)	Gemcitabine (n = 243)
G-CSF use*	59.9%	3.7%
Neutropenia	28.4%	26.0%
Diarrhea*	18.6%	3.7%
Peripheral sensory neuropathy*	9.3%	—
Vomiting*	5%	1.2%
Febrile neutropenia	2.9%	3.7%
Mucositis*	2.5%	0
Thrombocytopenia*	1.3%	4.5%
Hand-foot syndrome*	0.4%	—
Anemia	0	0.4%

*$p < 0.05$

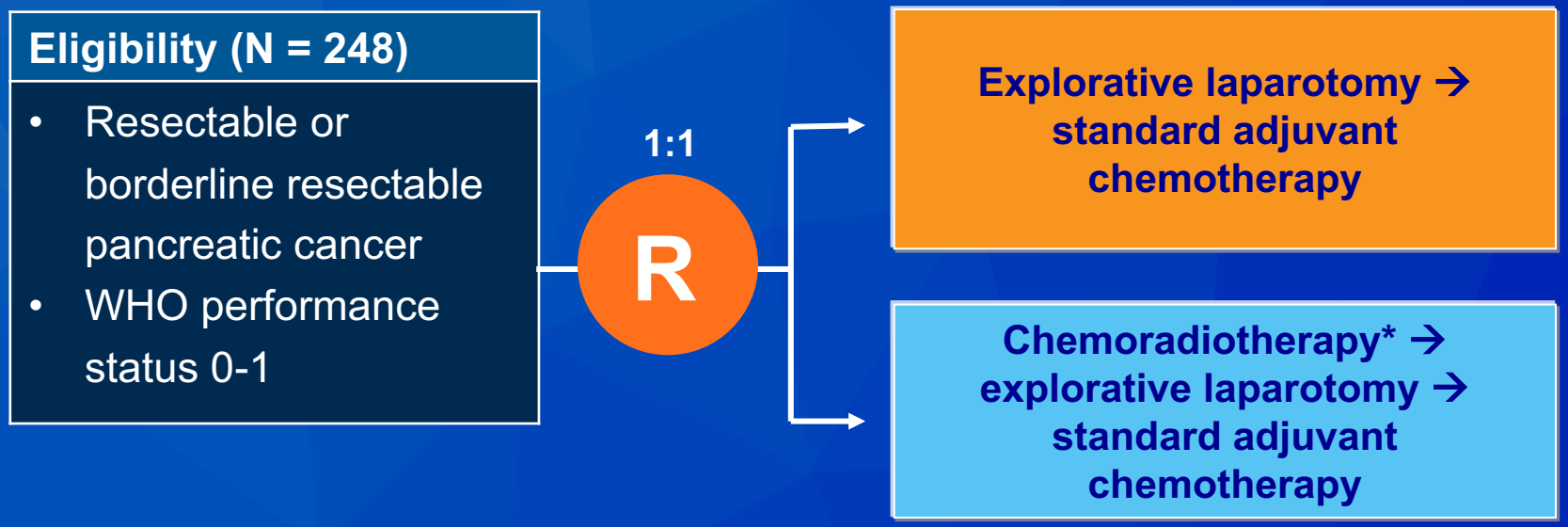
Conroy T et al. *Proc ASCO* 2018;Abstract LBA4001.

Preoperative Chemoradiotherapy versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC-1): A Randomized, Controlled, Multicenter Phase III Trial

Van Tienhoven G et al.

Proc ASCO 2018;Abstract LBA4002.

PREOPANC-1: Phase III Trial Design

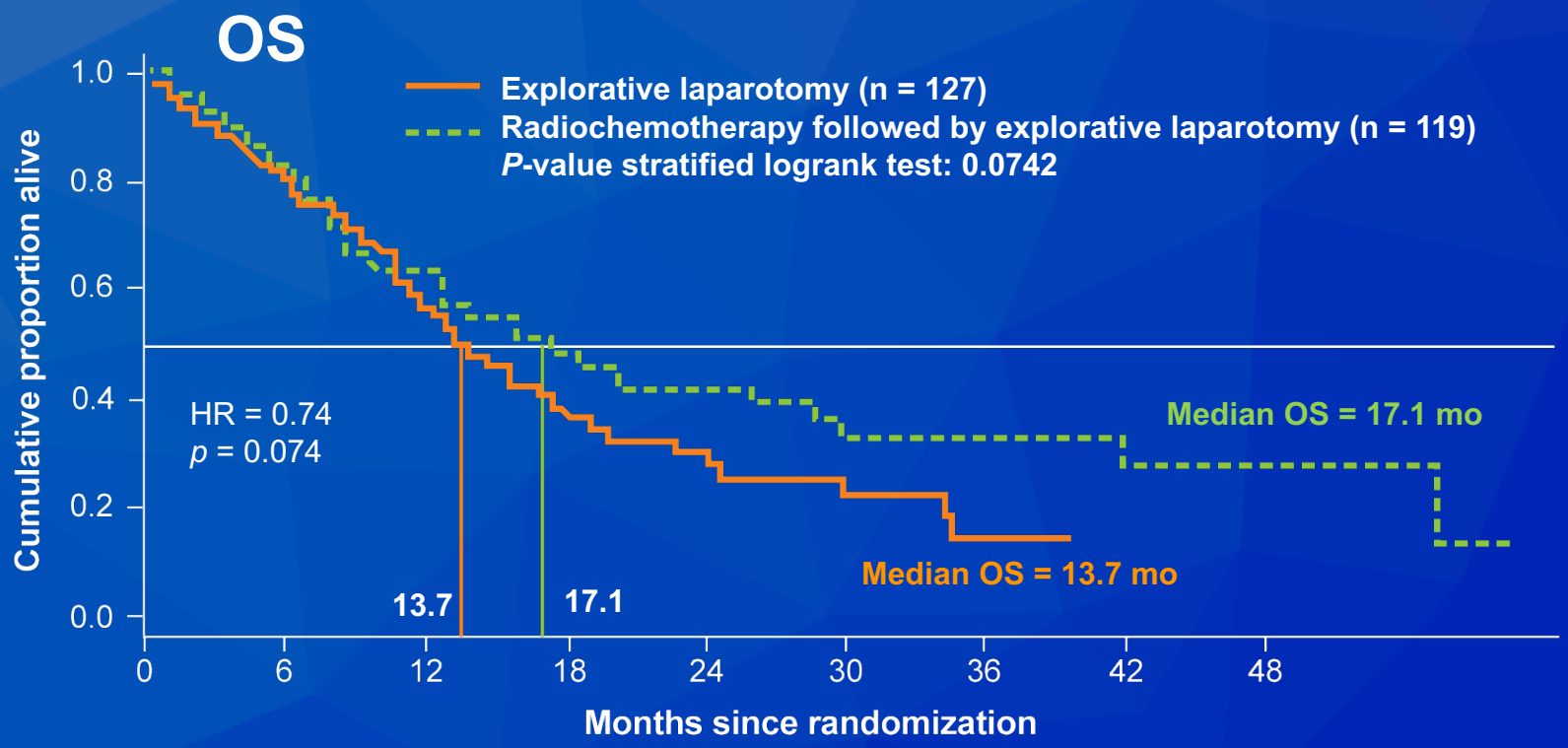


* Preoperative chemoradiotherapy consisted of 15 times of 2.4 Gray (Gy) combined with gemcitabine, 1,000 mg/m^2 on d1, 8 and 15, preceded and followed by a cycle of gemcitabine

- **Primary endpoint: OS in ITT population**
- Prior to randomization, patients were stratified by resectability and institution.

Van Tienhoven G et al. *Proc ASCO* 2018;Abstract LBA4002.

PREOPANC-1: Survival in ITT population

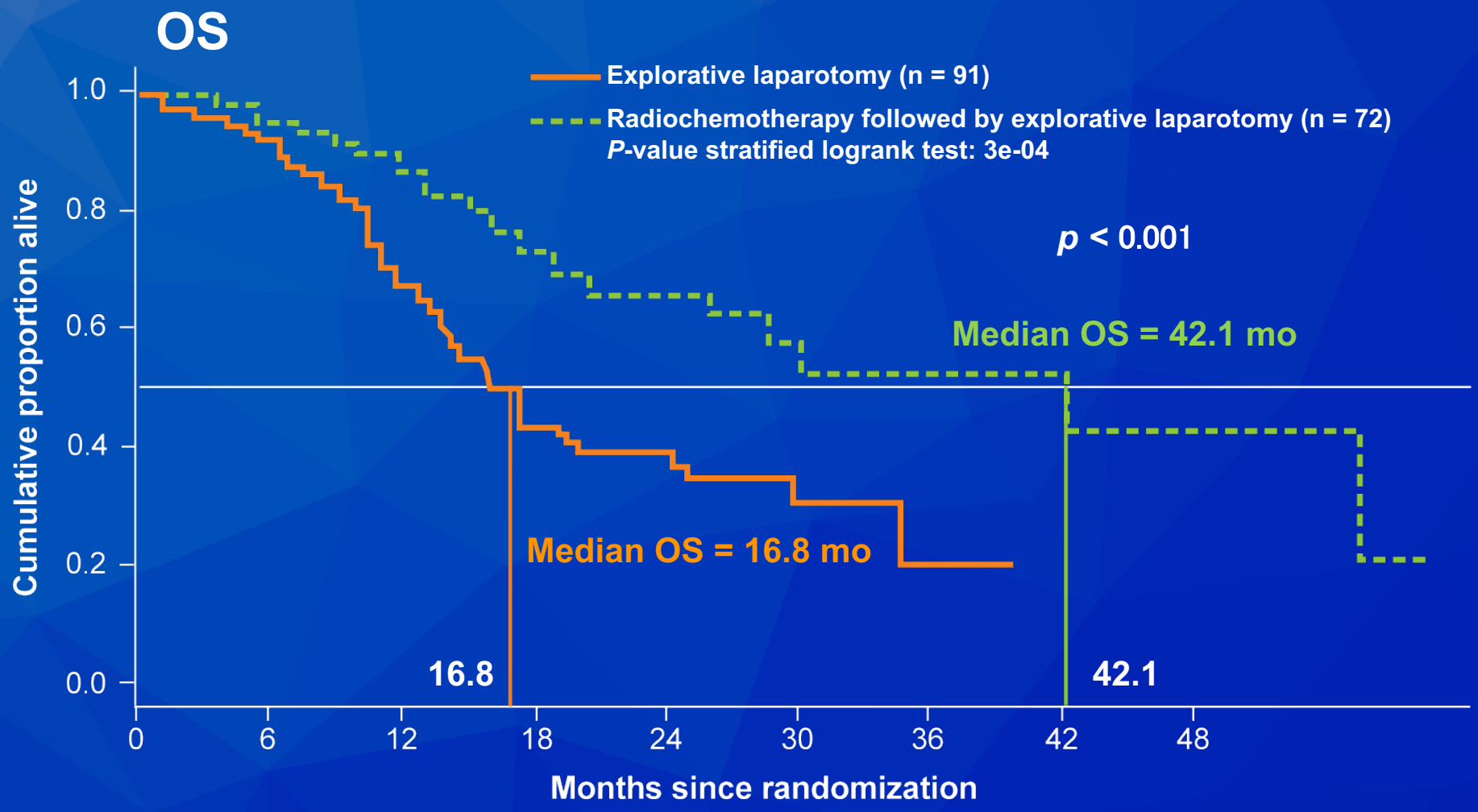


Survival	Radiochemotherapy (n = 119)	Explorative laparotomy (n = 127)	HR	*p*-value
Median DFS	9.9 mo	7.9 mo	0.71	0.023
Median DMFI	18.4 mo	10.6 mo	0.71	0.013
Median LRFI	Not reached	11.8 mo	0.55	0.002

DMFI = distant metastases-free interval; LRFI = locoregional recurrence-free interval; NR = not reached

Van Tienhoven G et al. *Proc ASCO* 2018;Abstract LBA4002.

PREOPANC-1: Subset Analysis of OS in Patients After R0/R1 Resection



Van Tienhoven G et al. *Proc ASCO* 2018;Abstract LBA4002.

FOLFIRINOX until Progression, FOLFIRINOX with Maintenance Treatment, or Sequential Treatment with Gemcitabine and FOLFIRI.3 for First-Line Treatment of Metastatic Pancreatic Cancer: A Randomized Phase II Trial (PRODIGE 35-PANOPTIMOX)

Dahan L et al.

Proc ASCO 2018;Abstract 4000.

PRODIGE 35 PANOPTIMOX: Phase II Trial Design

NCT02352337

Eligibility (N = 273)

- Metastatic pancreatic cancer
- No prior chemotherapy

1:1:1

R

FOLFIRINOX* x 12 cycles

(Arm A)

FOLFIRINOX x 8 cycles → 5-FU/ LV† for disease control and re-introduction of FOLFIRINOX in case of progression

(Arm B)

‡ Sequential treatment with FOLFIRINOX for 2 mo and gemcitabine for 2 mo

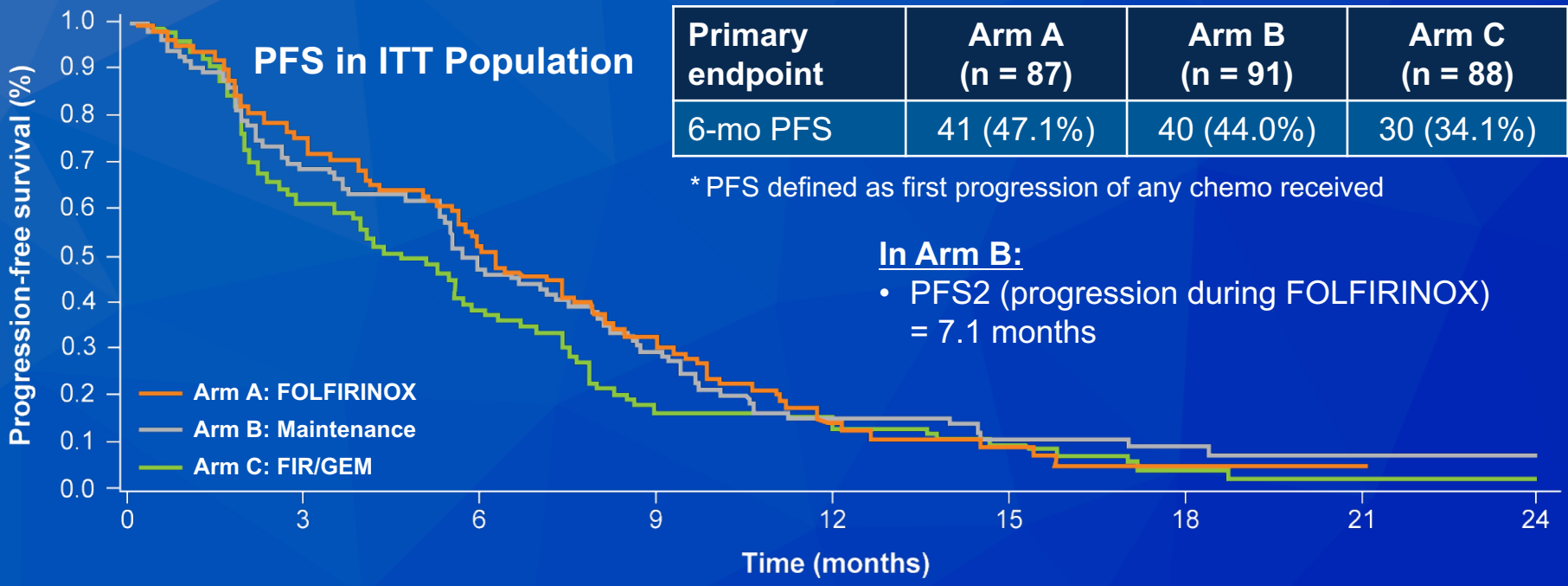
(Arm C)

* Oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, LV 200 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2,400 mg/m^2 for 46 h; 14 d cycle
† LV 200 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2,400 mg/m^2 for 46 h; 14 d cycle
‡ Irinotecan 90 mg/m^2 d1, LV 200 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2,400 mg/m^2 for 46 h, irinotecan 90 mg/m^2 on d3; 14 d cycle and gemcitabine 1,000 mg/m^2 on d1, 8, 15; 28 d cycle

- **Primary endpoint: 6-month PFS rate**
- Prior to randomization, patients were stratified by center, biliary stent and age (<65 vs >65 y).

Dahan L et al. *Proc ASCO* 2018;Abstract 4000; Clinicaltrials.gov.

PANOPTIMOX: Survival and Response



Primary endpoint	Arm A (n = 87)	Arm B (n = 91)	Arm C (n = 88)
6-mo PFS	41 (47.1%)	40 (44.0%)	30 (34.1%)

* PFS defined as first progression of any chemo received

In Arm B:

- PFS2 (progression during FOLFIRINOX) = 7.1 months

Survival	Arm A (n = 91)	Arm B (n = 92)	Arm C (n = 90)
Median PFS	6.3 mo	5.7 mo	4.5 mo
12-mo PFS	14.7%	14.9%	12.9%
Median OS	10.1 mo	11.0 mo	7.3 mo
12-mo OS	43.3%	44.1%	28.5%

- Objective response rate: 37.3% (Arm A) vs 38.3% (Arm B) vs 27.0% (Arm C)

Dahan L et al. *Proc ASCO* 2018;Abstract 4000.

PANOPTIMOX: Select AEs

Grade 3/4 AE	Arm A (n = 88)	Arm B (n = 91)	Arm C (n = 87)
Neutropenia	25 (28.4%)	23 (25.3%)	28 (32.2%)
Febrile neutropenia	1 (1.1%)	5 (5.5%)	—
Thrombocytopenia	4 (4.5%)	5 (5.5%)	7 (8.0%)
Anemia	6 (6.8%)	7 (7.7%)	6 (6.9%)
Asthenia	22 (25.0%)	28 (30.8%)	28 (32.2%)
Vomiting	11 (12.5%)	13 (14.3%)	13 (14.9%)
Diarrhea	10 (11.4%)	16 (17.6%)	16 (18.4%)
Sensory neuropathy	9 (10.2%)	17 (18.7%)	0

- Treatment-related deaths (n = 2): Sepsis on the FOLFIRNOX arm (n = 1) and hypertonicity-induced coma on the FIR/GEM arm (n = 1)
- Grade 3/4 neurotoxicity: 10.2% (Arm A) vs 18.7% (Arm B)

Dahan L et al. *Proc ASCO* 2018;Abstract 4000.

JOURNAL OF CLINICAL ONCOLOGY

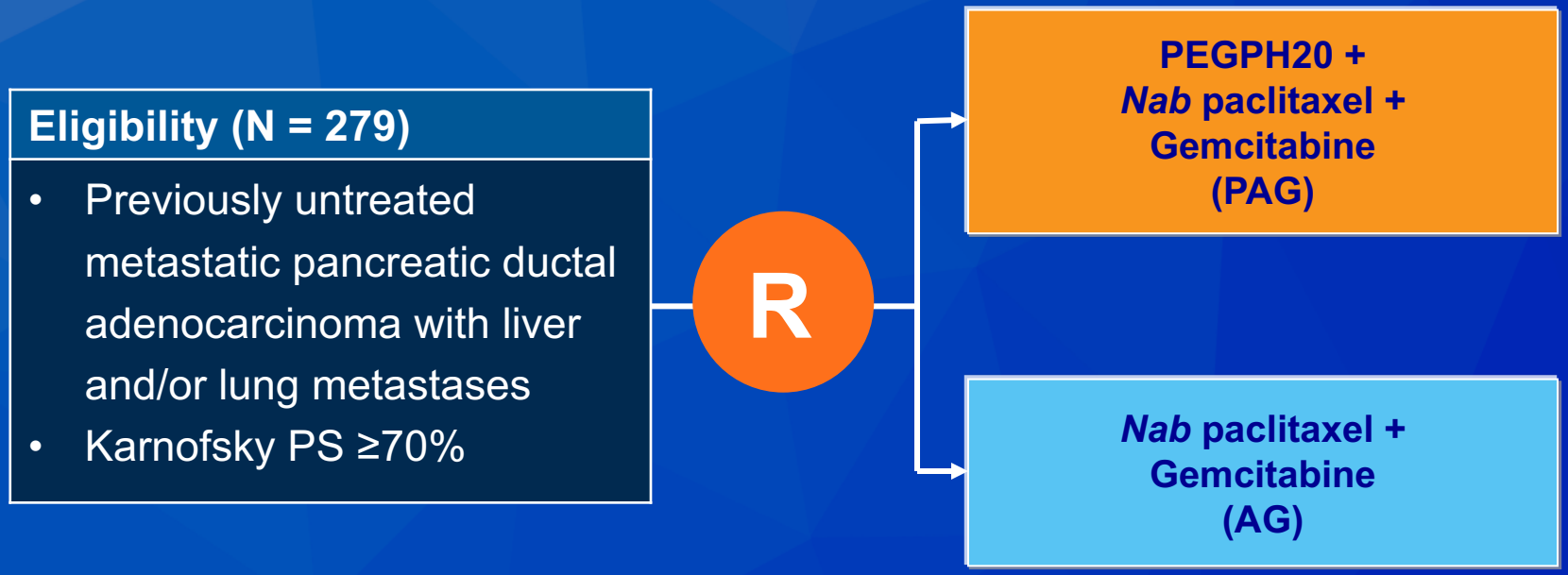
ORIGINAL REPORT

HALO 202: Randomized Phase II Study of PEGPH20 Plus Nab-Paclitaxel/Gemcitabine Versus Nab-Paclitaxel/ Gemcitabine in Patients With Untreated, Metastatic Pancreatic Ductal Adenocarcinoma

Sunil R. Hingorani, Lei Zheng, Andrea J. Bullock, Tara E. Seery, William P. Harris, Darren S. Sigal, Fadi Braiteh, Paul S. Ritch, Mark M. Zalupski, Nathan Bahary, Paul E. Oberstein, Andrea Wang-Gillam, Wilson Wu, Dimitrios Chondros, Ping Jiang, Sihem Khelifa, Jie Pu, Carrie Aldrich, and Andrew E. Hendifar

J Clin Oncol 2018;36(4):359-66.

HALO 202: Phase II Trial Design



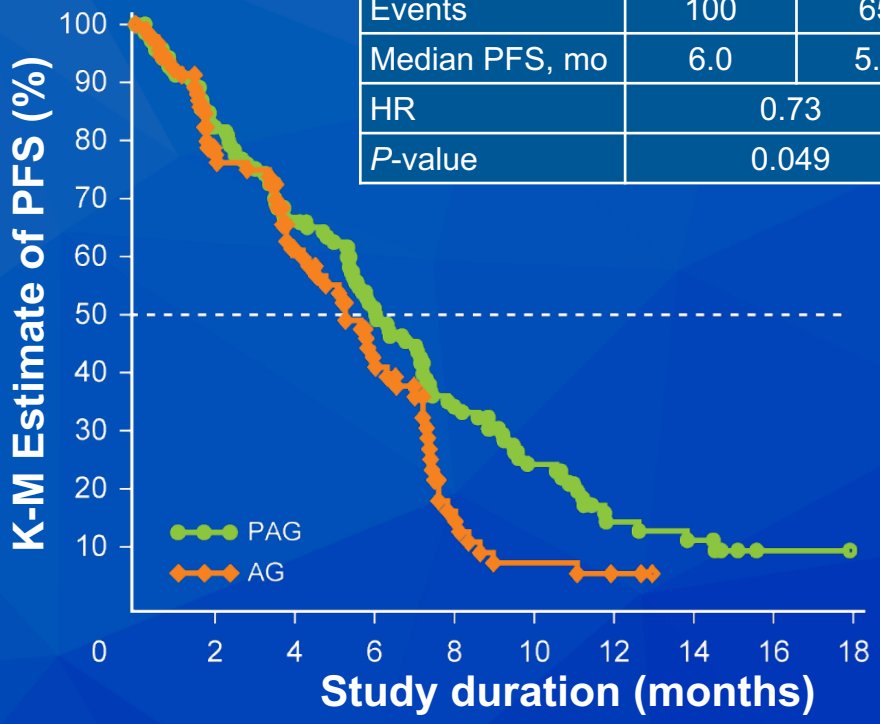
- **Primary endpoints: PFS overall and thromboembolic (TE) event rate**
- Tumor hyaluronan (HA) levels were measured retrospectively using a novel affinity histochemistry assay

Hingorani SR et al. *J Clin Oncol* 2018;36(4):359-66.

HALO 202: PFS and OS Results

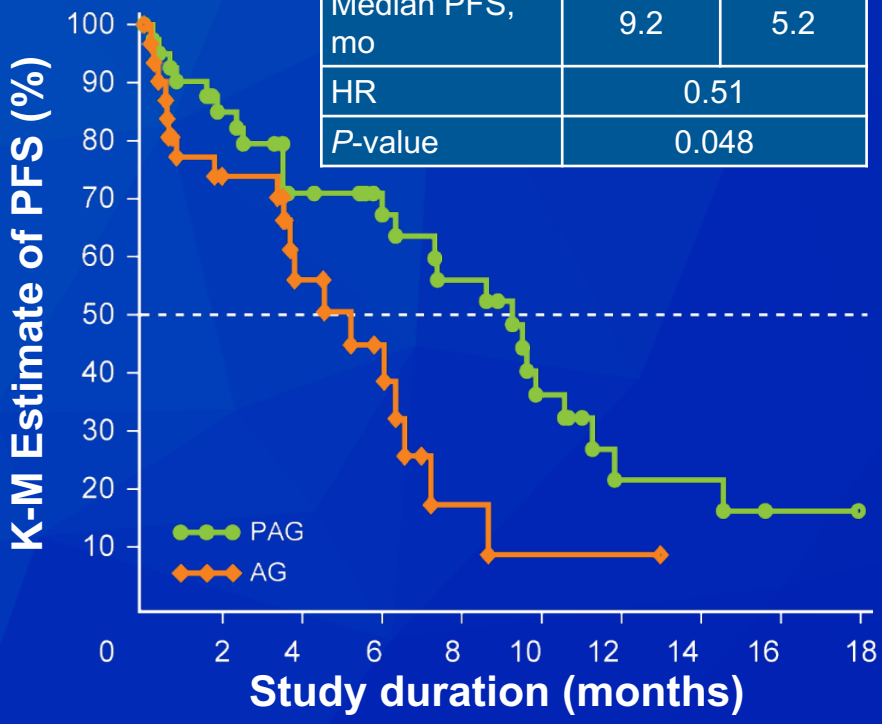
Overall PFS for Stages 1 & 2 (Evaluable Pts)

Stages 1 + 2	PAG (n = 139)	AG (n = 92)
Events	100	65
Median PFS, mo	6.0	5.3
HR	0.73	
P-value	0.049	



Pts with HA-high tumors in Stages 1 & 2 (ITT population)

Stages 1 + 2 (HA-High)	PAG (n = 49)	AG (n = 35)
Events	24	19
Median PFS, mo	9.2	5.2
HR	0.51	
P-value	0.048	



Median OS (Stages 1 & 2)	PAG	AG	HR	*p*-value
All patients (n = 166, 113)	9.6 mo	9.2 mo	0.90	0.45
Pts with HA-high tumors (n = 49, 35)	11.5 mo	8.5 mo	0.96	0.88

Hingorani SR et al. *J Clin Oncol* 2018;36(4):359-66.

HALO 202: TE Event Rate

Study stage	Enoxaparin prophylaxis dose	TE Rate (%)*		*p*-value
		PAG	AG	
Stage 1 (until 12/2016)†	N/A	32/74 (43%)	15/61 (25%)	0.03
Stage 2 (as of 12/2016)‡	40 mg/d§	5/18 (28%)	2/7 (29%)	1.0
	1 mg/kg/d	7/68 (10%)	2/32 (6%)	0.71
	Overall	12/86 (14%)	4/39 (10%)	0.77

* 2 arterial events each were reported in stage 1 and stage 2; none was considered to be treatment related.

† A brief clinical hold was instituted owing to an imbalance in TE events observed between arms (stage 1). The study was resumed with the exclusion of patients at high risk for TE events, and all patients received enoxaparin prophylaxis (stage 2).

‡ The incidence of all-grade adverse events of bleeding was similar across treatment arms (36.0% PAG vs 35.9% AG).

§ The dose for patients in the 40-mg/d group was subsequently adjusted to 1 mg/kg/d. Some patients may have received enoxaparin doses other than 40 mg/d.

Hingorani SR et al. *J Clin Oncol* 2018;36(4):359-66.

HALO 202: Select Treatment-Related AEs Occurring in ≥25% of Patients

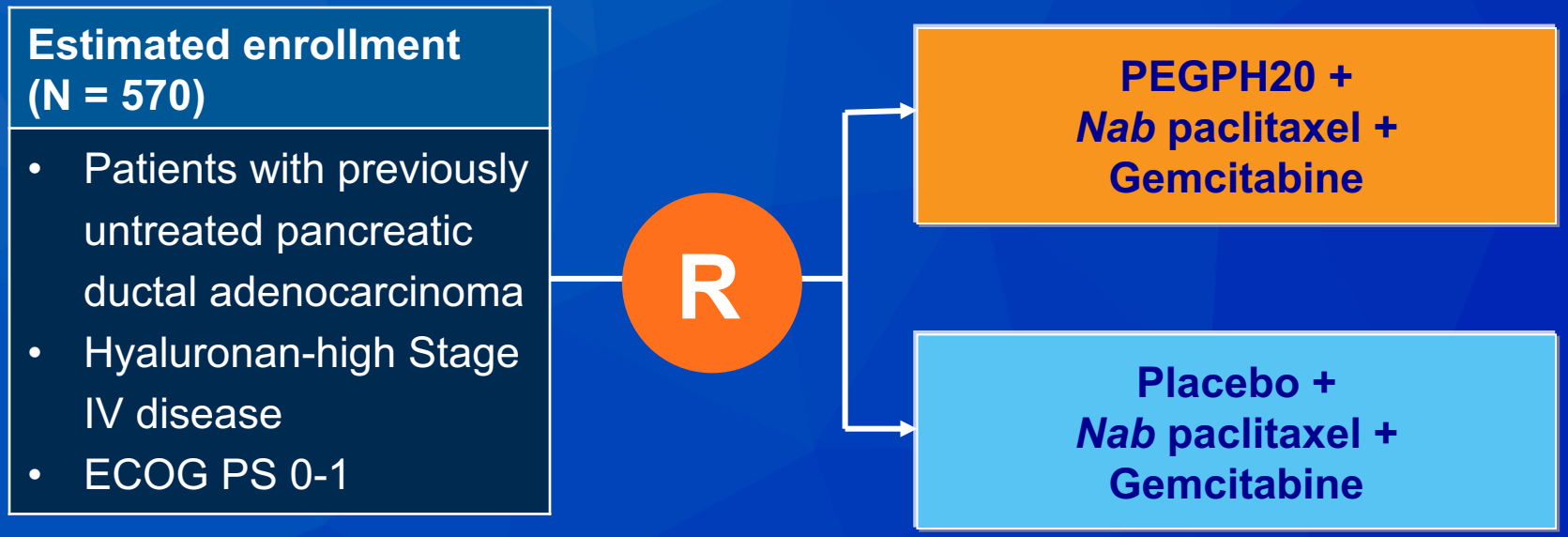
Event	PAG (n = 160)		AG (n = 100)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	72%	21%	66%	16%
Peripheral edema*	63%	5%	26%	4%
Muscle spasms*	56%	13%	3%	1%
Nausea	49%	5%	47%	4%
Diarrhea	40%	7%	39%	5%
Anemia	39%	17%	38%	20%
Neutropenia*	34%	29%	19%	18%
Peripheral neuropathy	29%	6%	31%	8%
Myalgia*	26%	5%	7%	0%
Thrombocytopenia	26%	16%	17%	9%

* Statistically significant differences observed between arms.

Hingorani SR et al. *J Clin Oncol* 2018;36(4):359-66.

HALO-109-301: Ongoing Phase III Trial Design

NCT02715804



- **Primary endpoints: PFS and OS**
- Secondary endpoints include: Objective response, duration of response and safety

Clinicaltrials.gov.

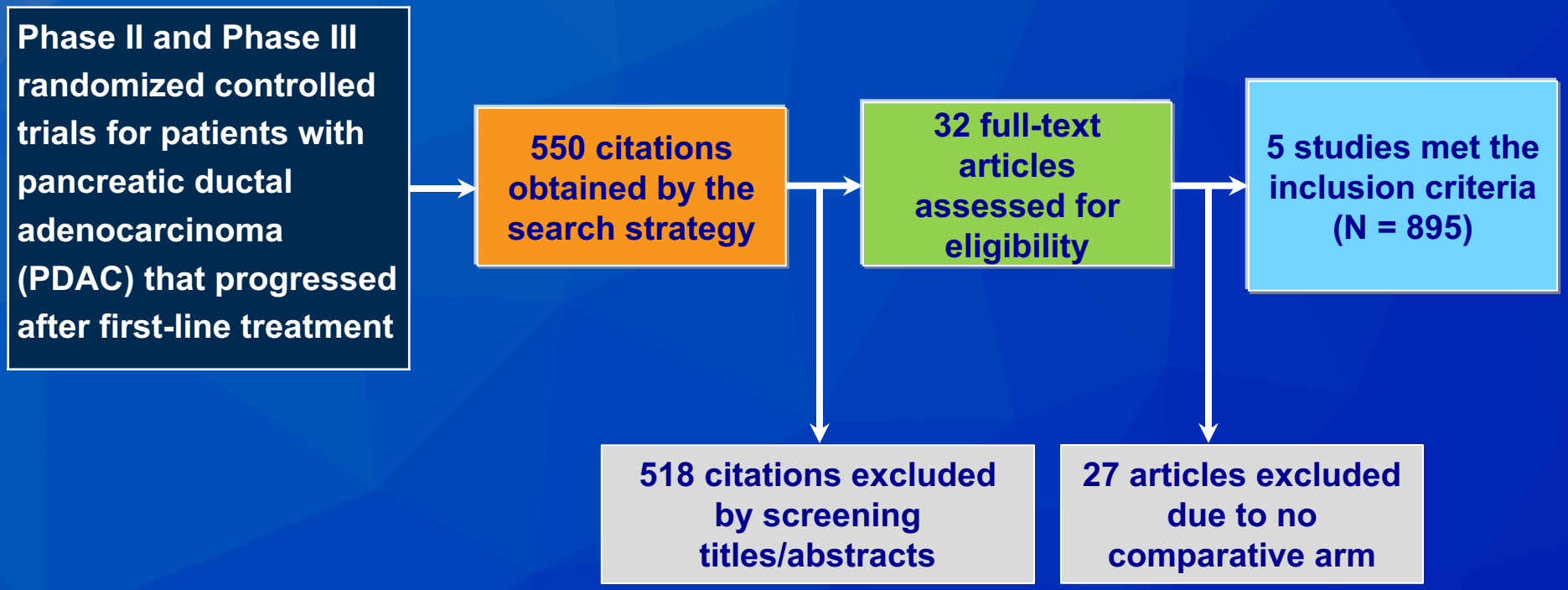
Original Article

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

Mohamad Bassam Sonbol, MD [1]; Belal Firwana, MD [2]; Zhen Wang, PhD [3]; Diana Almader-Douglas [4]; Mitesh J. Borad, MD [1]; Issam Makhoul, MD [2]; Ramesh K. Ramanathan, MD [1]; Daniel H. Ahn, DO [1]; and Tanios Bekaii-Saab, MD [1]

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

Meta-Analysis: Study Methods



- **Primary objective:** To determine the efficacy of combining a fluoropyrimidine (FP) with oxaliplatin (FPOX) or various irinotecan formulations (FPIRI) as second-line therapy for patients with PDAC
- Outcomes of interest: OS and PFS

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

Meta-Analysis: OS and PFS

- 5 trials (N = 895 patients) were identified comparing second-line FP alone to FP combinations including either FPOX or 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.

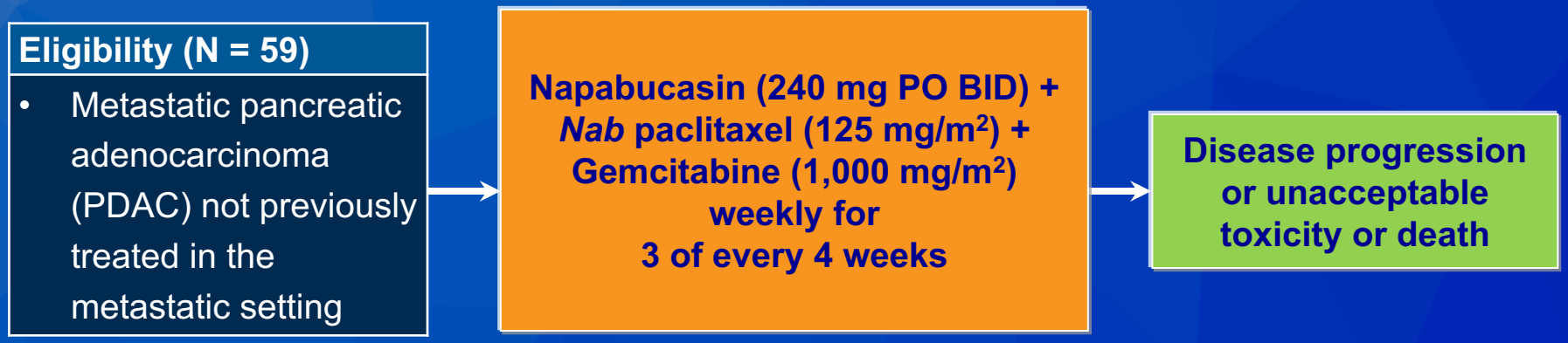
Sonbol MB et al. *Cancer* 2017;123(23):4680-6.

Phase 1b/2 Trial of Cancer Stemness Inhibitor Napabucasin (NAPA) + Nab-Paclitaxel (nPTX) and Gemcitabine (Gem) in Metastatic Pancreatic Adenocarcinoma (mPDAC)

Bekaii-Saab TS et al.

Proc ASCO 2018;Abstract 4110.

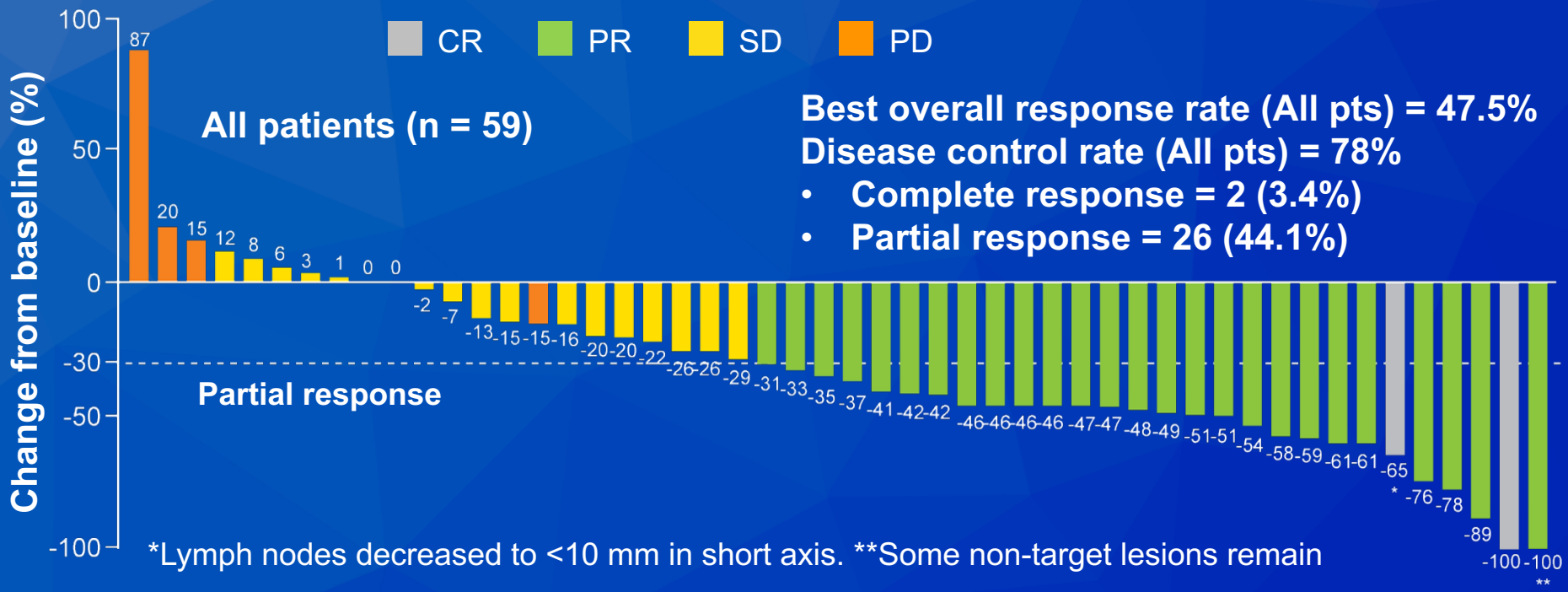
Phase Ib/II Trial Design



- **Primary endpoints:** R2PD, safety and tolerability
- Napabucasin at 240 mg BID can be combined with *nab* paclitaxel and gemcitabine at full dose.

Bekaii-Saab TS et al. *Proc ASCO* 2018;Abstract 4110.

Phase Ib/II Trial: Response and Survival Outcomes



- The ongoing Phase III CanStem111P trial is evaluating the efficacy of napabucasin + *nab* paclitaxel + gem as first-line therapy for patients with metastatic PDAC (NCT02993731).

Survival	Phase I/IIb trial (n = 59)	Pts meeting CanStem111P criteria (n = 29)
Median OS	9.59 mo	12.62 mo
Median PFS	7.06 mo	7.10 mo

Bekaii-Saab TS et al. *Proc ASCO* 2018;Abstract 4110.

Phase I/II Trial: Select Treatment-Emergent AEs in ≥20% of Patients

Event (n = 59)	Any grade	Grade ≥3
Diarrhea	41 (69.5%)	5 (8.5%)
Fatigue	39 (66.1%)	10 (16.9%)
Nausea	27 (45.8%)	1 (1.7%)
Peripheral neuropathy	23 (39.0%)	4 (6.8%)
Peripheral edema	19 (32.2%)	3 (5.1%)
Neutropenia	15 (25.4%)	14 (23.7%)
Anemia	15 (25.4%)	8 (13.6%)
Fever	14 (23.7%)	2 (3.4%)

- GI AEs seen with napabucasin were mainly Grade 1 or 2 and were manageable with supportive measures.
- Grade 3 GI AEs were low and resolved upon withholding napabucasin.

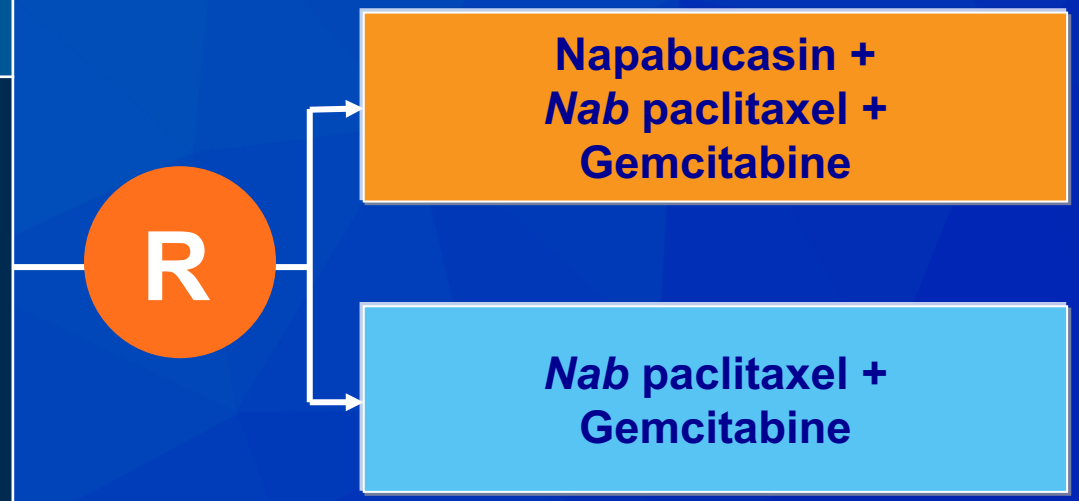
Bekaii-Saab TS et al. *Proc ASCO* 2018;Abstract 4110.

CanStem111P: Ongoing Phase III Trial Design

NCT02993731

Estimated Enrollment (N = 1,132)

- Metastatic PDAC
- Previously untreated
- ECOG PS 0-1
- Available archival tumor tissue
- No brain or leptomeningeal metastases



- **Primary endpoint: OS in all patients**
- Secondary endpoints include: OS in patients with biomarker-positive disease, PFS, response and safety

Bekaii-Saab TS et al. *Proc ASCO* 2018;Abstract 4110; Clinicaltrials.gov.

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Davendra P.S. Sohal, Erin B. Kennedy, Alok Khorana, Mehmet S. Copur, Christopher H. Crane, Ignacio Garrido-Laguna, Smitha Krishnamurthi, Cassadie Moravek, Eileen M. O'Reilly, Philip A. Philip, Ramesh K. Ramanathan, Joseph T. Ruggiero, Manish A. Shah, Susan Urba, Hope E. Uronis, Michelle W. Lau, and Daniel Laheru

J Clin Oncol 2018;36(24):2545-56.

ASCO Clinical Practice Guideline Update for Metastatic Pancreatic Cancer

Treatment stage	Recommendation
Initial assessment	• Use a multiphase CT scan of chest/abdomen/pelvis for dx extent • Evaluate baseline PS, symptom burden and comorbidity profile • Discuss care goals, pt preferences and support systems with pt • Use a multidisciplinary team to formulate treatment plans • Clinical trial information should be offered
1L treatment	• ECOG PS 0-1: FOLFIRINOX or gemcitabine/*nab* paclitaxel • ECOG PS 2: Gemcitabine alone or with capecitabine or erlotinib • ECOG PS ≥3: Case-by-case basis only with emphasis on optimizing supportive care measures
2L treatment	• Routine testing for dMMR/MSI-H by IHC, PCR or NGS if considered candidate for immune checkpoint inhibitor therapy • If dMMR/MSI-H positive, pembrolizumab is recommended • If pt received 1L FOLFIRINOX, has ECOG PS 0-1/favorable comorbidity profile, consider gemcitabine/*nab* paclitaxel • If pt received 1L gem/*nab*, has ECOG PS 0-1/favorable comorbidity profile, consider 5-FU/nal-IRI (preferred) or 5-FU + irinotecan or oxaliplatin

Sohal DPS et al. *J Clin Oncol* 2018;36(24):2545-56.

ASCO Clinical Practice Guideline Update for Metastatic Pancreatic Cancer (Continued)

Treatment stage	Recommendation
2L treatment cont'd	• If pt has ECOG PS 2 or a comorbidity profile precluding more aggressive regimens, consider gemcitabine or 5-FU
≥3L treatment	• No data are available for therapy with a cytotoxic agent. Clinical trial participation is encouraged
Palliative care	• Pts should undergo full assessment of symptom burden, psychological status and social supports as early as possible, preferably at first visit
Pain and symptom management	• Pts should be offered aggressive treatment of pain and symptoms of the cancer and/or anticancer therapy
Follow-up and surveillance	• Pts on active anticancer therapy off protocol: Offer imaging to assess first response at 2-3 months from treatment initiation. • Use of CT scans with contrast are preferred. • Routine use of PET scans is not recommended. • No data exist on the duration of anticancer therapy. • An ongoing discussion of care goals and assessment of treatment response and tolerability should guide decisions to hold or discontinue cancer-directed therapy.

Sohal DPS et al. *J Clin Oncol* 2018;36(24):2545-56.

Hepatocellular Cancer

Articles

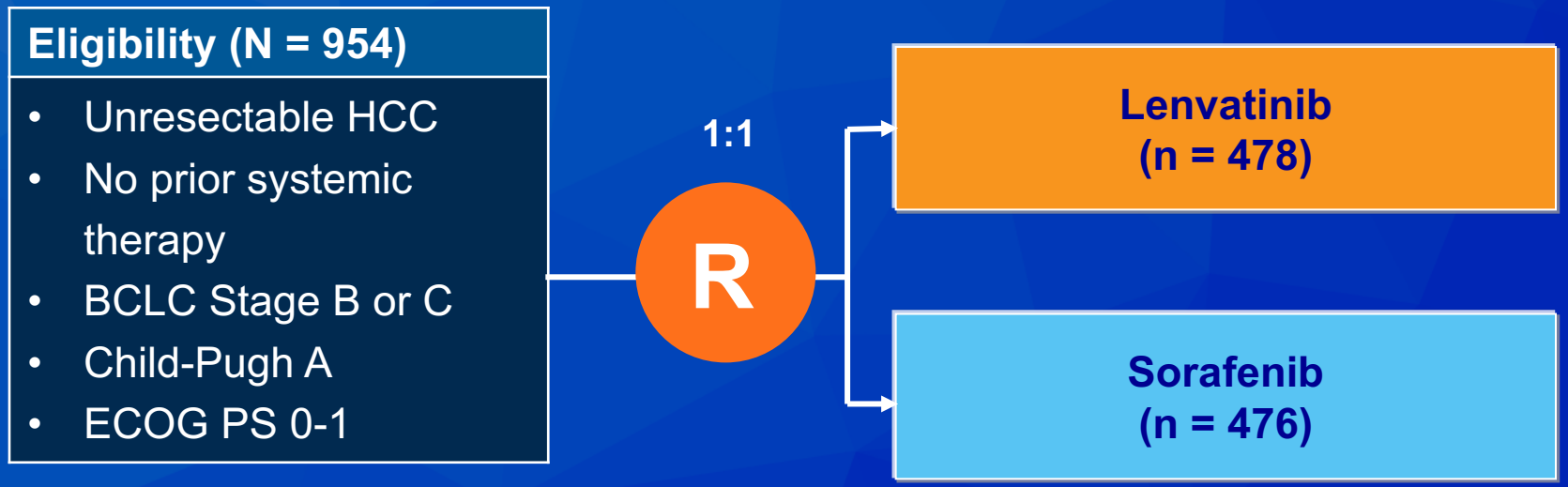
Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

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*

Lancet 2018;391(10126):1163-73.

REFLECT: Phase III Trial Design

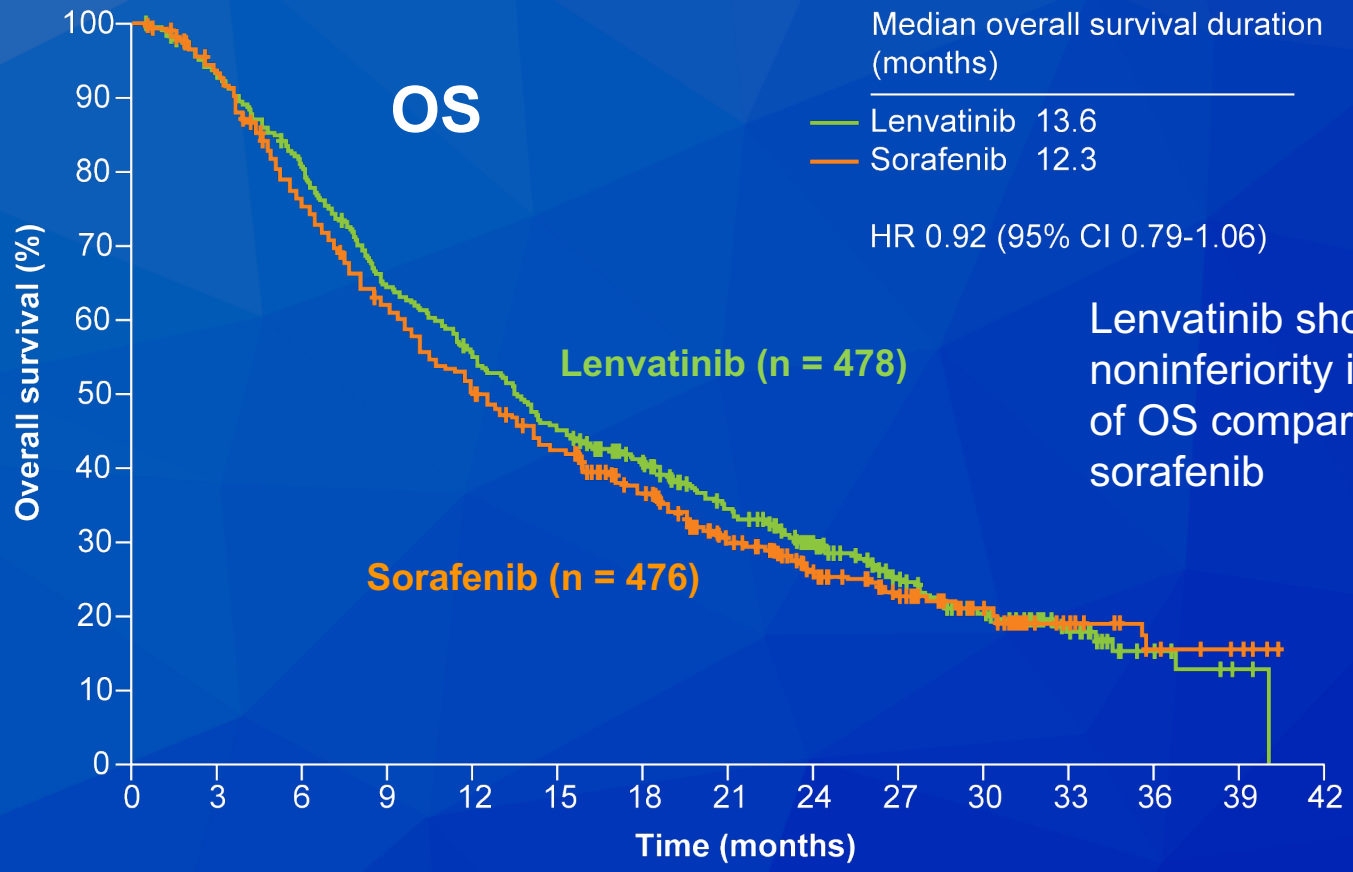
NCT01761266



- **Primary endpoint: OS**

Kudo M et al. *Lancet* 2018;391(10126):1163-73; Clinicaltrials.gov.

REFLECT: Survival and Response



Outcomes	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR* or OR†	*p*-value
Median PFS	7.4 mo	3.7 mo	*0.66	<0.0001
Median time to progression (TTP)	8.9 mo	3.7 mo	*0.63	<0.0001
Objective response rate	24.1%	9.2%	†3.13	<0.0001

Kudo M et al. *Lancet* 2018;391(10126):1163-73.

REFLECT: Select Treatment-Emergent AEs

Adverse event	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	42%	23%	30%	14%
Diarrhea	39%	4%	46%	4%
Decreased appetite	34%	5%	27%	1%
Decreased weight	31%	8%	22%	3%
Fatigue	30%	4%	25%	4%
Palmar-plantar erythrodysesthesia	27%	3%	52%	11%
Proteinuria	25%	6%	11%	2%
Dysphonia	24%	<1%	12%	0%
Nausea	20%	1%	14%	1%
Decreased platelet count	18%	5%	12%	3%
Vomiting	16%	1%	8%	1%

Kudo M et al. *Lancet* 2018;391(10126):1163-73.

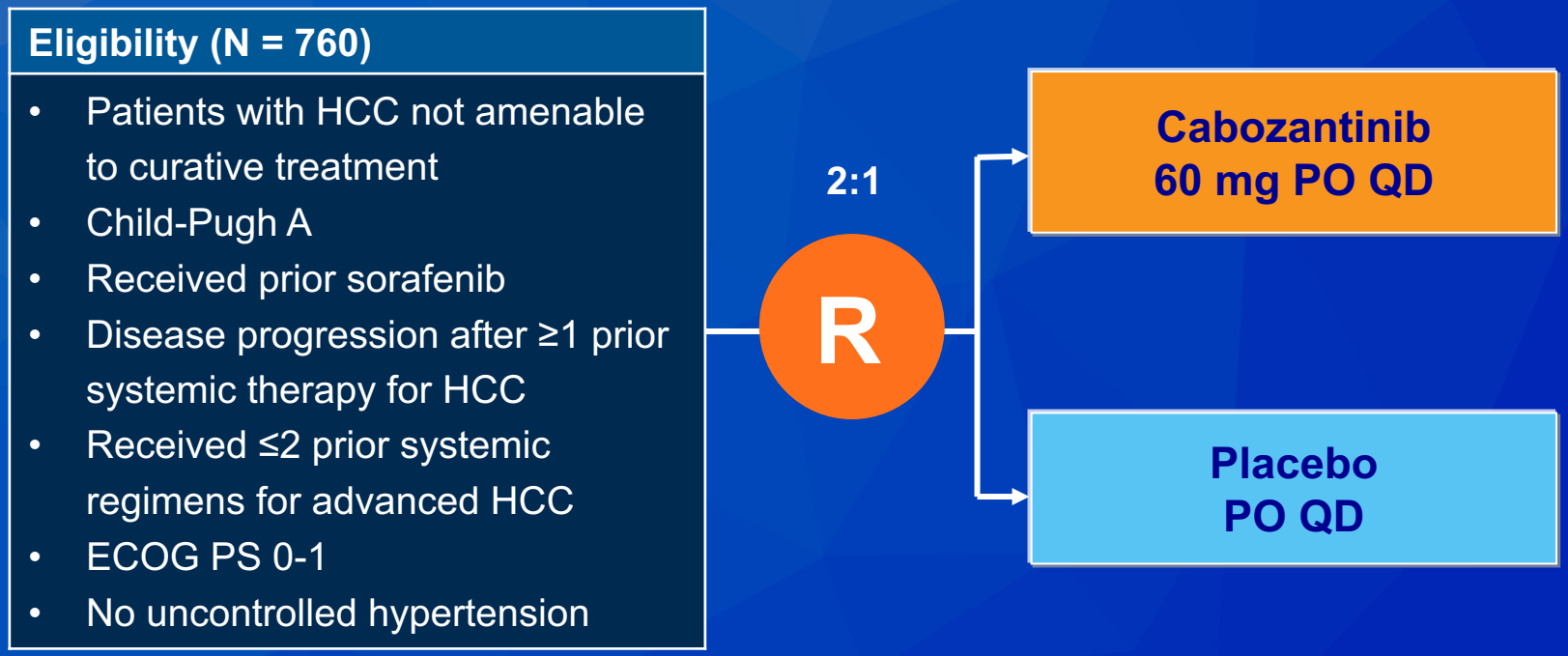
ORIGINAL ARTICLE

Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma

G.K. Abou-Alfa, T. Meyer, A.-L. Cheng, A.B. El-Khoueiry, L. Rimassa, B.-Y. Ryoo, I. Cicin, P. Merle, Y.H. Chen, J.-W. Park, J.-F. Blanc, L. Bolondi, H.-J. Klümpen, S.L. Chan, V. Zagonel, T. Pressiani, M.-H. Ryu, A.P. Venook, C. Hessel, A.E. Borgman-Hagey, G. Schwab, and R.K. Kelley

N Engl J Med 2018;379(1):54-63.

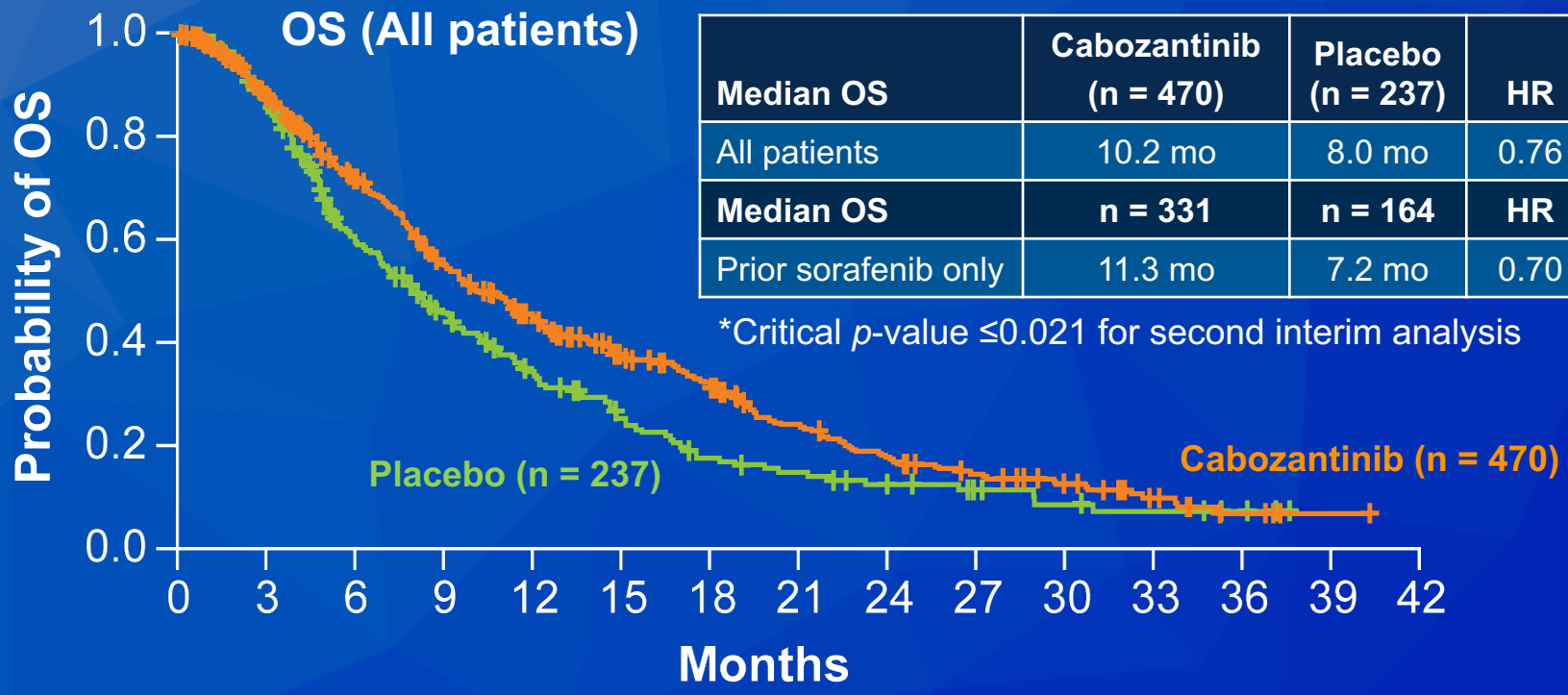
CELESTIAL: Phase III Trial Design



- **Primary endpoint: OS**
- Prior to randomization, patients were stratified by disease etiology (HBV, HCV, other), region (Asia vs other), presence of macrovascular invasion and/or extrahepatic spread of disease (yes or no)

Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; Abou-Alfa G et al. Gastrointestinal Cancers Symposium 2018;Abstract 207.

CELESTIAL: Survival and Response



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

*Critical *p*-value ≤0.021 for second interim analysis

Median PFS	Cabozantinib	Placebo	HR	*p*-value
All patients (n = 470, 237)	5.2 mo	1.9 mo	0.44	<0.001
Prior sorafenib only (n = 331, 164)	5.5 mo	1.9 mo	0.40	NR
Objective response rate	**Cabozantinib**	**Placebo**	**Odds ratio**	***p*-value**
All patients (n = 470, 237)	4%	0.4%	NR	0.0086

Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; Abou-Alfa G et al. Gastrointestinal Cancers Symposium 2018;Abstract 207.

CELESTIAL: AEs

Grade 3/4 AE	Cabozantinib (n = 467)	Placebo (n = 237)
Palmar-plantar erythrodysesthesia	17%	0%
Hypertension	16%	2%
Increased AST	12%	7%
Fatigue	10%	4%
Diarrhea	10%	2%
Asthenia	7%	2%
Decreased appetite	6%	<1%
Anemia	4%	5%

- Treatment-related Grade 5 AEs:
  - Cabozantinib (6 patients): Hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper GI hemorrhage, pulmonary embolism, hepatorenal syndrome
  - Placebo (1 patient): Hepatic failure

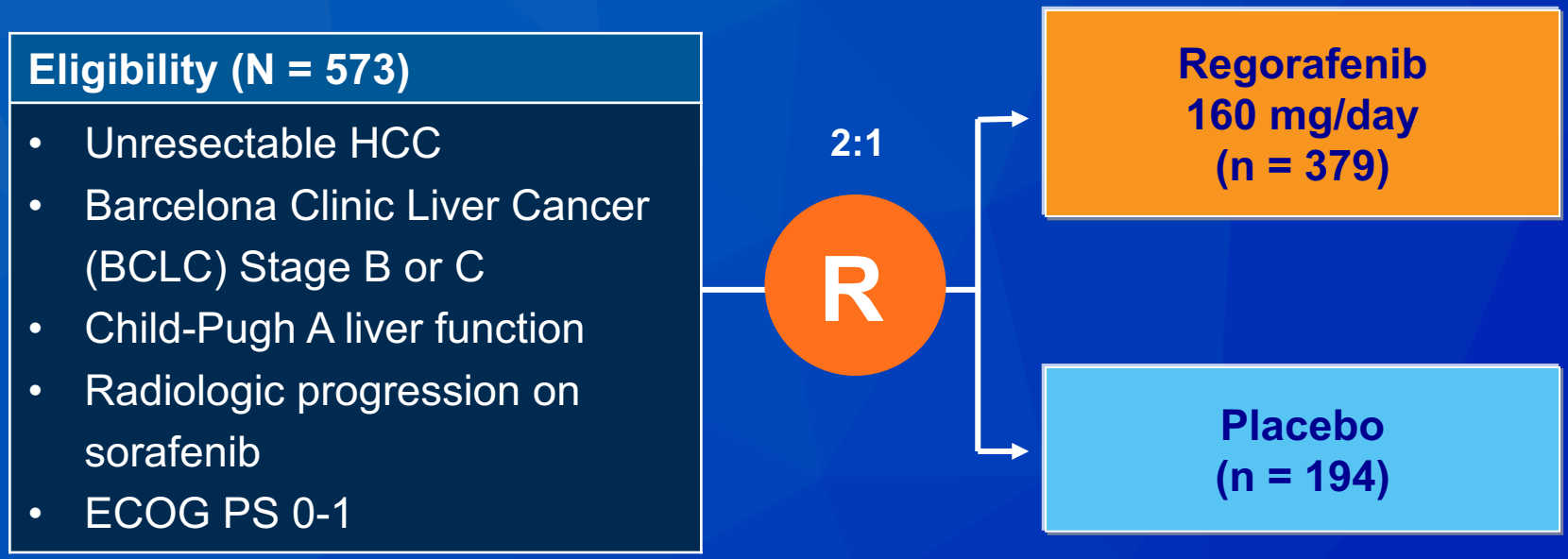
Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; Abou-Alfa G et al. Gastrointestinal Cancers Symposium 2018;Abstract 207.

Updated 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.

Proc ESMO World Congress GI 2017;Abstract O-009.

RESORCE: Phase III Trial Design



- **Primary endpoint: OS**

Bruix J et al. *Proc ESMO World Congress GI* 2017;Abstract O-009; Bruix J et al. *Lancet* 2017;289(10064):56-66.

RESORCE: Updated OS Analysis

	Regorafenib (n = 379)	Placebo (n = 194)	HR	*p*-value
Median OS (updated)	10.7 mo	7.9 mo	0.61	<0.0001
12-mo OS	47%	28%		
18-mo OS	32%	16%		
30-mo OS	16%	7%		

- OS results favored regorafenib in all preplanned subgroup analyses.
- **Conclusion:** The results of the updated OS analysis with a longer follow-up from the RESORCE trial confirm the results of the primary OS analysis showing that regorafenib is an effective treatment option for patients with HCC who progress on prior sorafenib treatment.

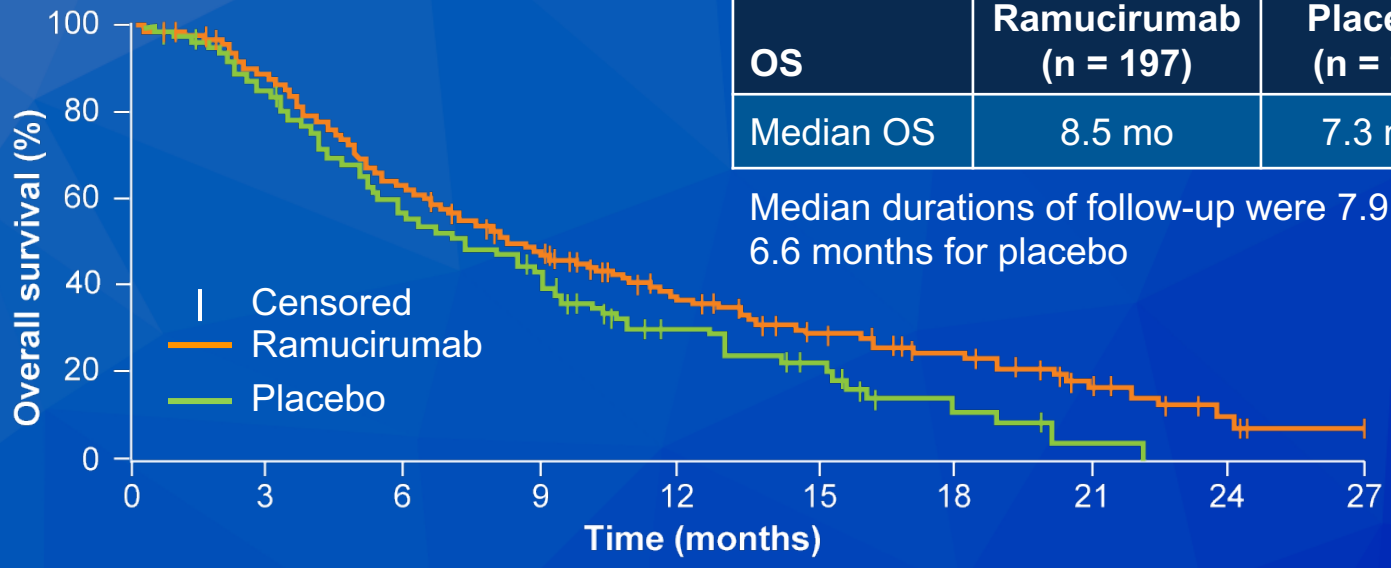
Bruix J et al. *Proc ESMO World Congress GI* 2017;Abstract O-009.

REACH-2: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Ramucirumab versus Placebo as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma (HCC) and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Sorafenib

Zhu AX et al.

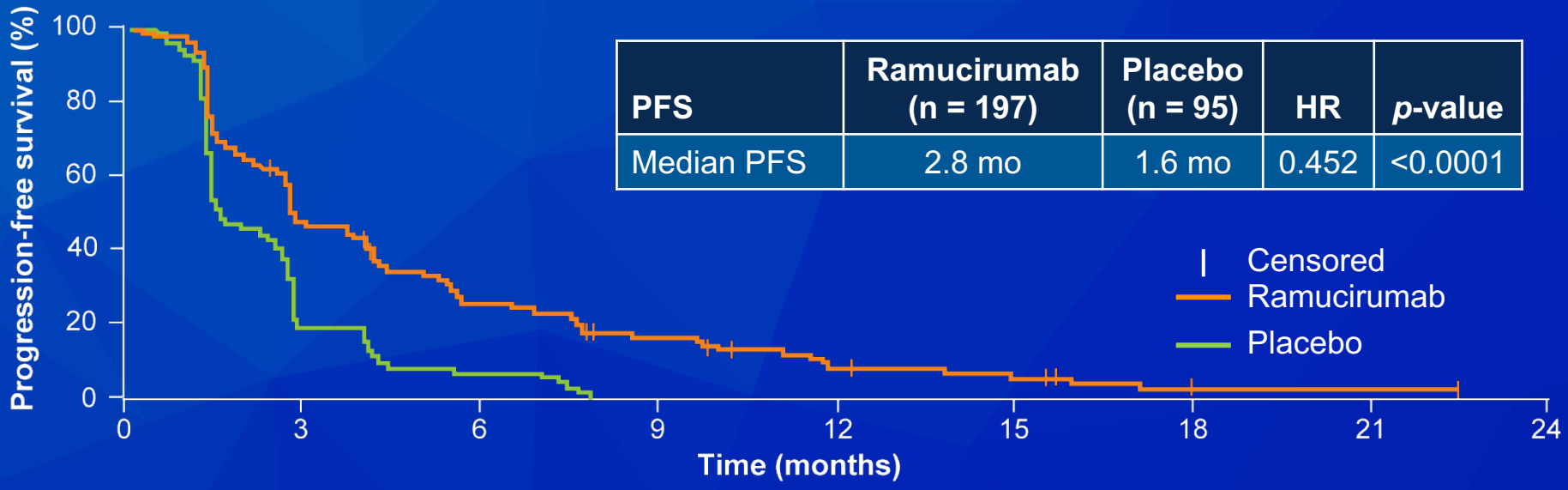
Proc ASCO 2018;Abstract 4003.

REACH-2: Survival



OS	Ramucirumab (n = 197)	Placebo (n = 95)	HR	*p*-value
Median OS	8.5 mo	7.3 mo	0.710	0.0199

Median durations of follow-up were 7.9 months for ramucirumab, 6.6 months for placebo



PFS	Ramucirumab (n = 197)	Placebo (n = 95)	HR	*p*-value
Median PFS	2.8 mo	1.6 mo	0.452	<0.0001

Zhu AX et al. *Proc ASCO* 2018;Abstract 4003.

REACH-2: Select AEs

Event	Ramucirumab (n = 197)		Placebo (n = 95)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	27.4%	3.6%	16.8%	3.2%
Peripheral edema	25.4%	1.5%	13.7%	0
Hypertension	24.4%	12.2%	12.6%	5.3%
Decreased appetite	23.4%	1.5%	20.0%	1.1%
Proteinuria	20.3%	2.0%	4.2%	0
Abdominal pain	19.8%	1.5%	12.6%	2.1%
Ascites	17.8%	4.1%	7.4%	2.1%
Diarrhea	16.2%	0	14.7%	1.1%

Zhu AX et al. *Proc ASCO* 2018;Abstract 4003.

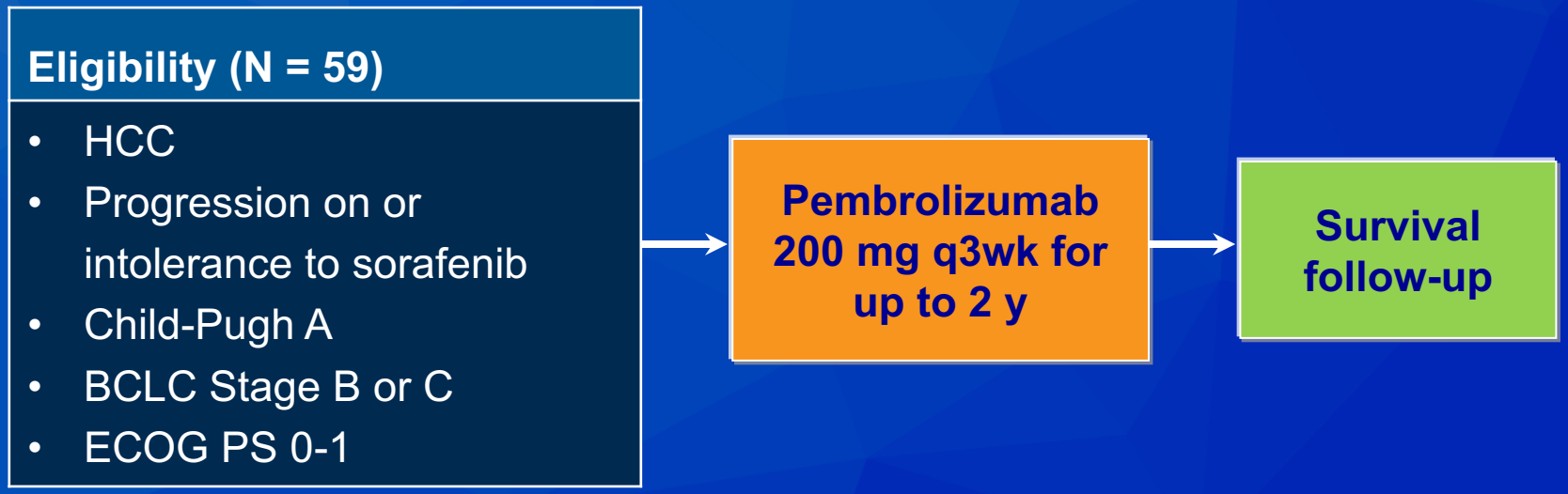
Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial

*Andrew X Zhu, Richard S Finn, Julien Edeline, Stephane Cattan, Sadahisa Ogasawara, Daniel Palmer, Chris Verslype, Vittorina Zagonel, Laetitia Fartoux, Arndt Vogel, Debashis Sarker, Gontran Verset, Stephen L Chan, Jennifer Knox, Bruno Daniele, Andrea L Webber, Scot W Ebbinghaus, Junshui Ma, Abby B Siegel, Ann-Lii Cheng, Masatoshi Kudo, for the KEYNOTE-224 investigators**

Lancet Oncol 2018;19(7):940-52.

KEYNOTE-224: Phase II Trial Design

NCT02702414

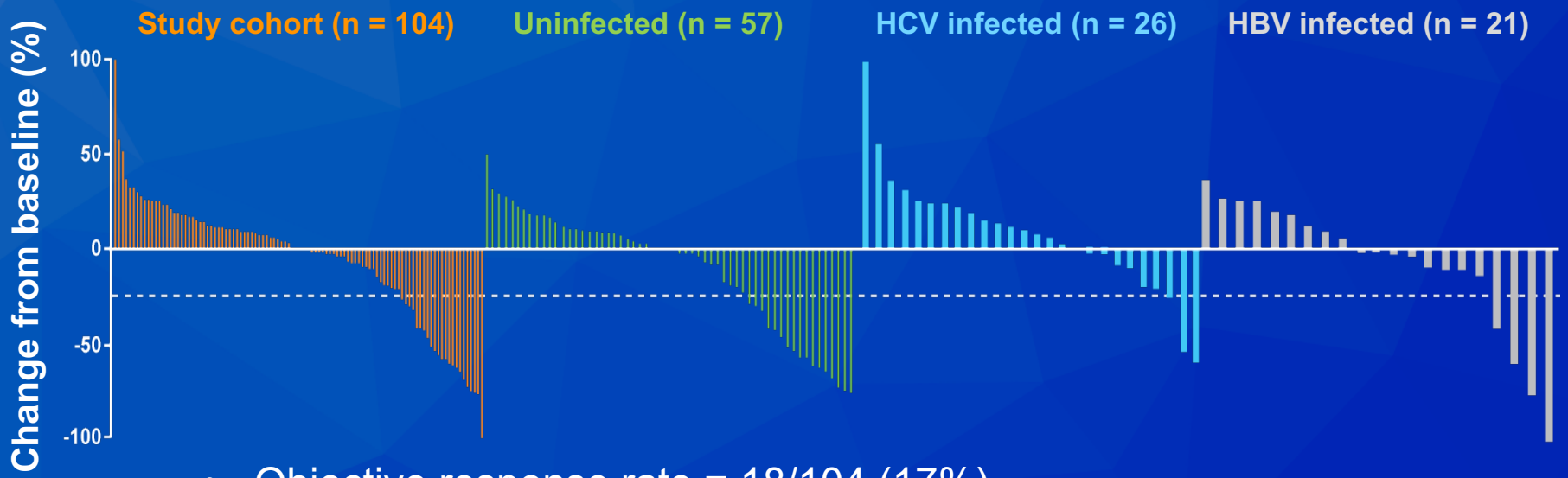


- **Primary endpoint:** Objective response rate

Zhu AX et al. *Lancet Oncol* 2018;19(7):940-52.

KEYNOTE-224: Response and Survival Results

Maximum Percentage Changes from Baseline in Target Lesions



- Objective response rate = 18/104 (17%)
  - CR = 1 (1%)
- Disease control rate = 64/104 (62%)
- Median time to response = 2.1 mo
- Median duration of response = Not reached
- Median OS = 12.9 mo; 12-mo OS = 54%
- Median PFS = 4.9 mo; 12-mo PFS = 28%

Zhu AX et al. *Lancet Oncol* 2018;19(7):940-52.

KEYNOTE-224: Select Treatment-Related AEs

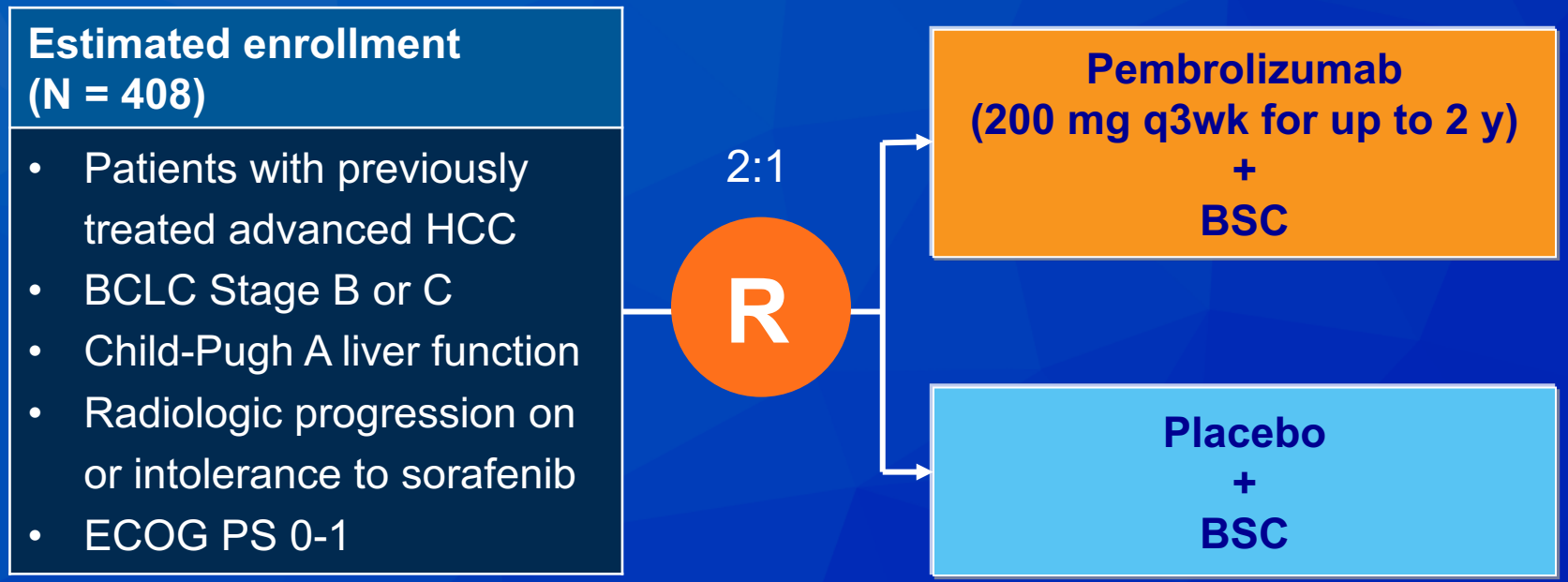
Event (N = 104)	All Grade	Grade ≥3
Fatigue	22 (21%)	4 (4%)
Increased AST	14 (13%)	7 (7%)
Decreased appetite	7 (7%)	1 (1%)
Increased ALT	9 (9%)	4 (4%)
Hyperbilirubinemia	5 (5%)	2 (2%)
Dyspnea	5 (5%)	1 (1%)
Anemia	3 (3%)	1 (1%)
Adrenal insufficiency	3 (3%)	2 (2%)
Cardiac failure	1 (1%)	1 (1%)

- One death associated with ulcerative esophagitis was attributed to treatment.
- Immune-mediated hepatitis occurred in 3 (3%) patients, but there were no reported cases of viral flares.

Zhu AX et al. *Lancet Oncol* 2018;19(7):940-52.

KEYNOTE-240: Ongoing Phase III Trial Design

NCT02702401



- **Primary endpoints: OS and PFS**

Clinicaltrials.gov.

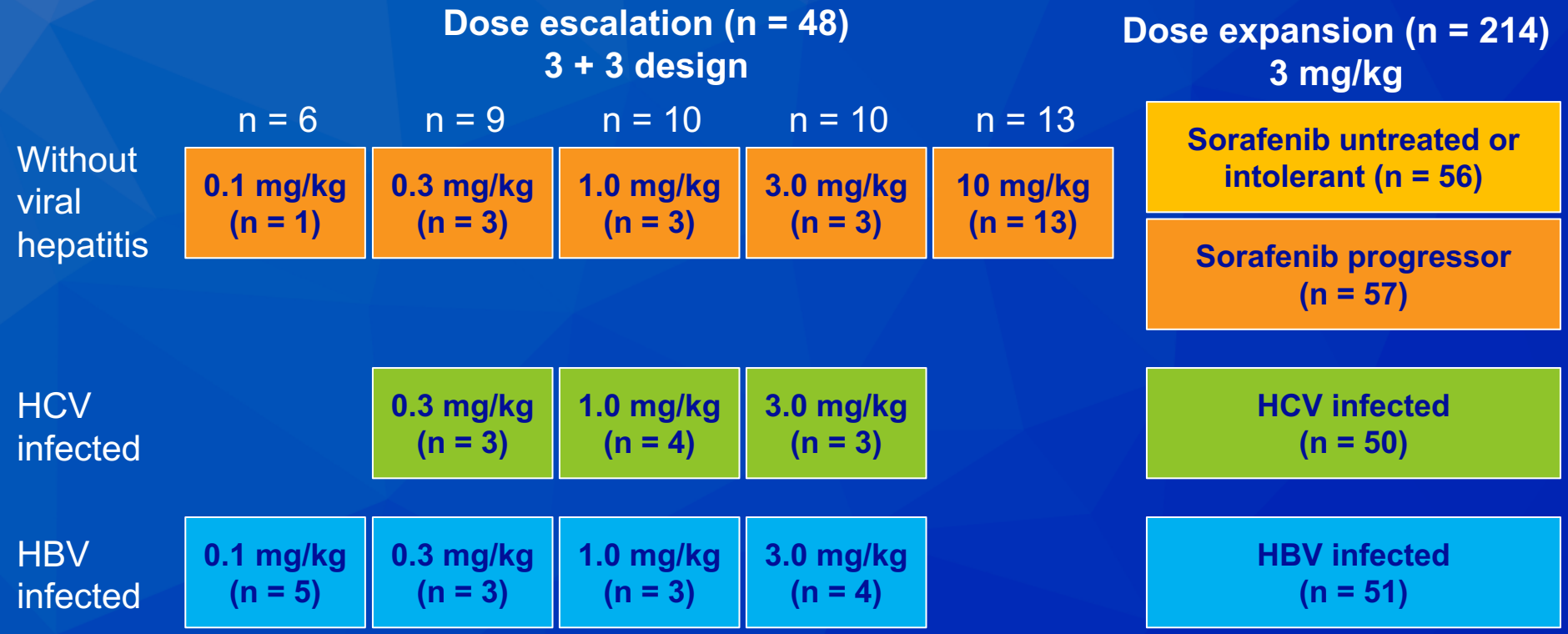
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Anthony B El-Khoueiry,*Bruno Sangro,*Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero

Lancet 2017;389(10088):2492-502.

CheckMate 040: Phase I/II Trial Design

Eligibility (N = 262)



HCV = Hepatitis C virus; HBV = Hepatitis B virus

- **Primary endpoints: Safety and tolerability (dose-escalation phase); objective response rate (dose-expansion phase)**

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

CheckMate 040: Response and Survival Outcomes

Response	Uninfected untreated/ intolerant (n = 56)	Uninfected progressor (n = 57)	HCV infected (n = 50)	HBV infected (n = 51)	All pts (n = 214)
Objective response	13 (23%)	12 (21%)	10 (20%)	7 (14%)	42 (20%)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Median DoR	8.4 mo	NYR	9.9 mo	NYR	9.9 mo
Median OS	NYR	13.2 mo	NYR	NYR	NYR
6-mo OS	89%	75%	85%	84%	83%
9-mo OS	82%	63%	81%	70%	74%
Median PFS	5.4 mo	4.0 mo	4.0 mo	4.0 mo	4.0 mo

NYR = not yet reached; DoR = duration of response

- Nivolumab at a dose of 3 mg/kg was chosen for the dose-expansion phase
- Objective response: 15% (dose escalation) and 20% (dose expansion)

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

CheckMate 040: Select AEs – Dose-Escalation Phase

Grade 3/4 AE	0.1 mg/kg (n = 6)	0.3 mg/kg (n = 9)	1 mg/kg (n = 10)	3 mg/kg (n = 10)	10 mg/kg (n = 13)	All pts (n = 48)
Fatigue	1 (17%)	0	0	0	0	1 (2%)
Increased AST	0	2 (22%)	2 (20%)	1 (10%)	0	5 (10%)
Increased ALT	0	2 (22%)	0	1 (10%)	0	3 (6%)
Increased lipase	1 (17%)	0	4 (40%)	1 (10%)	0	6 (13%)
Increased amylase	0	0	1 (10%)	1 (10%)	0	4 (4%)
Anemia	0	0	1 (10%)	0	0	1 (2%)

- There were no treatment-related deaths
- There were 3 AEs leading to discontinuation (1 each in the 0.3 mg/kg, 3 mg/kg and 10 mg/kg arms)

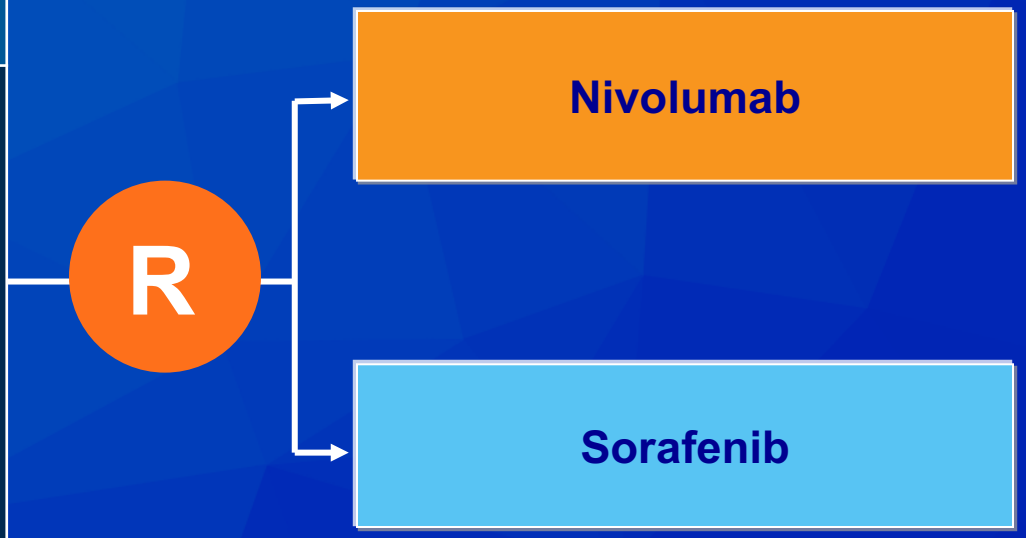
El-Khoueiry AB et al. *Lancet* 2017;389(10088):2492-502.

CheckMate 459: Ongoing Phase III Trial Design

NCT02576509

Estimated enrollment (N = 726)

- Patients with previously untreated advanced HCC
- Patients ineligible for surgical and/or locoregional therapies
- Child-Pugh A
- ECOG PS 0-1
- No known or suspected autoimmune disease



- **Primary endpoint: OS**

Clinicaltrials.gov.