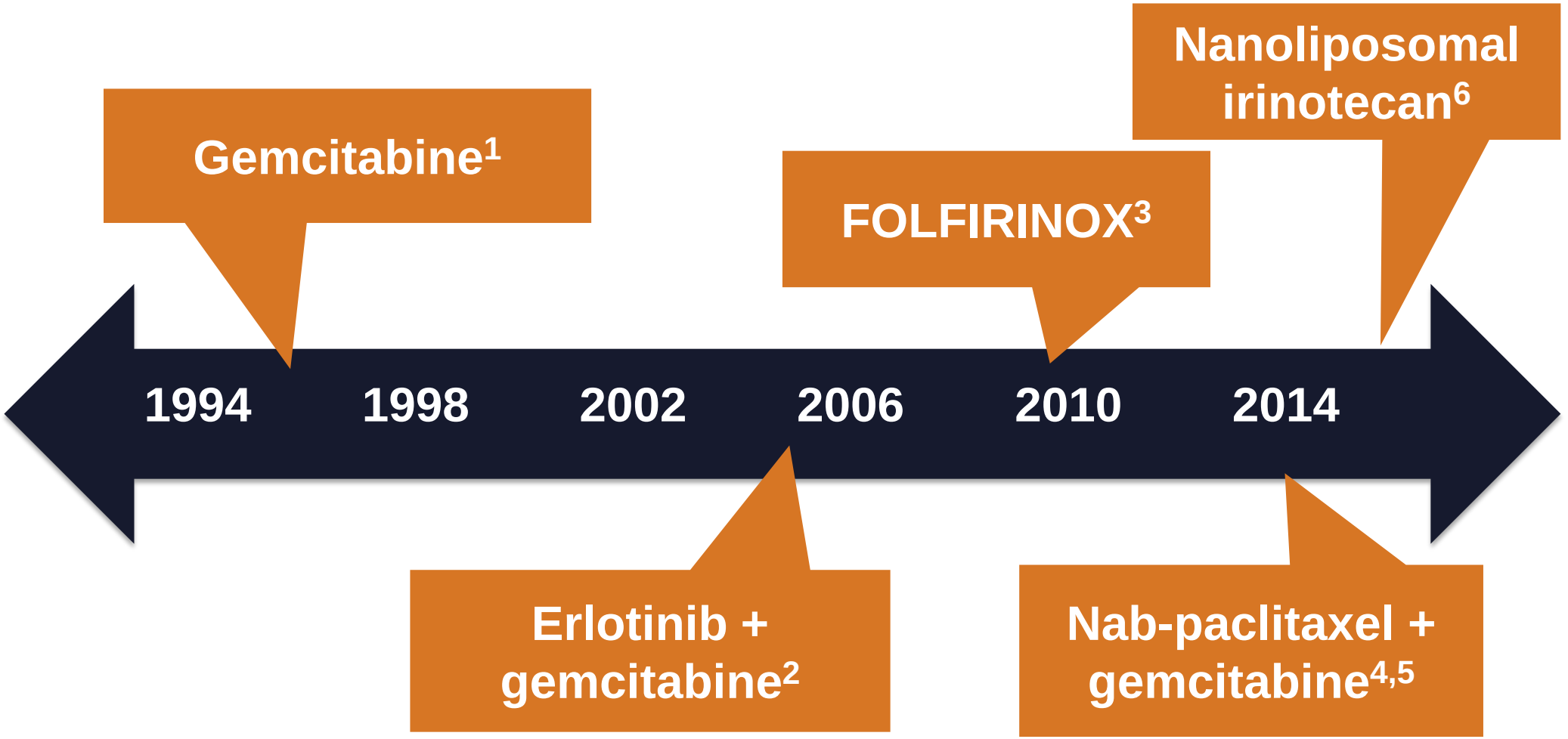
13TH ANNUAL NEW ORLEANS SUMMER CANCER MEETING

George P. Kim, M.D.
University of Florida Health Oncology

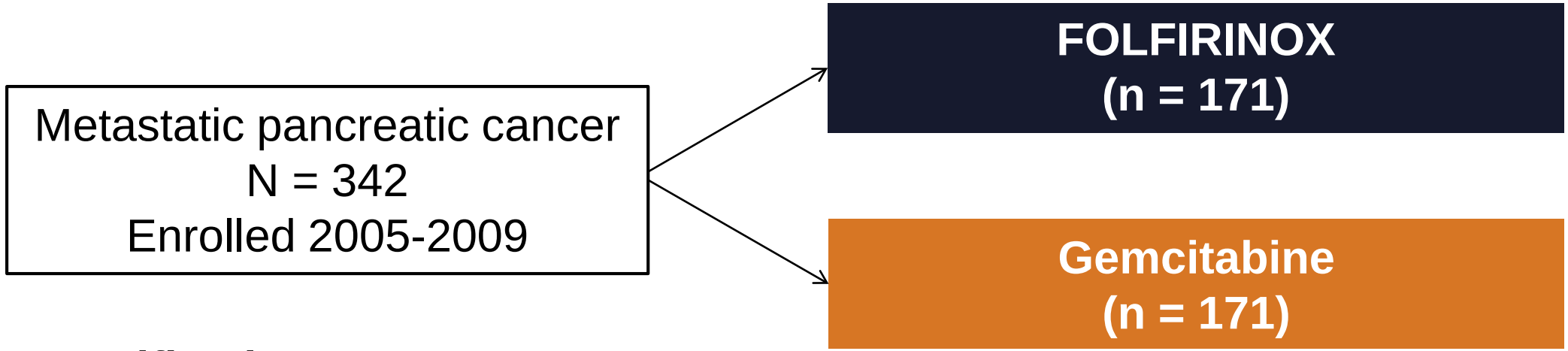
Pancreatic Cancer

Approved/Recommended Treatment Options for Pancreatic Cancer: A Timeline



1. Burris HA et al. *J Clin Oncol*. 1997;15:2403-2413. 2. Moore MJ et al. *J Clin Oncol.* 2007;25:1960-1966.
3. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825. 4. Von Hoff DD et al. *N Engl J Med*. 2013;369:1691-1703.
5. Goldstein D et al. *J Natl Cancer Inst*. 2015;107:djv279. 6. Wang-Gillam A et al. *Lancet.* 2016;387:545-557.

ACCORD: FOLFIRINOX Versus Gemcitabine[1]



Stratification

- PS: 0 or 1
- Tumor location
- Center

Endpoints

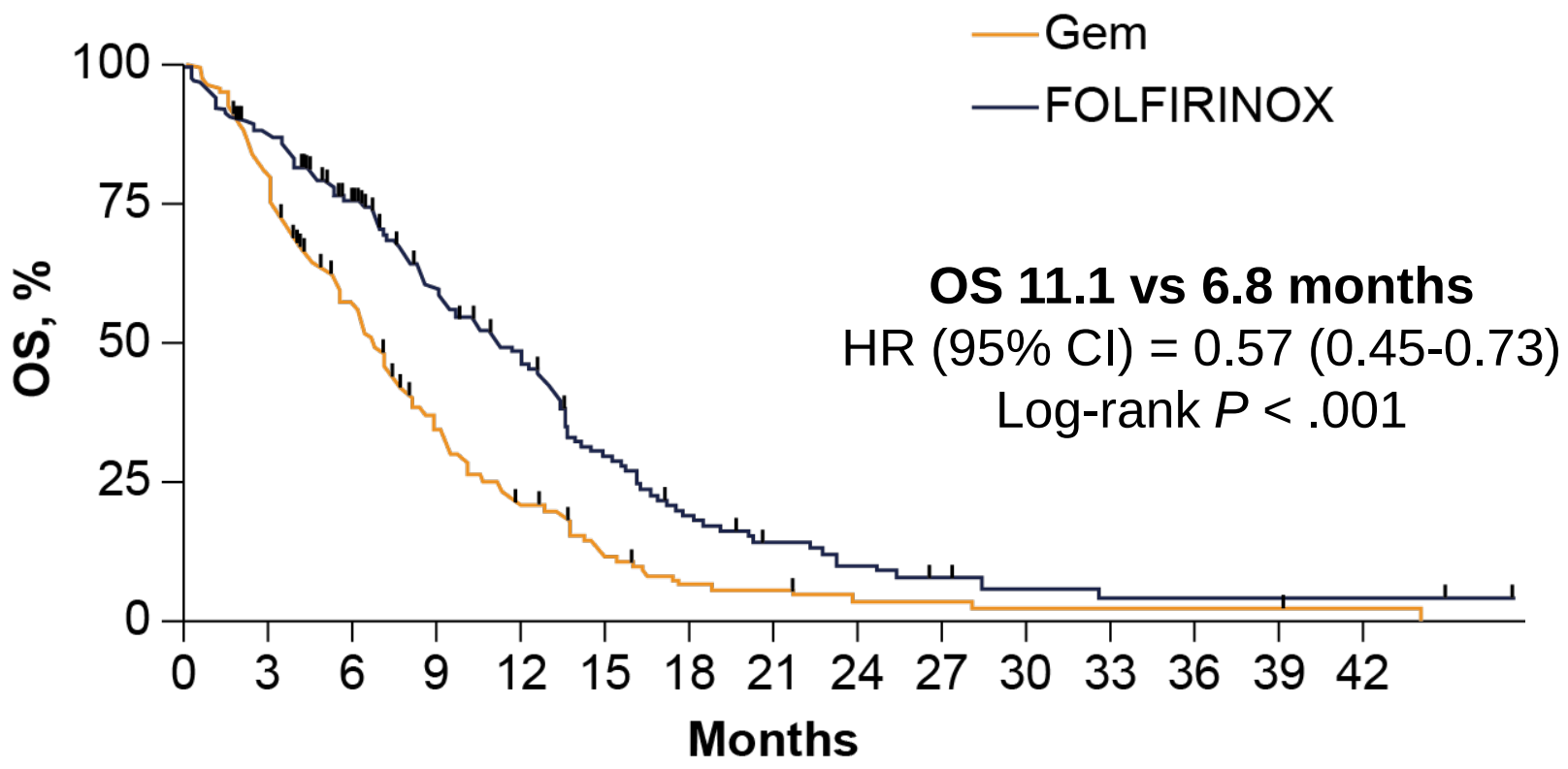
- Primary: OS
- Secondary: ORR, toxicity, PFS, and QOL

FOLFIRINOX

- Oxaliplatin 85 mg/m^2
- Leucovorin 400 mg/m^2
- Irinotecan 180 mg/m^2
- 5-FU 400 mg/m^2 bolus
- 5-FU 2,400 mg/m^2 over 46 h

1. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825.

ACCORD Results: Overall Survival[1]



No. at Risk

Gem	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

1. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825.

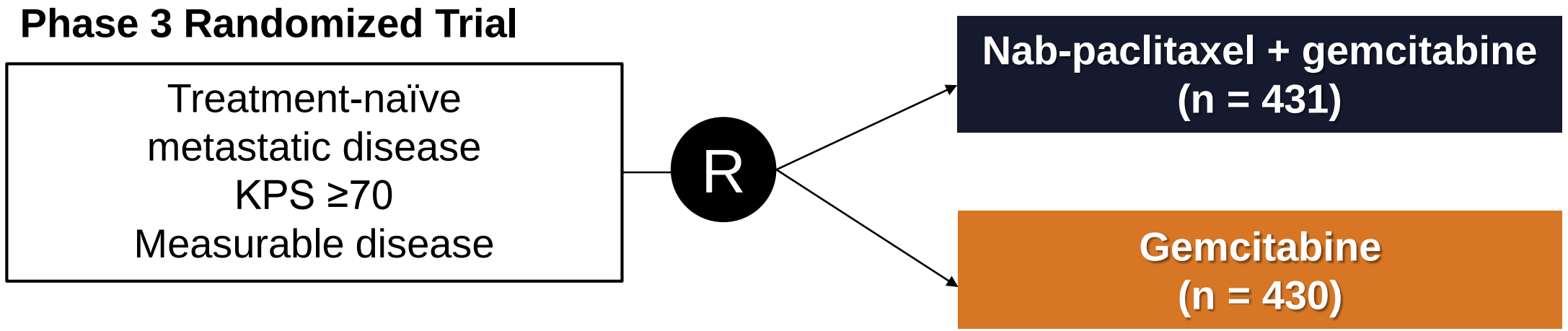
ACCORD: Common Grade 3 or 4 Adverse Events[1]

Event	FOLFIRINOX (n = 171)	Gemcitabine (n = 171)	*P*
	n/N (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	< .001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS

- **42.5% of patients who received FOLFIRINOX required growth factor support**

1. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825.

MPACT: Gemcitabine +/- Nab-Paclitaxel[1]



Stratification

- KPS
- Region
- Liver metastasis

Endpoints

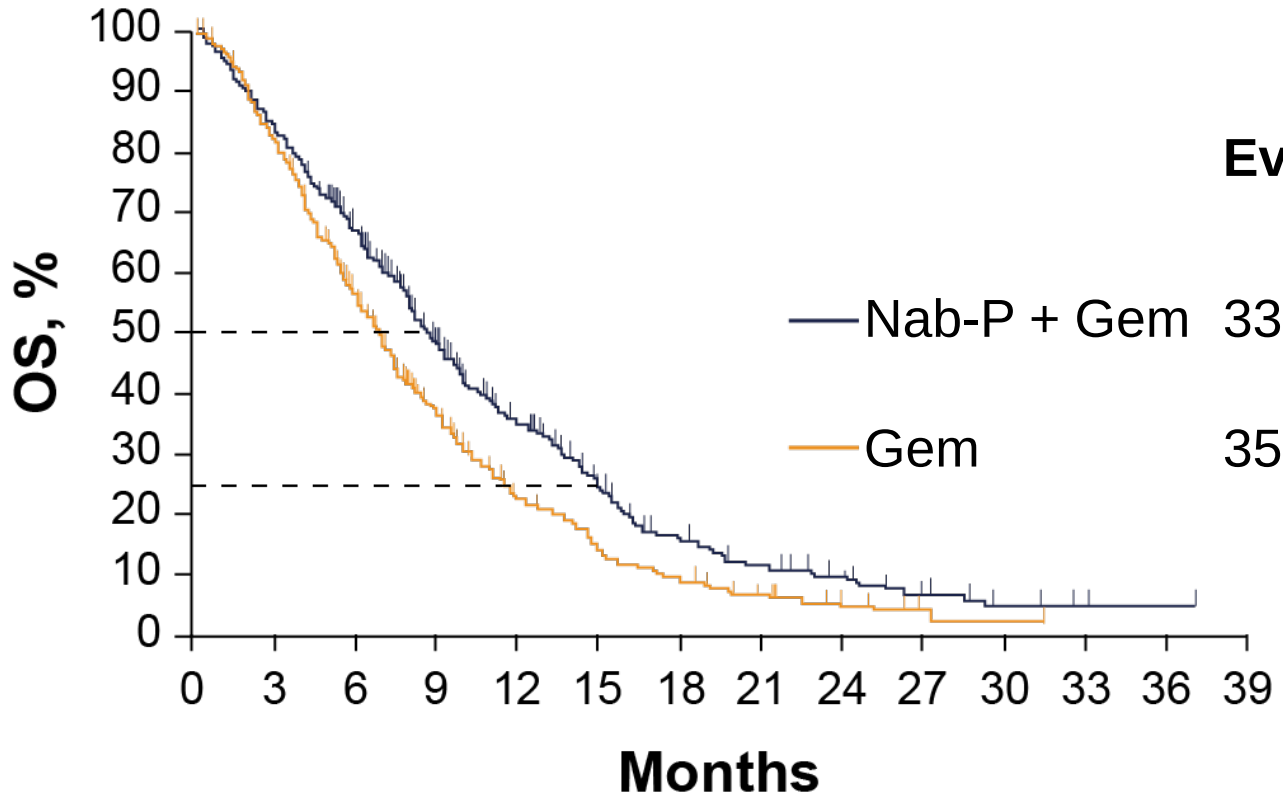
- Primary: OS
- Secondary
  - PFS
  - ORR by independent review
  - Safety and tolerability

Nab-paclitaxel: 125 mg/m^2 QW 3/4
Gemcitabine: 1,000 mg/m^2 QW 3/4

Gemcitabine: 1,000 mg/m^2 QW 7/8 then 3/4

1. Von Hoff DD et al. *N Engl J Med.* 2013;369:1691-1703.

MPACT: Overall Survival[1,2]



	OS, months		
	Events/n (%)	**Median (95% CI)**	**75th Percentile**
Nab-P + Gem	333/431 (77)	8.5 (7.89-9.53)	14.8
Gem	359/430 (83)	6.7 (6.01-7.23)	11.4

HR = 0.72 (0.617-0.835)
P = .000015

No. at Risk

nab-P + Gem	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem	430	340	220	124	69	40	26	15	7	3	1	0	0	0

1. Von Hoff DD et al. *N Engl J Med.* 2013;369:1691-1703. 2. Goldstein D et al. *J Natl Cancer Inst.* 2015;107. pii: dju413.

MPACT: Adverse Events and Growth Factor Use

Event	Nab-Paclitaxel + Gemcitabine (n = 421)	Gemcitabine (n = 402)
Grade ≥3 nonhematologic AE occurring in >5% of patients, n (%)		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset, d	140	113
Median time to improvement by one grade, d	21	29
Median time to improvement to grade ≤1, d	29	NR
Use of nab-paclitaxel resumed, n/N (%)	31/70 (44)	NA

1. Von Hoff DD et al. *N Engl J Med.* 2013;369:1691-1703.

Comparison: FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel Phase 3 Trials[1,2]

	FOLFIRINOX	Gemcitabine/Nab-Paclitaxel
Sample size	342	861
Locations	France	North America, Europe, Australia
Eligibility criteria, PS	ECOG 0-1	KPS 70-100 (ECOG 2)
Survival, median (months)	11.1	8.5 (12.6)
1-year survival, %	48	35
Objective response, %	32	23[a] (29[b])
Toxicity (grade 3/4)	Fatigue, 24% Neutropenia, 46% Neuropathy, 9%	Fatigue, 17% Neutropenia, 38% Neuropathy, 17%
Poorer PS patients?	N/A	Benefit maintained in KPS 70-80 pts
QOL data?	Yes	Yes
More cost effective than gem?	Yes	Yes

[a] Independent review. [b] Investigator review.

1. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825. 2. Von Hoff DD et al. *N Engl J Med.* 2013;369:1691-1703.

Guideline Recommendations: Metastatic Disease[1,2]

Good Performance Status[a]

- **Clinical trials**
- **Preferred**
  - FOLFIRINOX (PS 0-1)
  - Gemcitabine + nab-paclitaxel (KPS ≥70)
- Gemcitabine + erlotinib
- Gemcitabine

Poor Performance Status

- Gemcitabine[b]
- Capecitabine[c]
- Continuous 5-FU[c]

ASCO guidelines recommend gemcitabine alone for patients with PS = 2 or comorbidities; for PS ≥3 emphasis on supportive care measures

[a] All NCCN category 1 recommendations. [b] Category 2A recommendation. [c] Category 2B recommendation.

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 11, 2018.
2. Sohal DPS et al. *J Clin Oncol*. 2016;34:2784-2796.

Guideline Recommendations: Second-Line Therapy[1,2]

Prior Gemcitabine

Category 1

- 5-FU/LV + nal-IRI
  - ASCO recommends PS 0-1

Category 2A

- FOLFIRINOX
- Oxaliplatin/5-FU/LV
- FOLFOX
- Capecitabine/oxaliplatin
- Capecitabine
- 5-FU continuous

Prior Fluoropyrimidine

Category 2A

- Gemcitabine + nab-paclitaxel
- Gemcitabine
- Gemcitabine cisplatin
- Gemcitabine erlotinib
- 5-FU/LV + nal-IRI (no prior irinotecan)

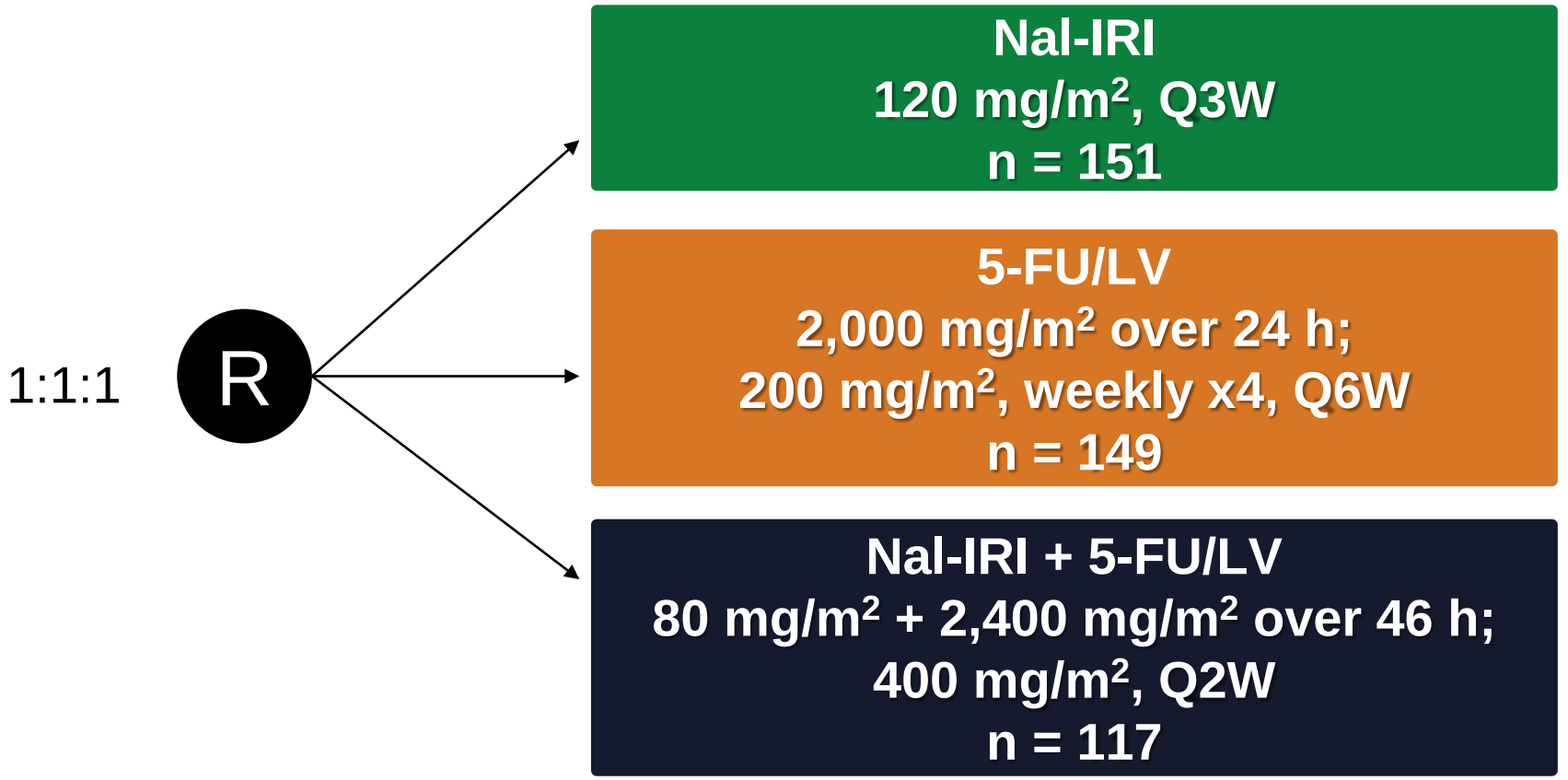
1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 11, 2018.
2. Sohal DPS et al. *J Clin Oncol*. 2016;34:2784-2796.

NAPOLI-1 Study of Nal-IRI[1]

Metastatic pancreatic cancer
Received prior gemcitabine-based therapy
N = 417

Stratification factors

- Albumin (<4.0 g/dL vs ≥4.0 g/dL)
- KPS (70 and 80 vs ≥90)
- Ethnicity (Caucasian vs East Asian vs others)

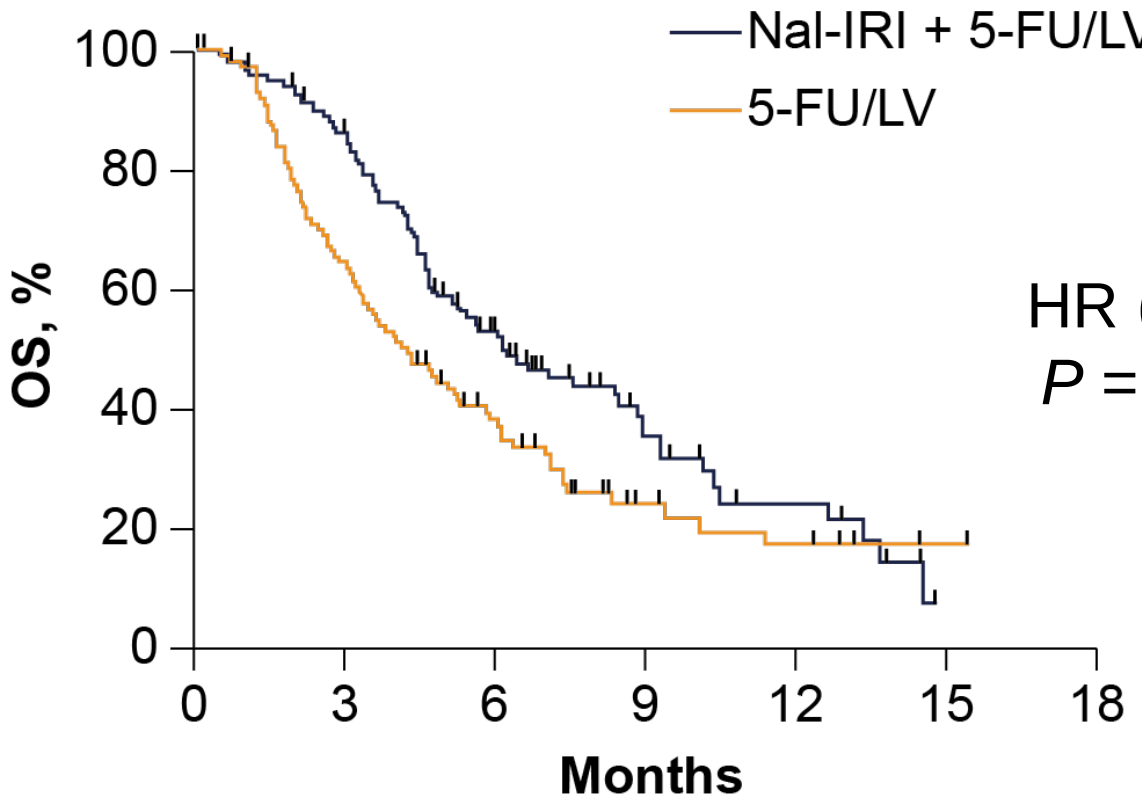


Primary endpoint: OS

Secondary endpoints: PFS, ORR, CA 19-9 response, and safety

1. Wang-Gillam A et al. *Lancet.* 2016;387:545-557.

NAPOLI-1: Overall Survival[1]



OS 6.1 vs 4.2 months

HR (95% CI) = 0.67 (0.49-0.92)

P = .012 (unstratified log-rank)

No. at Risk

Nal-IRI + 5-FU/LV	117	97	51	20	8	0	0
5-FU/LV	119	68	34	11	6	1	0

1. Wang-Gillam A et al. *Lancet.* 2016;387:545-557.

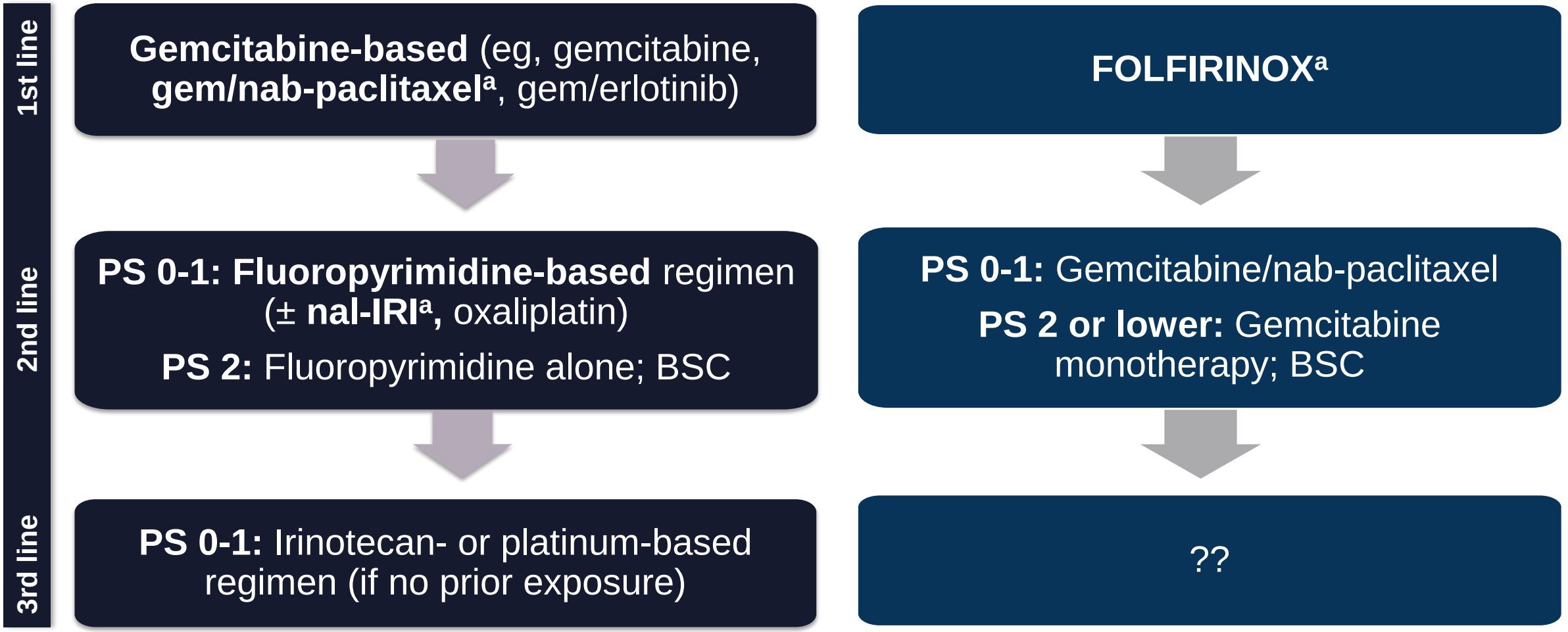
NAPOLI-1: Toxicities[1]

Event, n (%)	Nal-IRI + 5-FU/LV (n = 117)		5-FU/LV (n = 134)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
Diarrhea	69 (59)	15 (13)	35 (26)	6 (4)
Vomiting	61 (52)	13 (11)	35 (26)	4 (3)
Nausea	60 (51)	9 (8)	46 (34)	4 (3)
Decreased appetite	52 (44)	5 (4)	43 (32)	3 (2)
Fatigue	47 (40)	16 (14)	37 (28)	5 (4)
Neutropenia[a]	46 (39)	32 (27)	7 (5)	2 (1)
Anemia	44 (38)	11 (9)	31 (23)	9 (7)
Hypokalemia	14 (12)	4 (3)	12 (9)	3 (2)

[a] Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia

1. Wang-Gillam A et al. *Lancet*. 2016;387:545-557.

Practice Point: Current Approaches in Treatment Sequencing for Advanced Pancreatic Cancer



[a] Category 1 NCCN recommendation.[1]

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 11, 2018.

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

Canadian Cancer Trials Group

Groupe canadien des essais sur le cancer

unicancer

LA LIGUE CONTRE LE CANCER

PRODIGE 24/CCTG PA.6, an Unicancer GI trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J-L. Raoul, L. Choné, E. François, P. Artru, J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, C. Jouffroy, P. Rat, F. Castan, J-B. Bachet, for the CCTG and the UNICANCER-GI /PRODIGE Group

Institut de Cancérologie de Lorraine, Nancy; Hôpital Beaujon, Clichy; Hôpital Huriez, Lille; Centre Paul Strauss, Strasbourg; Princess Margaret Hospital, Toronto; Institut Paoli-Calmettes, Marseille; University hospital, Nancy; Centre Antoine-Lacassagne, Nice; Hôpital Jean-Mermoz, Lyon; Kingston General Hospital, Kingston; Hôpital Trousseau, Tours; University Hospital, Montpellier; CHD Vendée, La Roche-sur-Yon; Institut du Cancer de Montpellier, Montpellier; Centre Hospitalier Universitaire, Dijon; Hôpital Pitié-Salpétrière, Paris; Canadian Cancer Trials Group, Kingston, Canada; R&D UNICANCER, Paris; France

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Thierry Conroy

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

Background

- 6 months Gemcitabine (Gem) and/or fluoropyrimidine (S-1 in Japan) are standard adjuvant treatments for resected pancreatic cancer (PC) patients

Neuhaus P. *et al.* ASCO Annual Meeting 2008; #LBA4504
Uesaka K *et al.* Lancet 2016;388:248-57
Neoptolemos JP *et al.* Lancet 2017; 389:1011-24.

- However 71%-76% of patients still relapse within 2 years despite these treatments and there is an obvious need for a better drug or drugs' combination

Neoptolemos JP *et al.* JAMA. 2010;304:1073-81
Oettle H *et al.* JAMA. 2013;310:1473-81
Sinn M *et al.* J Clin Oncol. 2017;35:3330-7

- FOLFIRINOX is more effective than Gem as first-line treatment in metastatic PC for patients with good Performance Status

Conroy T *et al.* N Engl J Med 2011;364:1817-25

- The « modified » FOLFIRINOX regimen with no bolus fluorouracil is associated with less hematological toxicities and less diarrhea rate but maintained efficacy.

Mahaseth H *et al.* Pancreas. 2013;42:1311-5

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE

1:1

mFolfirinox

Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
**Reduced to 150 mg/m² after patient 162*

Gemcitabine

1000 mg/m², qw 3/4 *weeks;*
6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

Key Inclusion Criteria

- Histologically confirmed resected pancreatic ductal adenocarcinoma
- Macroscopically complete resection (R0 or R1 resection)
- Patients able to receive chemotherapy within 12 weeks after resection
- ECOG performance status 0 or 1
- Patients aged from 18 to 79 years
- No prior radiotherapy or chemotherapy
- Adequate hematologic/blood chemistry levels
- Patient information and written informed consent

Key Exclusion Criteria

- Metastatic disease, or macroscopic incomplete tumor removal (R2 resection)
- Postoperative CA 19-9 ≥ 180 U/ml assessed within 21 days of randomization
- Symptomatic heart failure or coronary heart disease
- Major comorbidity, active infection, history of HIV or uncontrolled diabetes
- Inflammatory bowel disease, or occlusion or sub-occlusion of the intestine or severe postoperative uncontrolled diarrhea
- Concomitant occurrence of another cancer, or significant history of cancer

Endpoints

- **Primary: Disease-Free Survival (DFS)**
- **Secondary:**
  - **Toxicity (NCI-CTC version 4.0 grading)**
  - **Overall survival (OS)**
  - **Cancer specific survival (SS)**
  - **Metastasis-free survival (MFS)**

Statistical considerations

Hypothesis:

- Study designed to have 80% power to detect an increase of 10% in 3 year-DFS (17% to 27%) corresponding to a hazard ratio (HR) = 0.74
- DFS defined as the first occurrence of any tumor recurrence or metastases, second cancer or death from any cause

Required sample size:

- 490 patients required to reach 342 events for final analysis, based on the use of the log-rank test with a two-sided significance level of 5%

Patients baseline characteristics

Characteristics		mFolfirinox N=247	Gemcitabine N=246	p
Median age (yrs) [range]		63 [30-79]	64 [30-81]	0.09
Gender male		57.5 %	55.6 %	0.67
ECOG PS	0	49.8 %	52.5 %	0.55
	1	50.2 %	47.5 %	
Diabetes		25.3 %	26.6 %	0.44

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

Pancreatic tumors baseline characteristics

Characteristics	mFolfirinox N=247	Gemcitabine N=246	p
Median size of primary tumor [mm, range]	**30** [8-90]	**30** [6-120]	**0.50**
T1-2/T3-4 (%)	**12.5/87.5**	**9.8 /90.2**	**0.33**
N0/N1 (%)	**22.3 /77.7**	**24.5 /75.5**	**0.60**
Stage: I/IIA/IIB/III-IV (%)	**4.9/17.4 /74.1/3.6**	**5.7/19.1 /72.8/2.4**	**0.81**
Tumor grading : well/moderately/poorly differentiated (%)	**30.6/54.1/15.3**	**33.9/53.7/12.5**	**0.58**
Whipple resection procedure (%)	**82.1**	**76.8**	**0.53**
R1 resection (%)	**40.1**	**45.7**	**0.24**
Venous resection (%)	**21.3**	**28.2**	**0.08**
Lymphovascular emboli (%)	**73.7**	**63.1**	**0.02**

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

Six-month treatment completion

	mFolfirinox No = 238	Gemcitabine No = 243	P
All cycles of chemotherapy	66.4%	79.0%	0.002
Planned administrations	12	18	–
Median No. administrations	12 [1-12]	18 [1-18]	
No. administrations delayed	14.4%	3.9%	< 0.001
Relative dose-intensity > 0.70	48.7%	91.4%	< 0.001
Early stop	80 (33.6%)	51 (21.0%)	0.002
due to :			
- relapse	15 (6.3%)	26 (10.7%)	
- toxicity	21 (8.8%)	11 (4.5%)	
- Principal Investigator's decision	7 (2.9%)	2 (0.8%)	
- patient decision	13 (5.4%)	2 (0.8%)	

Safety: hematologic AEs

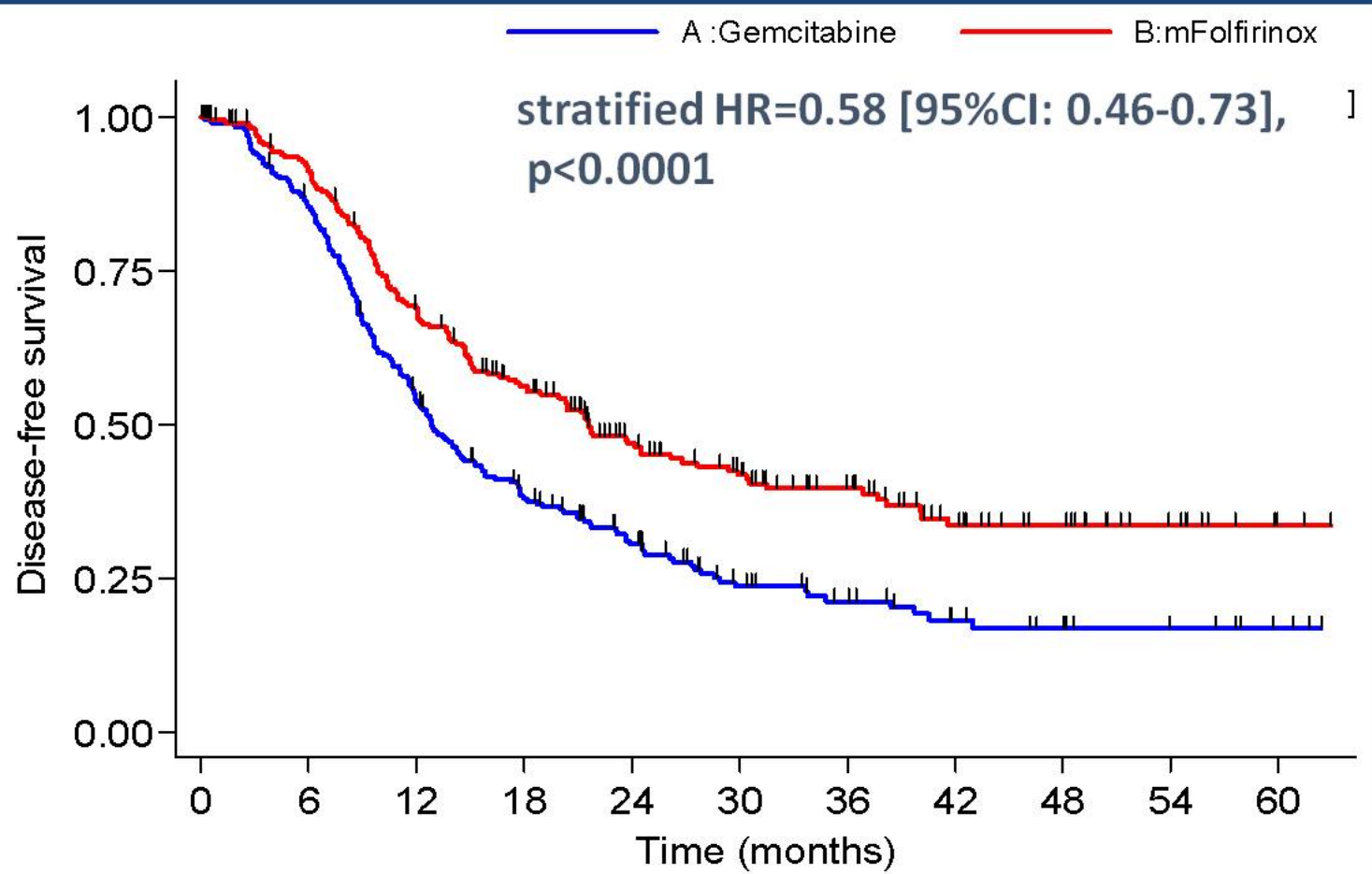
Grade 3-4 adverse events, % per patient	mFolfirinox N=238	Gemcitabine N=243	p
Anemia	0.0%	0.4%	1.00
Neutropenia	28.4 %	26.0 %	0.56
G-CSF use	59.9 %	3.7 %	<0.001
Febrile neutropenia	2.9 %	3.7 %	0.65
Lymphopenia	1.3 %	2.9 %	0.34
Thrombocytopenia	1.3 %	4.5 %	0.03

Safety: main nonhematologic AEs

AE, % per patient	mFolfirinox N=238		Gemcitabine N=243		p-value all grades
	All grades	Grade 3/4	All grades	Grade 3/4	
Diarrhea	84.4 %	18.6 %*	49 %	3.7 %	< 0.001
Sensory peripheral neuropathy	61.2 %	9.3 %	8.7 %	-	< 0.001
Fatigue	84 %	11 %	77.6 %	4.6 %	0.003
Vomiting	46 %	5 %	29 %	1.2 %	< 0.001
Mucositis	33.8 %	2.5 %	14.9 %	0 %	< 0.001
Alopecia	27 %	-	19.5 %	-	0.07
Hand-foot syndrome	5 %	0.4 %	0.8 %	-	0.023

* 8.6% during cycle 1; 6.3% during cycle 2; 3% at cycles 3-5; 1% at cycles 6-12
Grade 3-4 diarrhea is significantly related to a higher number of lymph nodes examined, p = 0.02.

Disease-Free Survival



Number at risk

A:Gemcitabine	246	205	127	85	59	34	24	15	10	7	3
B:mFolfirinox	247	210	156	118	80	60	46	29	21	11	2

No DFS events: 314

Median DFS:

- **21.6 mths [95%CI: 17.7-27.6] with mFolfirinox**
- **12.8 mths [95%CI: 11.7-15.2] with Gemcitabine**

3-year DFS:

- **39.7% [95%CI: 32.8-46.6] with mFolfirinox**
- **21.4% [95%CI: 15.8-27.5] with Gemcitabine**

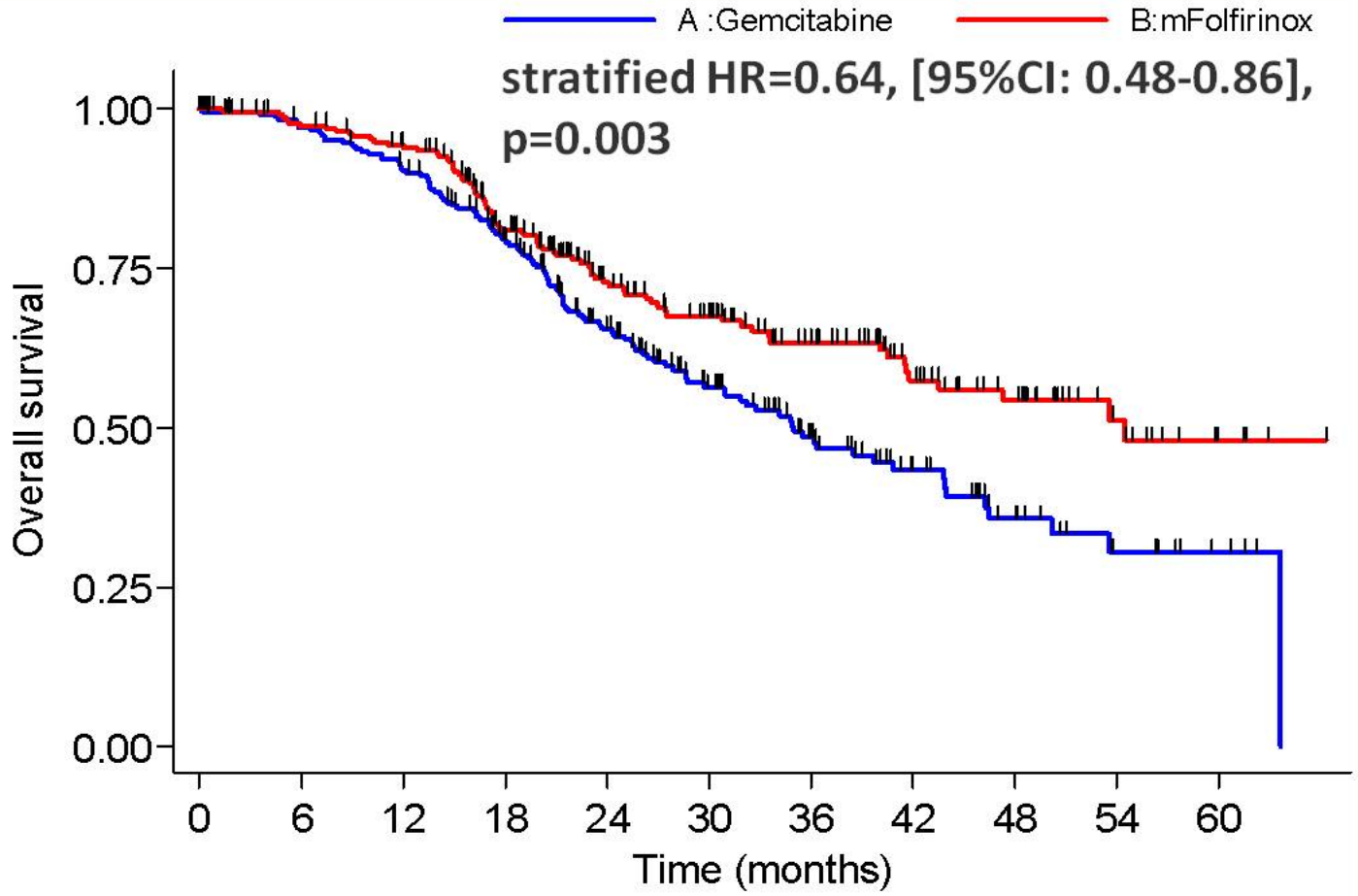
Prognostic factors for DFS

Univariate analysis			Multivariate analysis N=434 Events=280		
Factor	HR [95 % CI]	p-value	Factor	HR [95 % CI]*	p-value**
mFolfirinox group	0.58 [0.46-0.73]*	< 0.001	mFolfirinox group	0.59 [0.46-0.75]	< 0.001
Moderately or poorly differentiated tumor	1.34 [1.04-1.71]	0.02	Moderately or poorly differentiated tumor	1.42 [1.09-1.86]	<0.001
pN+	1.67 [1.25-2.22]	< 0.001	Portal vein resection	1.43 [1.05-1.94]	<0.001
R1 resection	1.45 [1.16-1.81]	0.001			
VMS resection	1.52 [1.05-2.20]	0.027			
Portal resection	1.43 [1.07-1.92]	0.014			
6 months treatment	0.60 [0.37-0.96]	0.03			

*Stratified on lymph node status, resection margins, and postoperative CA19-9

** Likelihood-ratio test

Overall Survival



Number at risk

A:Gemcitabine	246	233	215	171	120	81	55	33	18	9	4
B:mFolfirinox	247	223	210	165	119	91	68	46	32	16	4

Median overall survival:

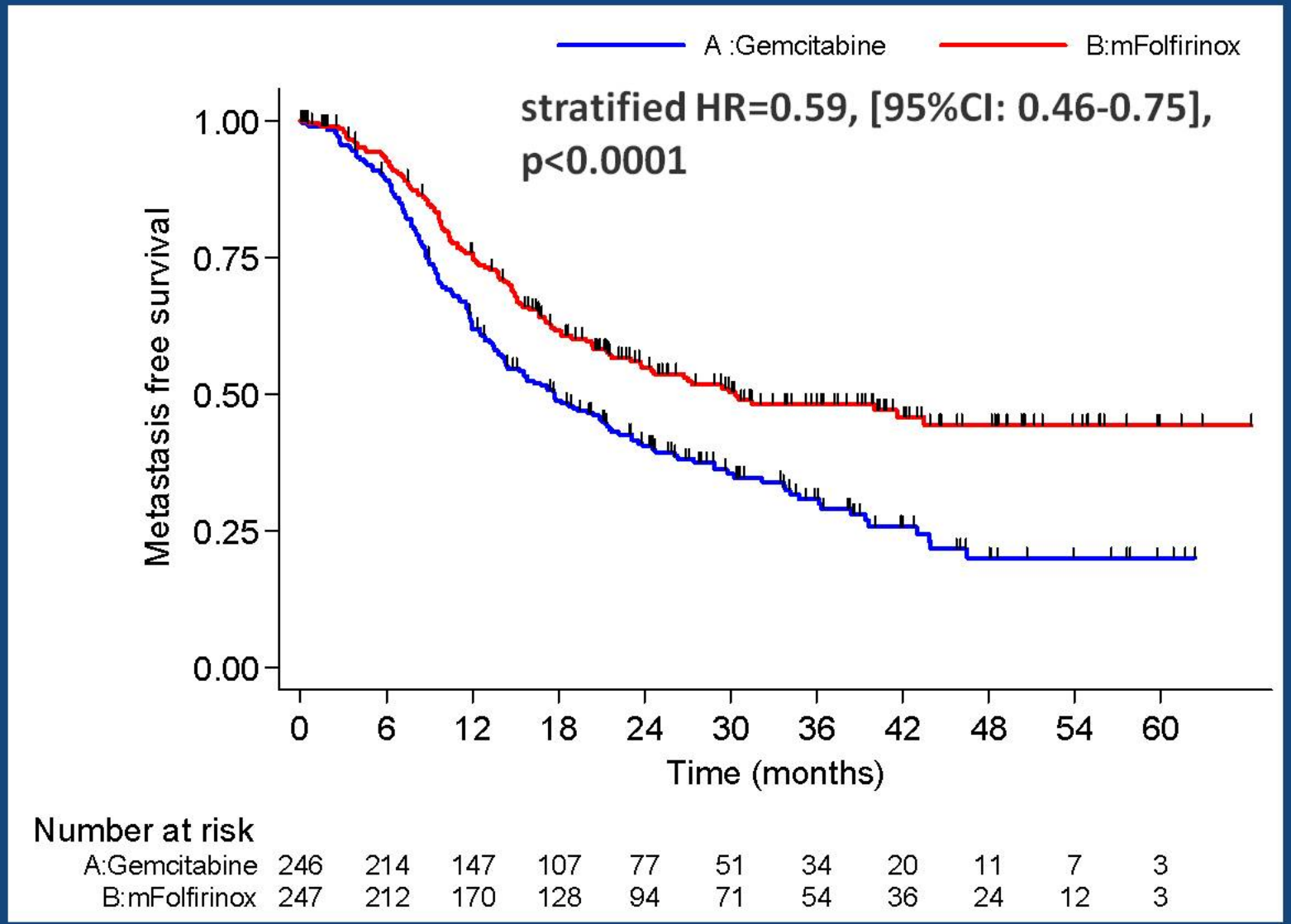
- **54.4 months** [95%CI: 41.8-NR] **with mFolfirinox**
- **35.0 months** [95%CI: 28.7-43.9] **with Gemcitabine**

3-year overall survival:

No OS events=192

- **63.4% (mFolfirinox) vs 48.6 % (Gem)**

Metastasis-free Survival



No MFS events: 273

Median:

- **30.4 months**
  [95%CI: 21.7-NR]
  with mFolfirinox
- **17.7 months**
  [95%CI: 14.2-21.5]
  with Gemcitabine

Presented By Thierry Conroy at 2018 ASCO Annual Meeting

Conclusions

- **Adjuvant chemotherapy with mFOLFIRINOX in resected PC patients is superior to Gem, with significantly improved Disease-Free Survival, Metastasis-free Survival, Specific Survival and Overall Survival**
- **Its superiority is observed in all predefined subgroups**
- **mFOLFIRINOX is more toxic than Gem, but is a safe regimen with manageable toxicities**
- **mFOLFIRINOX should now be considered a new standard of care after pancreatic cancer resection in patients with good performance status, at least in Western countries**

PRODIGE 24- Remaining Questions

What treatments were given with recurrence, which chemo regimens, balanced?

Was radiation given with local recurrence?

Based on treatment intensity, can adjuvant FNOX be given for 3 vs. 6 months?

Will APACT trial be positive and if not, will this impact metastatic treatment choices?

How will this impact neoadjuvant approaches?

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 Laetitia, PHELIP Jean-Marc, Le MALICOT Karine, WILLIET Nicolas, DESRAME Jérôme, VOLET Julien , PETORIN Caroline, MALKA David, REBISCHUNG Christine, APARICIO Thomas, LECAILLE Cédric, RINALDI Yves, TURPIN Anthony, BIGNON Anne-Laure, BACHET Jean-Baptiste, SEITZ Jean-François, LEPAGE Come, FRANCOIS Eric

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

 # 4000

FFCD unicancer

BACKGROUND

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

- The limiting toxicities of FOLFIRINOX regimen are hematologic and non-hematologic (digestive, neurotoxicities…)
- In our study we aimed to assess an oxaliplatin 'stop-and-go' strategy as OPTIMOX 1 in colorectal cancer* and an alternative sequential strategy

*Tournigand C JCO 2006; 20: 394-400

Design of PRODIGE 35 PANOPTIMOX study

Patients with metastatic pancreatic cancer
Not pretreated with CT

R

Arm A: 12 cycles of Folfirinox*

Arm B: Folfirinox (8 cycles) followed by LV5FU2** for disease control and reintroduction of Folfirinox in case of progression

Arm C: sequential treatment with Folfiri 3*** (2 months) and Gemcitabine**** (2 months)

Stratification factors
- Center
- Biliary stent
- Age <65 vs >65 years

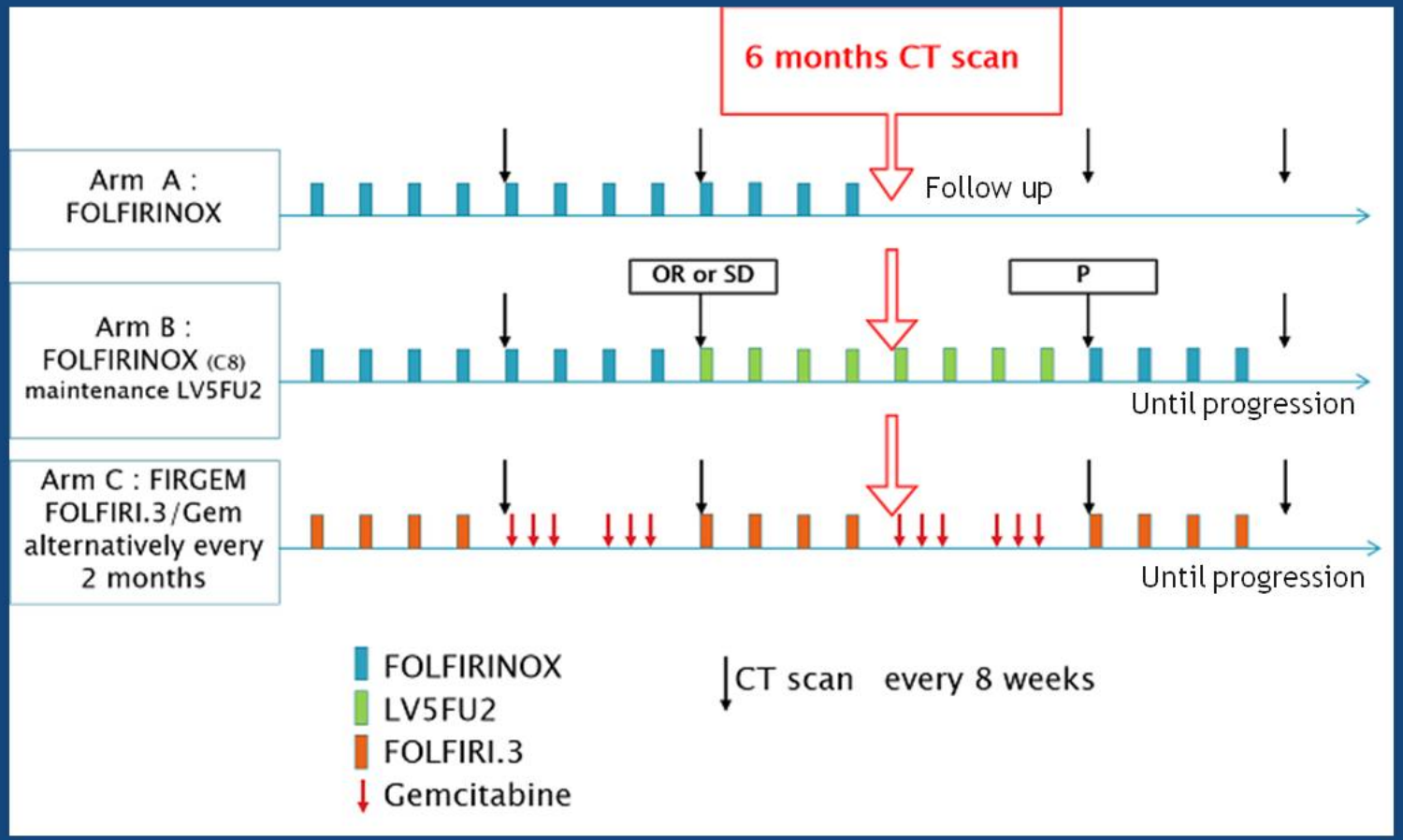
*Oxaliplatine 85 mg/m2, Irinotecan 180 mg/m2, Leucovorin 200 mg/m2, 5FU bolus 400 mg/m2, 5FU infusion 2400 mg/m2 46h; 14 days cycle

** Leucovorin 200 mg/m2, 5FU bolus 400 mg/m2, 5FU infusion 2400 mg/m2 46h; 14 days cycle

*** Irinotecan 90 mg/m2 D1, leucovorin 200 mg/m2, 5FU bolus 400 mg/m2, 5FU infusion 2400 mg/m2 46h, Irinotecan 90 mg/m2 D3; 14 days cycle

****Gemcitabine 1000 mg/m2 D1,D8,D15; 28 days cycle

Design of PRODIGE 35 PANOPTIMOX study



OBJECTIVES

- **Primary endpoint**: 6 months progression free survival rate (clinic or radiologic)

- **Secondary endpoints**:
  - overall survival
  - progression free survival
  - best response rate
  - safety (neurotoxicity)
  - second line therapy

PRIMARY ENDPOINT (mITT): 6 months Progression Free Survival rate

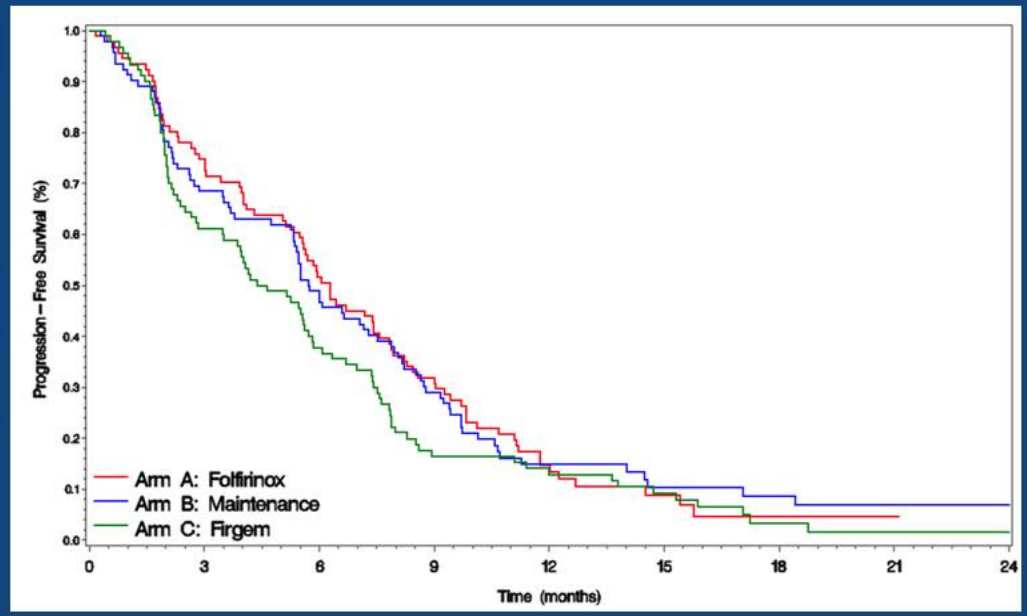
	Arm A (N = 87)	Arm B (N = 91)	Arm C (N = 88)
6 months PFS rate : N (%) [95% one-sided CI]	41 (47.1)	40 (44.0) [35.1 ; 53.1]	30 (34.1) [25.7 ; 43.3]

- Arm A results were consistent with PRODIGE 4 survival rate
- Firgem (arm C) was considered as ineffective
- **Folfirinox with maintenance by 5FU (arm B) was considered as effective**

PROGRESSION FREE SURVIVAL (PFS)

ITT Set	Arm A (N = 91)	Arm B (N = 92)	Arm C (N = 90)
Overall PFS* (mo) - Median - 95%CI	 6.3 5.3-7.6	 5.7 5.3-7.5	 4.5 3.5-5.7
9 months PFS (%)	31.9	29.1	16.4
12 months PFS(%)	14.7	14.9	12.9

*PFS was defined by first progression as any chemotherapy received

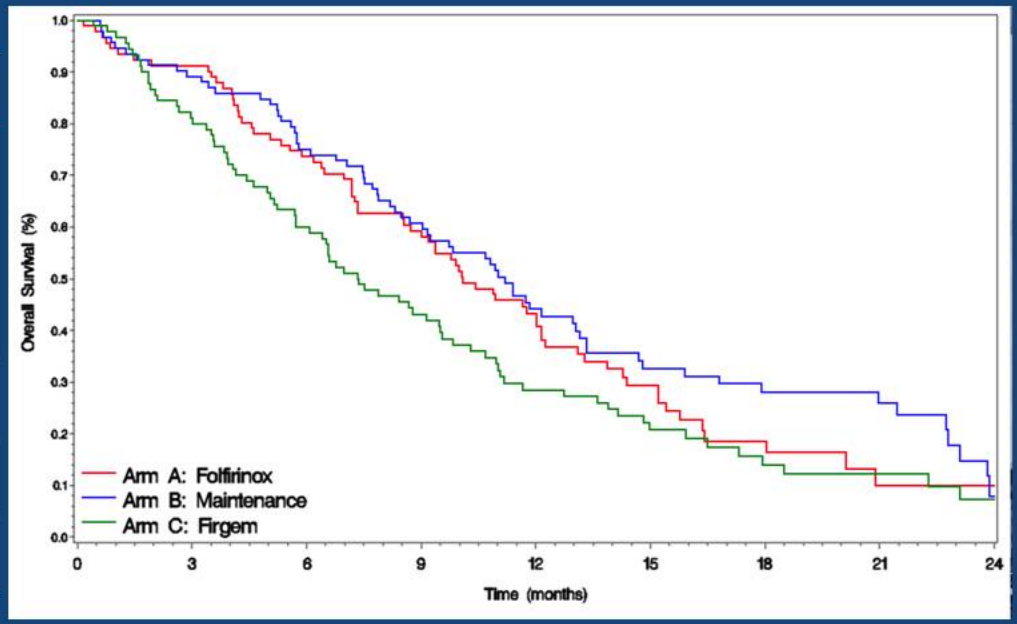


In arm B (maintenance therapy):

- PFS2 (progression during Folfirinox regimen): 7.1 months [5.32-8.05]
- Reintroduction of Folfirinox 29.7% (27 patients among 52 disease control at 6 months)

OVERALL SURVIVAL (OS)

ITT Set	Arm A (N = 91)	Arm B (N = 92)	Arm C (N = 90)
Overall survival (months) - Median - 95% CI	 10.1 8.5-12.2	 11.0 8.7-13.1	 7.3 5.7-9.5
6 months OS (%)	73.6	75.0	60.0
12 months OS (%)	43.3	44.1	28.5
18 months OS (%)	18.5	28*	13.9



*Exploratory analysis for overall survival: $p < 0.05$

BEST RESPONSE RATE

	Arm A (N = 83)	Arm B (N = 81)	Arm C (N = 74)
Objective response N (%)	31 (37.3)	31 (38.3)	20 (27.0)
Stable disease N (%)	35 (42.2)	31 (38.3)	37 (50.0)
Progression N (%)	17 (20.5)	19 (23.5)	17 (23.0)

TREATMENT

Intent-to-treat	Arm A (N = 88)	Arm B (N = 91)	Arm C (N = 87)
Mean number of cycles*	8.63	13.64	9.83
Mean duration of treatment (mo)	4.19	6.95	5.95
Mean duration of maintenance treatment (mo) in arm B	-	4.49	-
Number of folfirinox cycles in arm A and B (mean [SD])	8.66 [3.87]	7.7 [4.3]	-
Number of folfirinox cycles in arm A and B within first 6 months (mean [SD])	5.59 [3.34]	4.22 [2.38]	-
Number of folfirinox cycles in arm A and B after 6 months (mean [SD])	1.25 [0.45]	3.68 [2.58]	-

*all sequences

TOLERANCE:
Most common grade 3-4 adverse events

Two patients died from treatment-related cause: one from sepsis in the folfirinox arm, one from hypertonicity-induced coma in the firgem group

SP Set	Arm A (N = 88)	Arm B (N = 91)	Arm C (N = 87)
Hematologic	1 (1.1)	5 (5.5)	1 (1.1)
- Neutropenia	25 (28.4)	23 (25.3)	28 (32.2)
- Febrile neutropenia	1 (1.1)	5 (5.5)	-
- Thrombopenia	4 (4.5)	5 (5.5)	7 (8.0)
- Anemia	6 (6.8)	7 (7.7)	6 (6.9)
Non hematologic			
- 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 (0)

TOLERANCE: Neurotoxicity grade 3-4

	Arm A (N = 88)	Arm B (N = 91)
Neurotoxicity Gr 3-4 (ITT)- N (%)	9 (10.2)	17 (18.7)
Neurotoxicity Gr 3-4 within First 6 months- N (%)	9 (10.2)	10 (11.0)
Max Grade neurotoxicity reached (whatever max grade is)		
- First 6 months N (%) - After 6 months N (%)	64 (94.1) 4 (5.9)	49 (70.0) 21 (30.0)
Median ratio of oxaliplatine (%)* [Range]	83 [46.9;102.5]	92 [92.1; 104.6]

*Ratio between received dose and targeted dose

CONCLUSIONS

- FOLFIRINOX with maintenance by LV5FU2 in patients with metastatic pancreatic cancer controlled after four months of induction chemotherapy appears to be feasible and effective. Firgem regimen seems to be ineffective in our study

- Unexpectedly maximal severe neurotoxicity rate was higher in the maintenance therapy arm, mostly due to a higher cumulative oxaliplatin dose delivered. Moreover, grade 3 or 4 neurotoxicity occurred later in maintenance arm.

- Other analyses are in progress, we are waiting for results about quality of life, duration of disease control, and sub groups analyses

- A phase III trial comparing folfirinox versus folfirinox maintenance with 5FU is needed to confirm these results

Pancreatic Cancer ASCO

Assenat et al. (Abs 4109)
Sequential nab-paclitaxel-FOLFIRINOX, alternating monthly
ORR of 63.2% PFS 9.6 months. OS 17.8 mos

Bekail-Saab et al. (Abs 4110)
Phase 1b/2 napabucasin, gem/nab-pac
cancer stemness inhibitor, RR 47%, mPFS 7.10, mOS 12.6 mo

Dean et al. (Abs 4111)
Phase 1/2 NAPOX
60 mg/m2 nanoliposomal irinotecan/oxali, 4/7 pts treated >24 weeks
PRs in 6/24 patients

Pancreatic Cancer ASCO

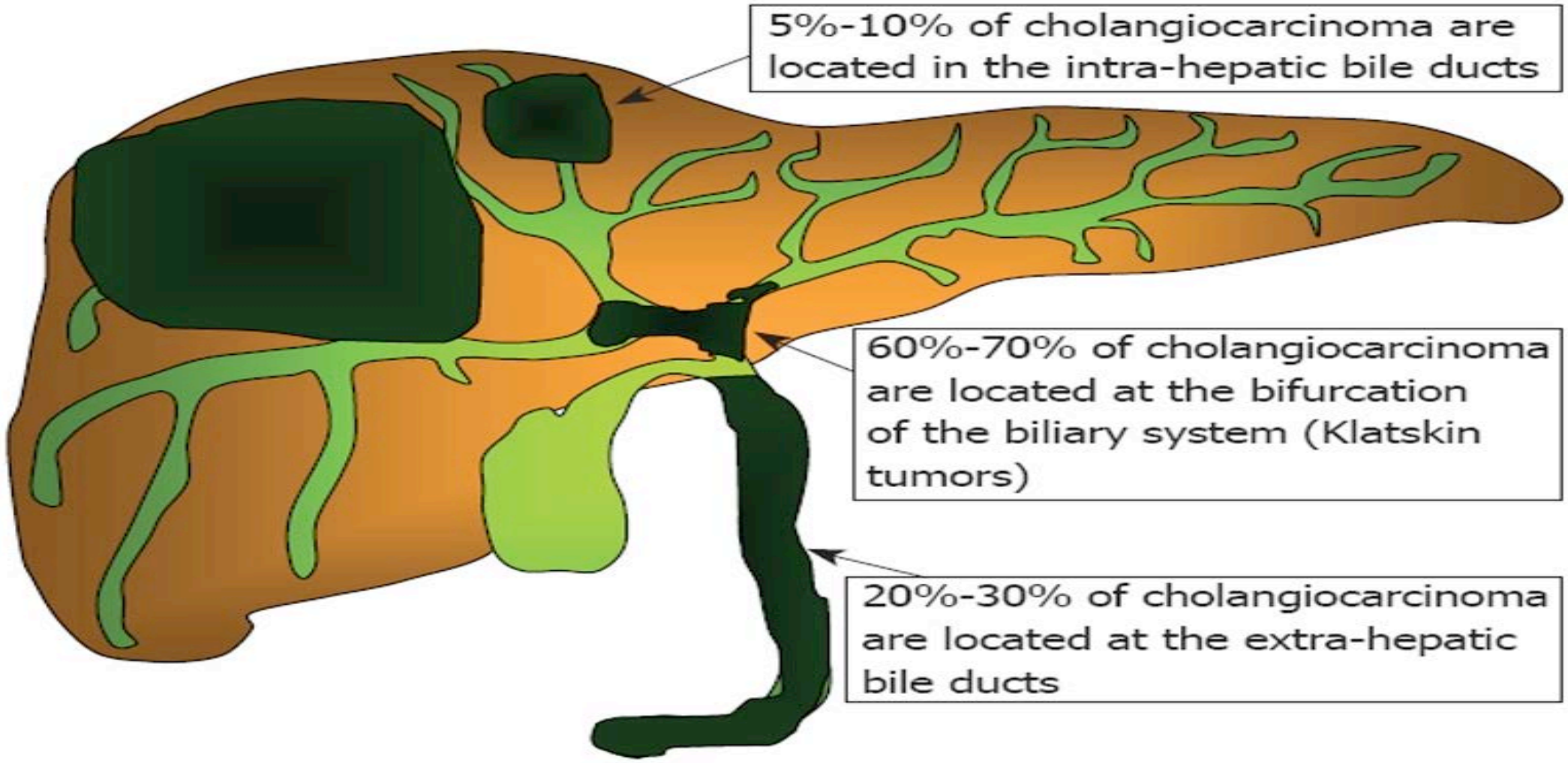
Bahary et al. (Abs 4015)
Phase 2 IDO inhibitor indoximod, gem/nab-pac
104 pts, ORR 46%, 1 CR, mOS 10.9 months
Responders w/ intra-tumoral CD8 compared to non-resps (p = 0.030)

Lum et al. (Abs 4108)
Activated T cells anti-CD3 x anti-EGFR bispecific antibody
9 LA/met pts, 8 infusions of 10^{10} EGFRBi BATs
Ph 1- OS 5 pts was 31.0 mos, TTP 7.0 months
Ph II study 2/4 SD; OS for all 9 patients- 31 mos

Overman et al. (Abs 4123)
MEDI9447 (oleclumab) +/- durvalumab in CRC/Panc
Anti-CD73 inhibits production of immunosuppressive adenosine
Decreased tumoral CD73 expression (5/9), increasing CD8+
PR 2/20 panc pts; SD 3/20 panc pts

Bile Duct Cancer

BILIARY TRACT CANCERS



Al Jaffiry, WJG 2009

ABC-02 Study for Advanced Biliary Cancer

Eligible patients (n=400*)

+ QoL

Randomized 1:1

(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A

Gem *1000 mg/m²* *D1,8,15 q 28d*

24 weeks (6 cycles)

Arm B

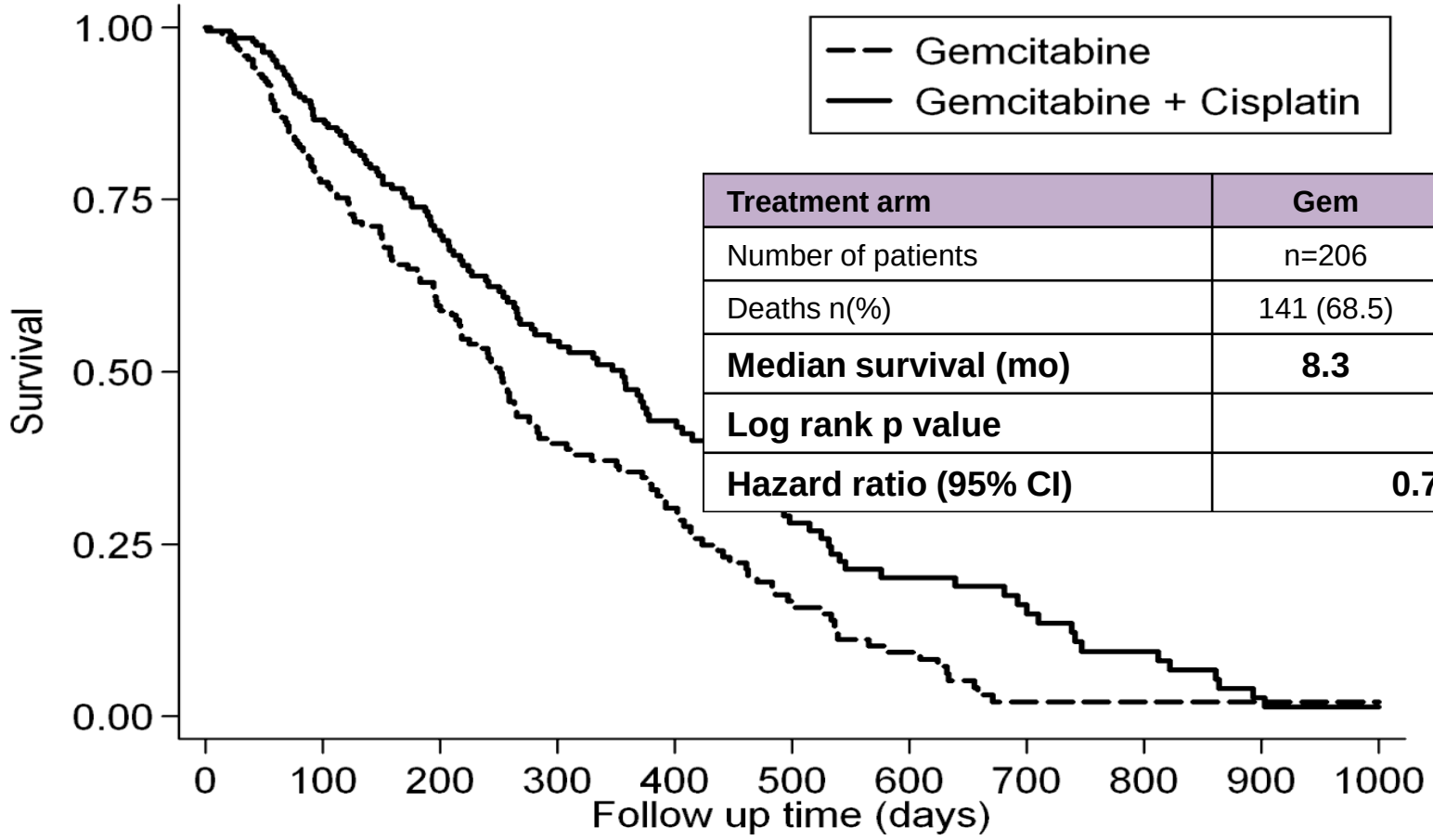
Cisplatin *25 mg/m²*

+ Gem *1000 mg/m²*

D1,8 q 21d

24 weeks (8 cycles)

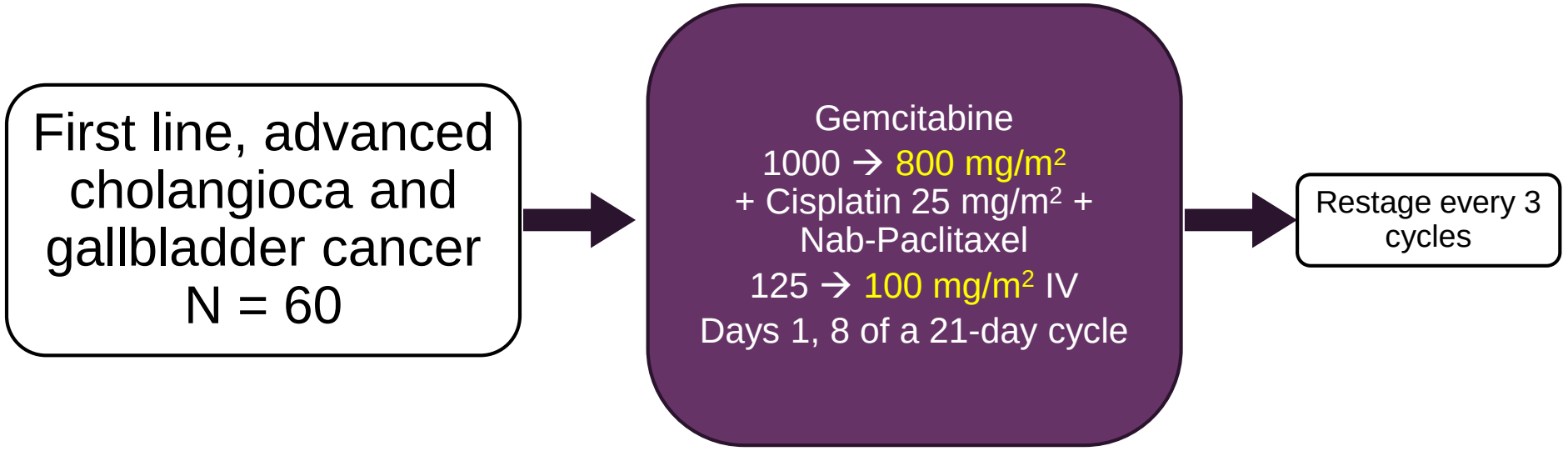
ABC-02: Overall Survival



Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
Deaths n(%)	141 (68.5)	122 (59.8)
Median survival (mo)	**8.3**	**11.7**
Log rank p value	**0.002**	
Hazard ratio (95% CI)	**0.70 (0.54, 0.89)**	

GAP: Study Schema

Primary EP: PFS (data maturing)
Secondary: ORR, OS



Correlatives: Mechanisms of resistance, ERCC1, RRM

30 patients on starting dose level and subsequent patients at lower dose

Bayesian analysis for ongoing toxicity and efficacy
PFS: from 8 to 10 months

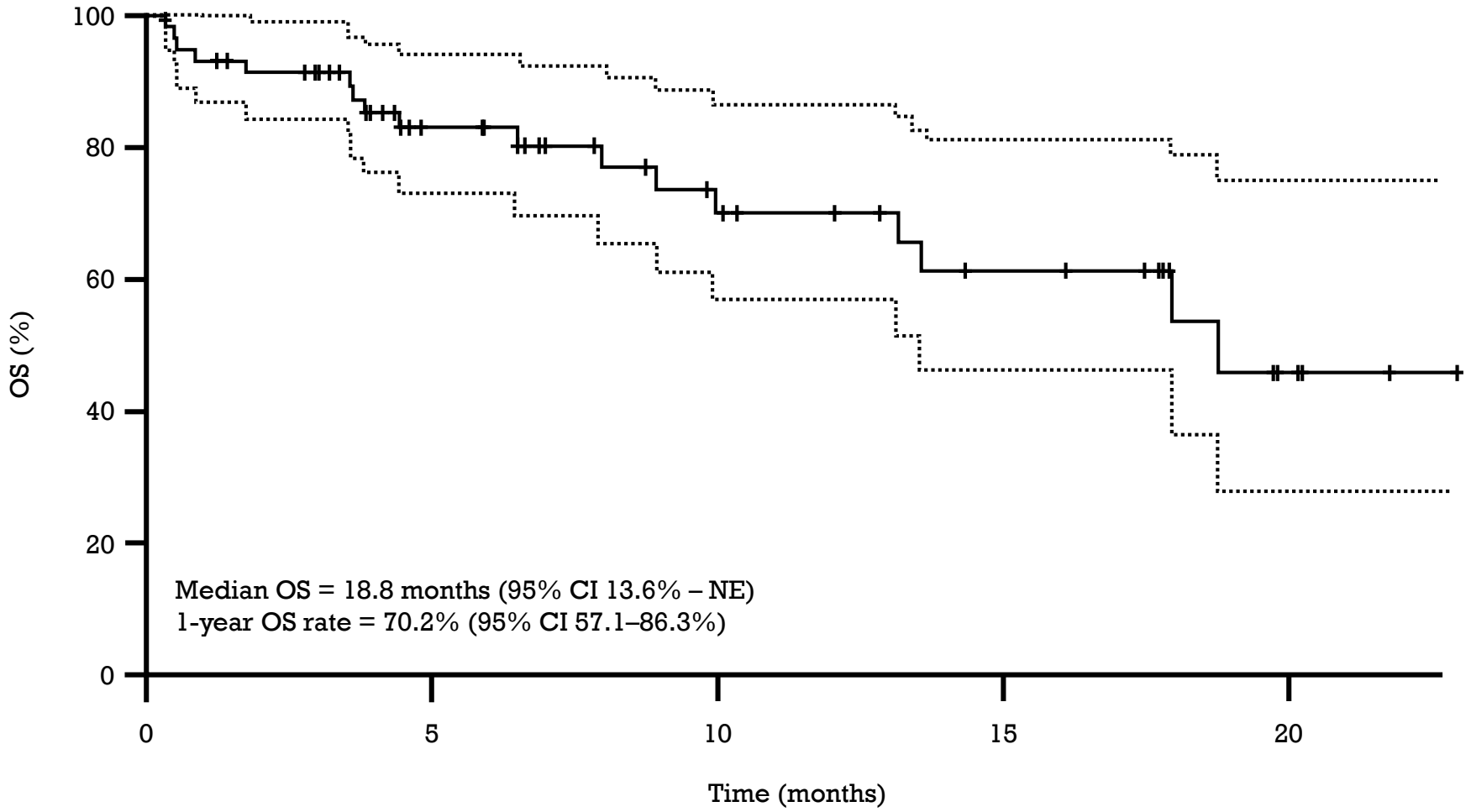
Shroff, et al, ASCO Annual Meeting 2017

GAP: Efficacy results

	All treated patients (N=59)*	All evaluable patients (N=50)**
Median PFS, months	8.6	11.8
Median OS, months	18.8	–
DCR, %	71.2	84.0
PR, n (%)	17 (28.8)	17 (34.0)
SD, n (%)	25 (42.4)	25 (50.0)
PD, n (%)	8 (13.6)	8 (16.0)

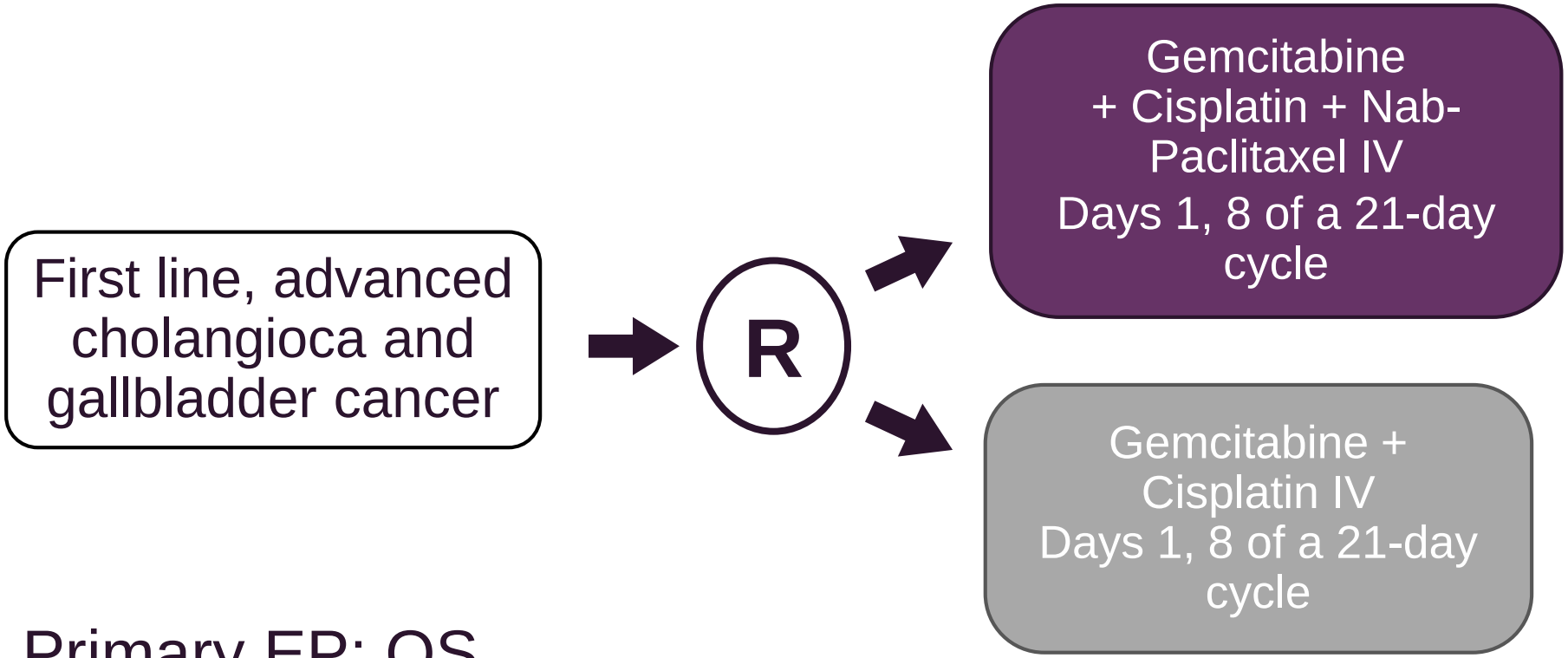
- 3 patients in the high-dose group and 4 in the reduced-dose group underwent surgery following conversion to resectable disease
- 1 patient in the high-dose group achieved a pathologic complete response

GAP OS: all treated patients



NE, not evaluable

GAP Phase III: Proposed Study Design



Primary EP: OS

Secondary: ORR,PFS

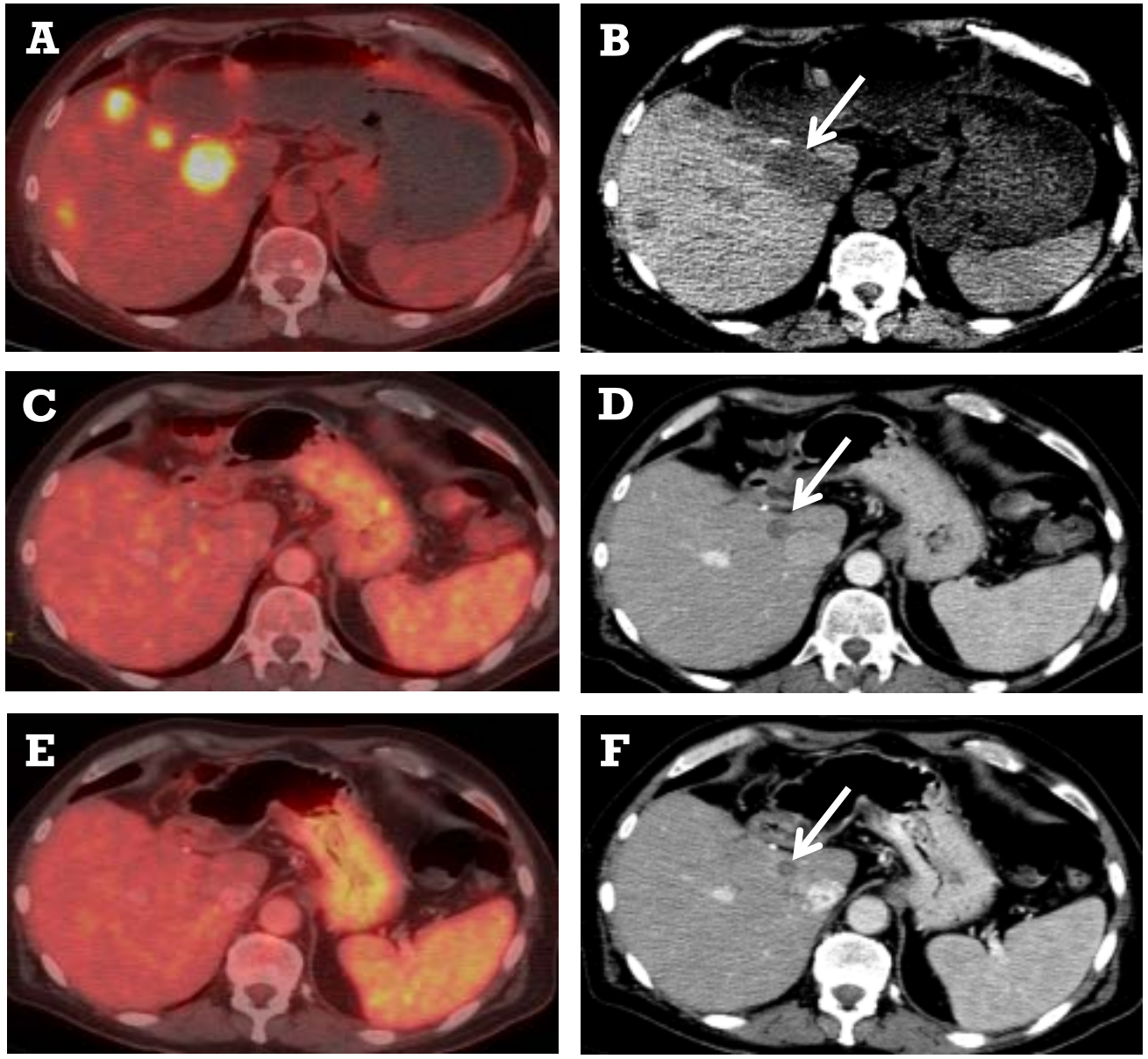
Molecular Profiling

- Novel biomarkers and targets can be used to improve the outcomes.
- Stratification into subgroups can also provide prognostic implications.
- These targets can be explored for their therapeutic value using novel inhibitors.

Molecular Heterogeneity in BTC

CGP Findings	IHCCA	EHCCA	GBCA
Total GA/patient	3.6	4.4	4.0
CRGA/patient	2.0	2.1	2.0
ERBB2 Amplification	4%	**11%**	**16%**
BRAF Substitutions	**5%**	**3%**	1%
KRAS Substitutions	22%	42%	11%
PI3KCA Substitution	5%	**7%**	14%
FGFR1-3 Fusions and Amplifications	**11%**	0	3%
CDKN2A/B Loss	27%	17%	19%
IDH1/2 Substitutions	**20%**	0	0
ARID1A Alterations	18%	12%	13%
MET Amplification	2%	0	1%

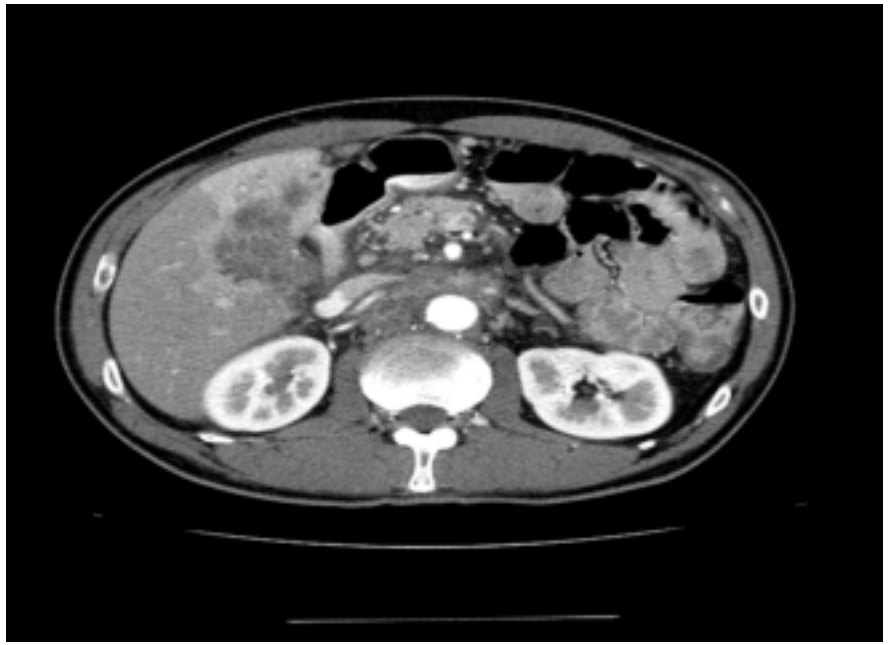
Cancer. 2016;122(24):3838-3847

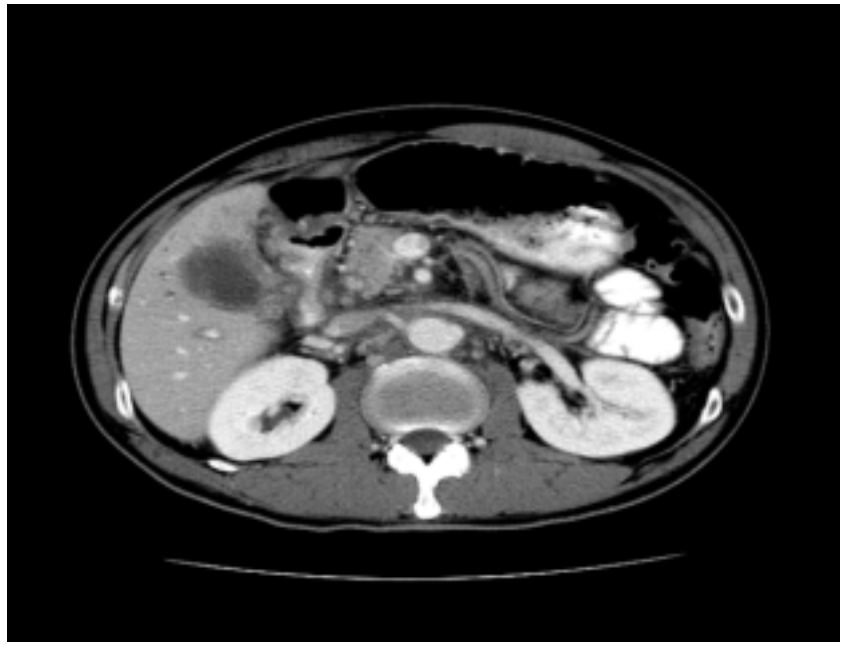


IHCCA with *BRAF* V600E Mutation Responds to RAF Kinase Inhibition

A 67 year old male with metastatic intrahepatic cholangiocarcinoma, who had progressed on conventional chemotherapy. B-Raf mutation detected. Axial (A) fused PET-CT and (B) unenhanced CT images from a PET scan demonstrate FDG avidity of multiple liver metastases. After 8 weeks of b-raf inhibitor therapy, axial (C) fused PET-CT and (D) contrast-enhanced CT images demonstrate lack of FDG avidity and decreased size of liver metastases, e.g., the dominant lesion adjacent to the IVC (arrow) decreased from 3.7 cm to 1.6 cm. After 16 weeks of therapy, axial (E) fused PET-CT and (F) contrast-enhanced CT images demonstrate continued lack of FDG avidity and further decreased size of liver metastases, e.g., the dominant lesion (arrow) now measures 1.3 cm.

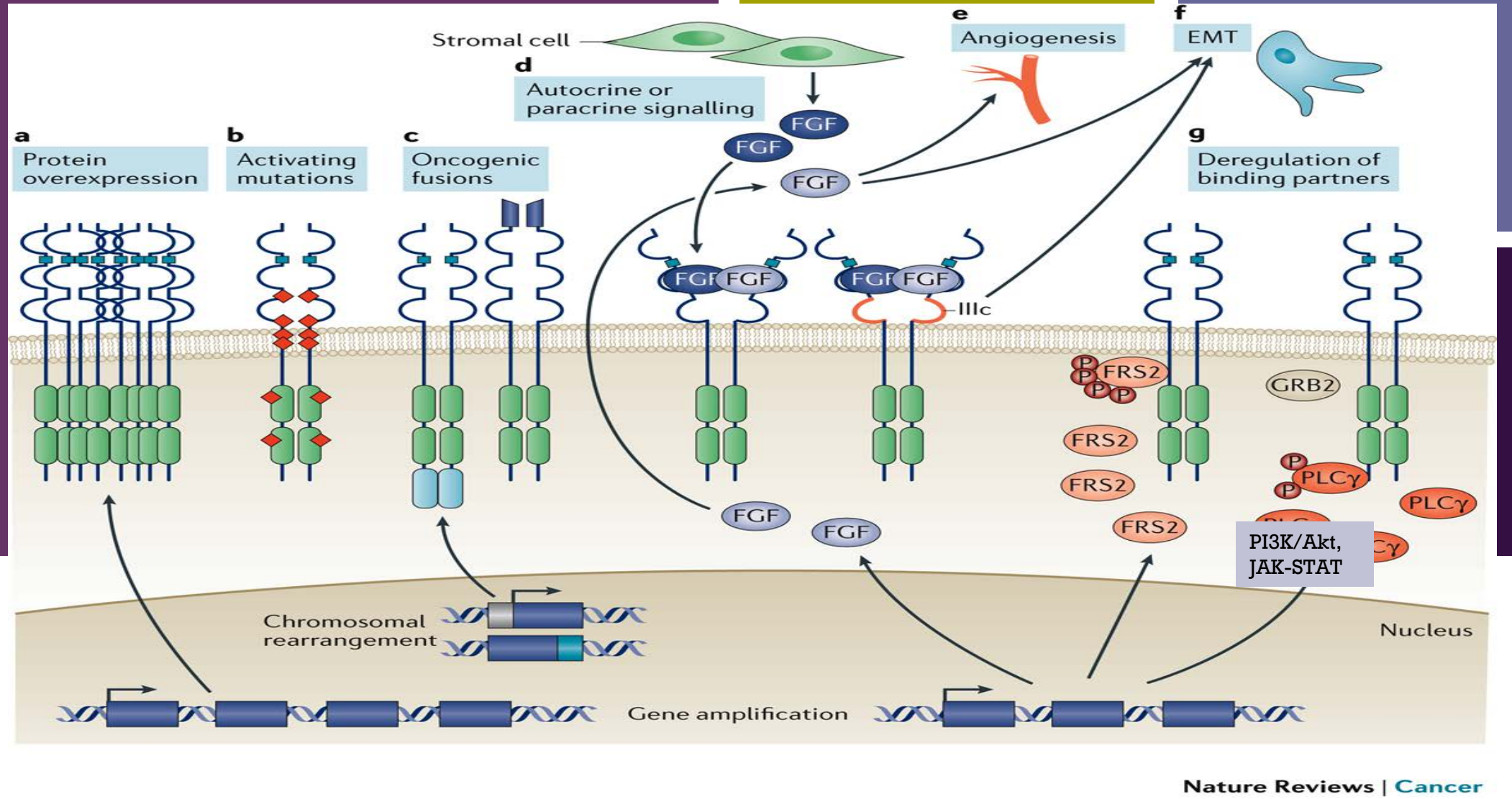
EGFR amplification in GBCA with Response to Neoadjuvant Erlotinib in Combination with Systemic Therapy





A 67 year old woman with GBCA who developed liver metastases. Genomic profiling of the liver metastasis specimen in this patient revealed focal amplification of *EGFR* (16 copies), amplification of *CCND1* (13 copies) and mutations in *PIK3CA* and *TP53*. On the left is CT of pre- gemcitabine + erlotinib neo-adjuvant treatment and the CT image on the right is post-completion of neoadjuvant treatment.

MECHANISMS OF ONCOGENIC FGFR SIGNALING



Babina, Nature Reviews Cancer, May 2017

	Agent	Activity	Disease
Non-Selective	Dovitinib	FLT3, c-KIT, FGFR1,3, VEGFR1,3	Gastric, urothelial, renal
	Ponatinib	ABL, PDGFRa, VEGFR2, FGFR1, c-SRC	Biliary, Advanced solid tumors
	Lucitanib ARQ087	VEGFR1-2, FGFR 1-2 (83nM) FGFR 1-3 (1.8-4.5 nM), KIT, RET, PDGFRB	Breast, Lung CCA
	AZD4547	FGFR1, 2,3 (1-2.5nM)	NSCLC
Selective	BGJ398	FGFR1,2,3 (1nM) FGFR4 (60nM)	SCC, Bladder, Biliary
	JNJ-42756493	FGFR1-4 (<1nM)	Liver, bladder, NSCLC, Gastric
	INCB054828 DEBIO 1347	FGFR 1-3, VEGFR2 FGFR 1-3	
	TAS-120 LY2874455	FGFR1-4 VEGFR2, FGFR 1-4	Solid tumors, CCA
AB Ligand Trap	FP-1039 FPA114	FGF2 FGFR2-IIb	Solid tumors

Phase 2 study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma

- Multicenter, open-label, phase 2 study adults with advanced CCA with *FGFR2* fusions or *FGFR* alterations who had progressed on prior therapy
- The primary endpoint-overall response rate
- BGJ398 125 mg once daily for 21 days, then 7 days off (28-day cycles).
- Sixty-one patients (35 women; median age 57 years) with *FGFR2* fusion (n=48), mutation (n=8), or amplification (n=3)

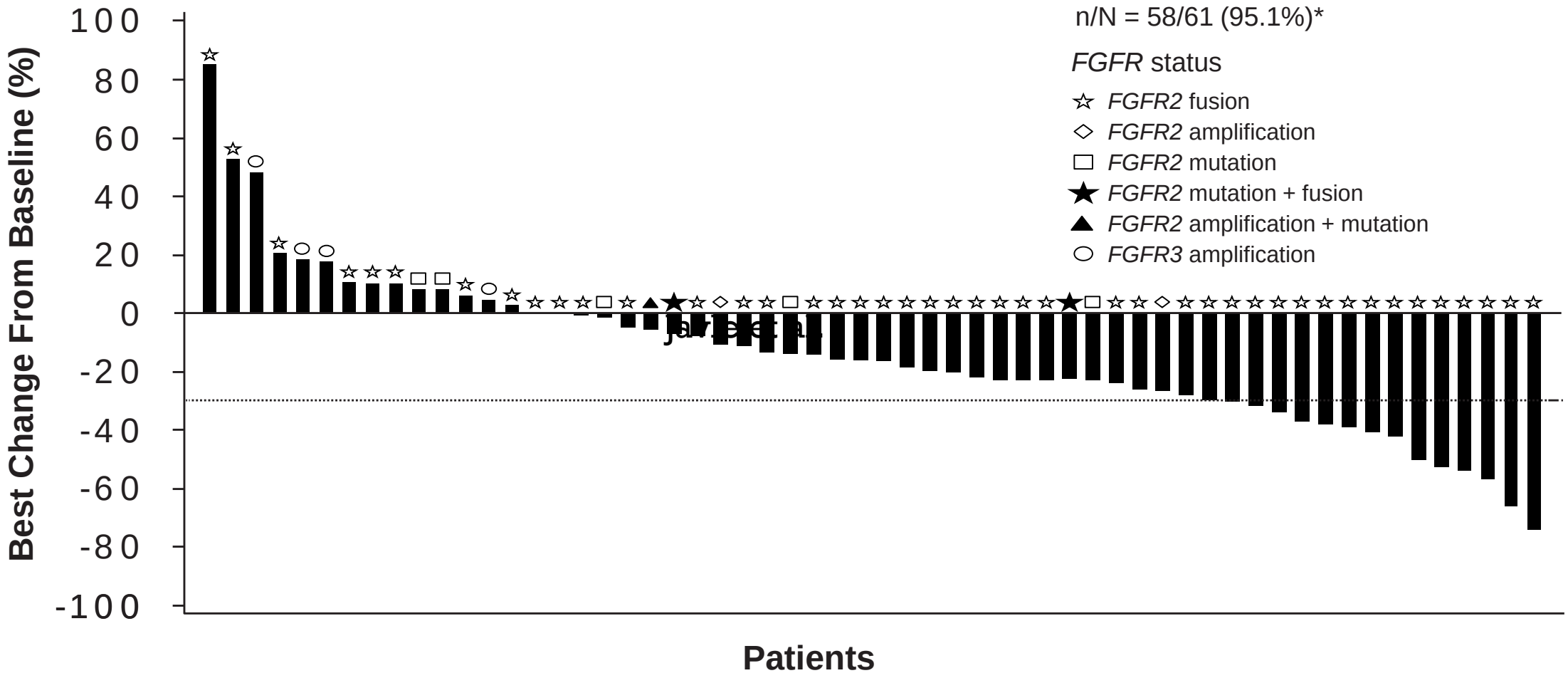
Javle et al. Clin Oncol 2017

Phase 2 study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma

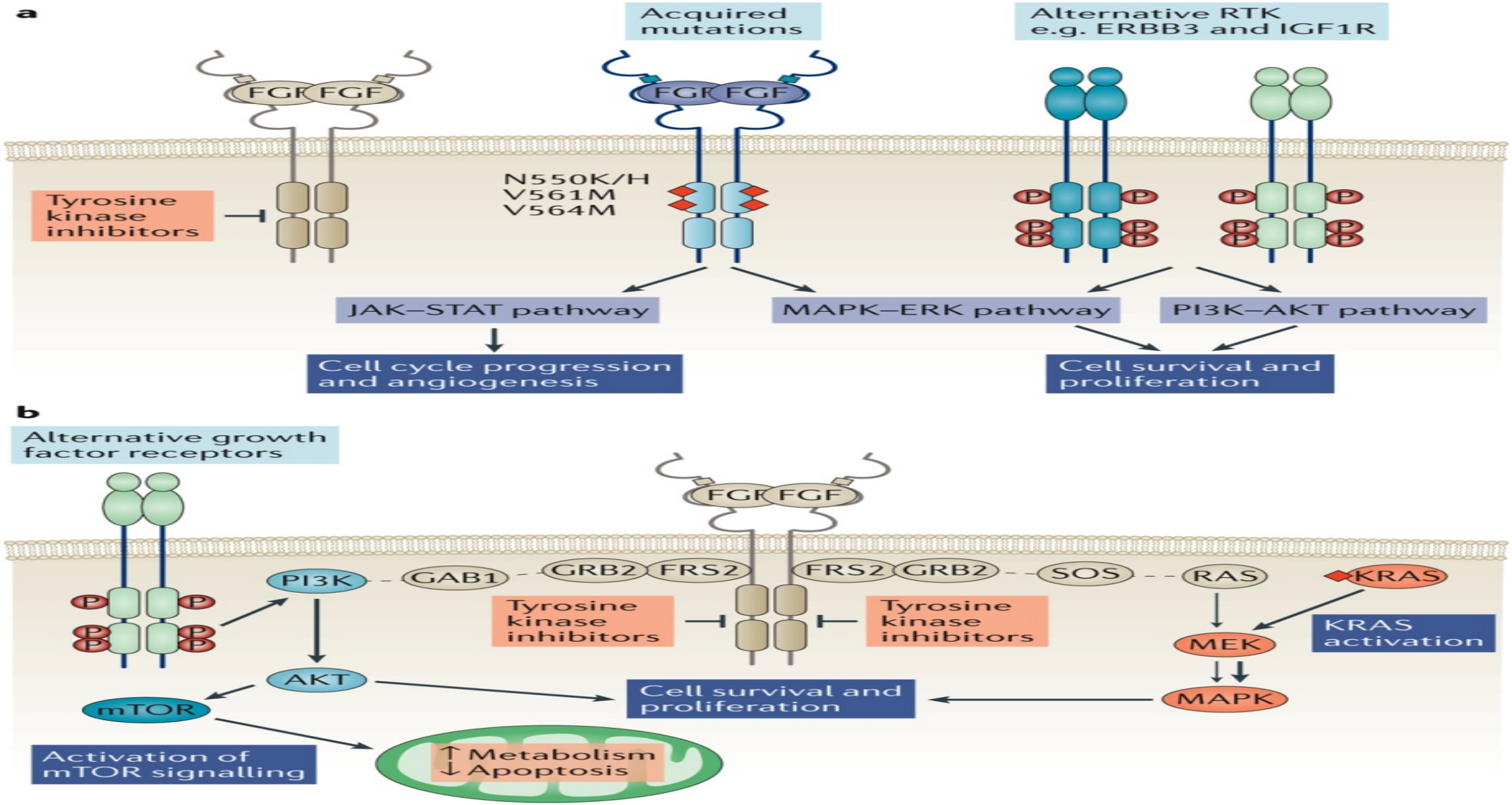
- ORR=14·8% (18.8% *FGFR2* fusions only),
- DCR was 75·4% (83.3% *FGFR2* fusions only) > 6 months, despite prior therapies, median PFS was 5·8 months
- Adverse events included hyperphosphatemia (72·1% all grade), fatigue (36·1%), stomatitis (29·5%), and alopecia (26·2%).
- Grade 3/4 (41%) and included hyperphosphatemia (16·4%), stomatitis (6·6%), and palmar-plantar erythrodysaesthesia (4·9%).
- Rare class effects: keratopathy, eye dryness, asymptomatic retinal detachment

Javle et al. J Clin Oncol 2017

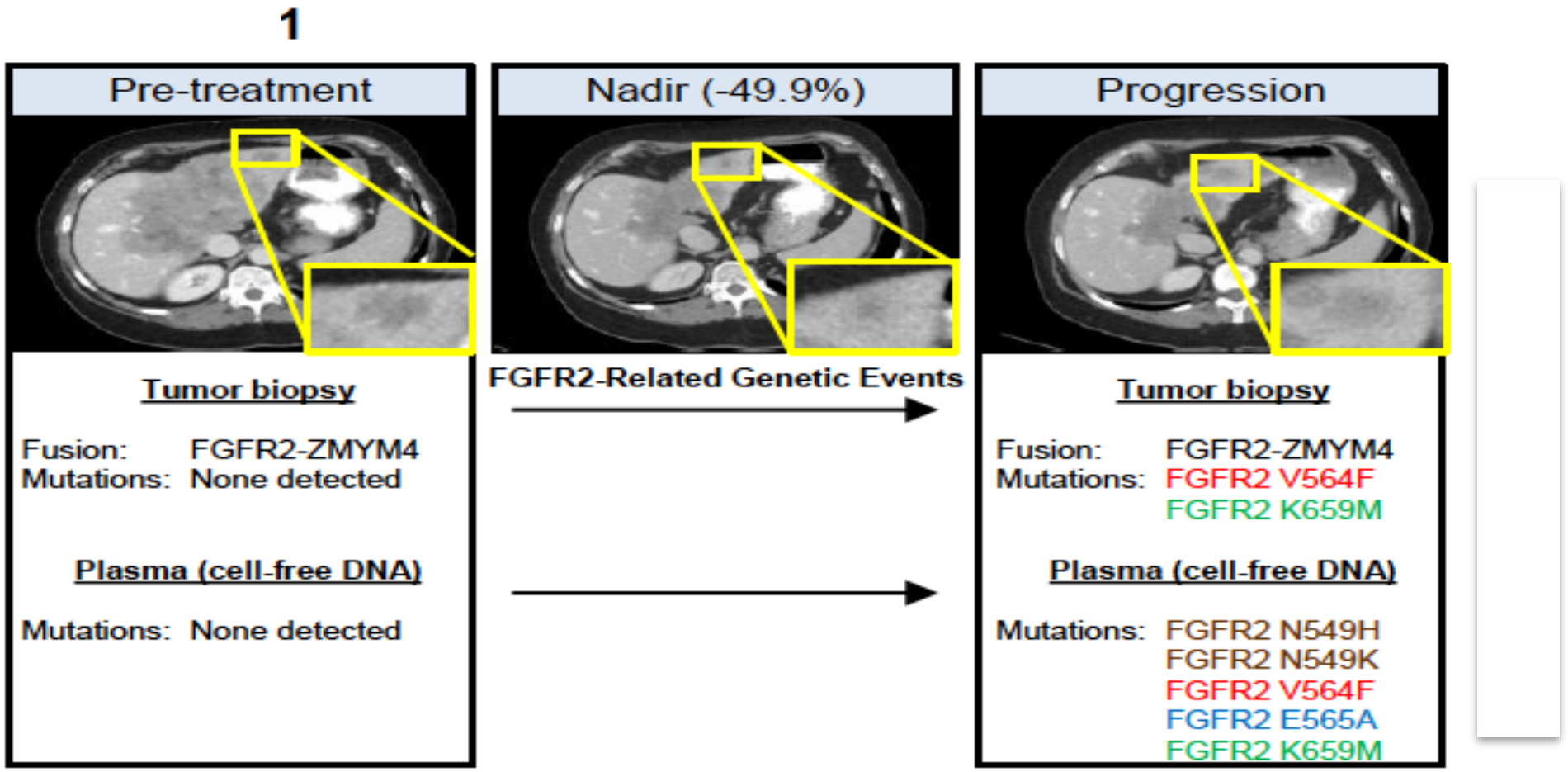
RESPONSES



Javle et al. J Clin Oncol 2017


a
Acquired mutations
Alternative RTK e.g. ERBB3 and IGF1R
FGF
FGF
FGF
FGF
Tyrosine kinase inhibitors
N550K/H
V561M
V564M
P
JAK–STAT pathway
MAPK–ERK pathway
PI3K–AKT pathway
Cell cycle progression and angiogenesis
Cell survival and proliferation
b
Alternative growth factor receptors
FGF
FGF
PI3K
GAB1
GRB2
FRS2
FRS2
GRB2
SOS
RAS
KRAS
Tyrosine kinase inhibitors
Tyrosine kinase inhibitors
MEK
KRAS activation
AKT
mTOR
Cell survival and proliferation
MAPK
Activation of mTOR signalling
↑Metabolism
↓Apoptosis

Patient treated with BGJ398, Secondary Gatekeeper Mutations. Successfully treated with TAS-120.



Cancer Discovery Dec 2016

TAIHO ONCOLOGY PRESENTS DATA ON KEY INVESTIGATIONAL COMPOUND TAS-120 AT ESMO 20TH WORLD CONGRESS ON GASTROINTESTINAL CANCER 2018

JUN 20, 2018

45 CCA patients harboring FGF/FGFR aberrations (e.g., FGFR2 gene fusions, mutations, amplifications and re-arrangements)

28 patients with FGFR2 gene fusions, 71% tumor shrinkage, 7 pts achieved cPR, ORR 25%, 54% SD, DCR 79%.
17 patients with other FGF/FGFR aberrations 18% cPR.
13 patients who had received prior FGFR inhibitors, 31% achieved cPR.

Adverse events- most common - hyperphos (78%), AST (29%), dry skin (29%), diarrhea (27), dry mouth (27%). Grade ≥3 treatment-related AEs- 22%

TAS-120 demonstrated clinical activity CCA pts with FGFR2 gene fusions, and in patients who progressed on prior FGFR inhibitors.

Biliary Cancer Ongoing Research

IDH1 Inhibitors

oncometabolite 2-hydroxyglutarate, de-differentiated cell proliferation

Ivosidenib (AG-120), oral, reversible inhibitor mutant IDH1
phase I- 73 refractory patients, RR 5%, SD 56%; 12-mos PFS 20.7%.
phase III ClarIDHy 186 pts, 2nd/3rd line ongoing

BAY1436032
Olaparib

Other targets

BRAF- MATCH
BRCA1/2- TAPUR
MSI-H

MET
Multi-TKIs

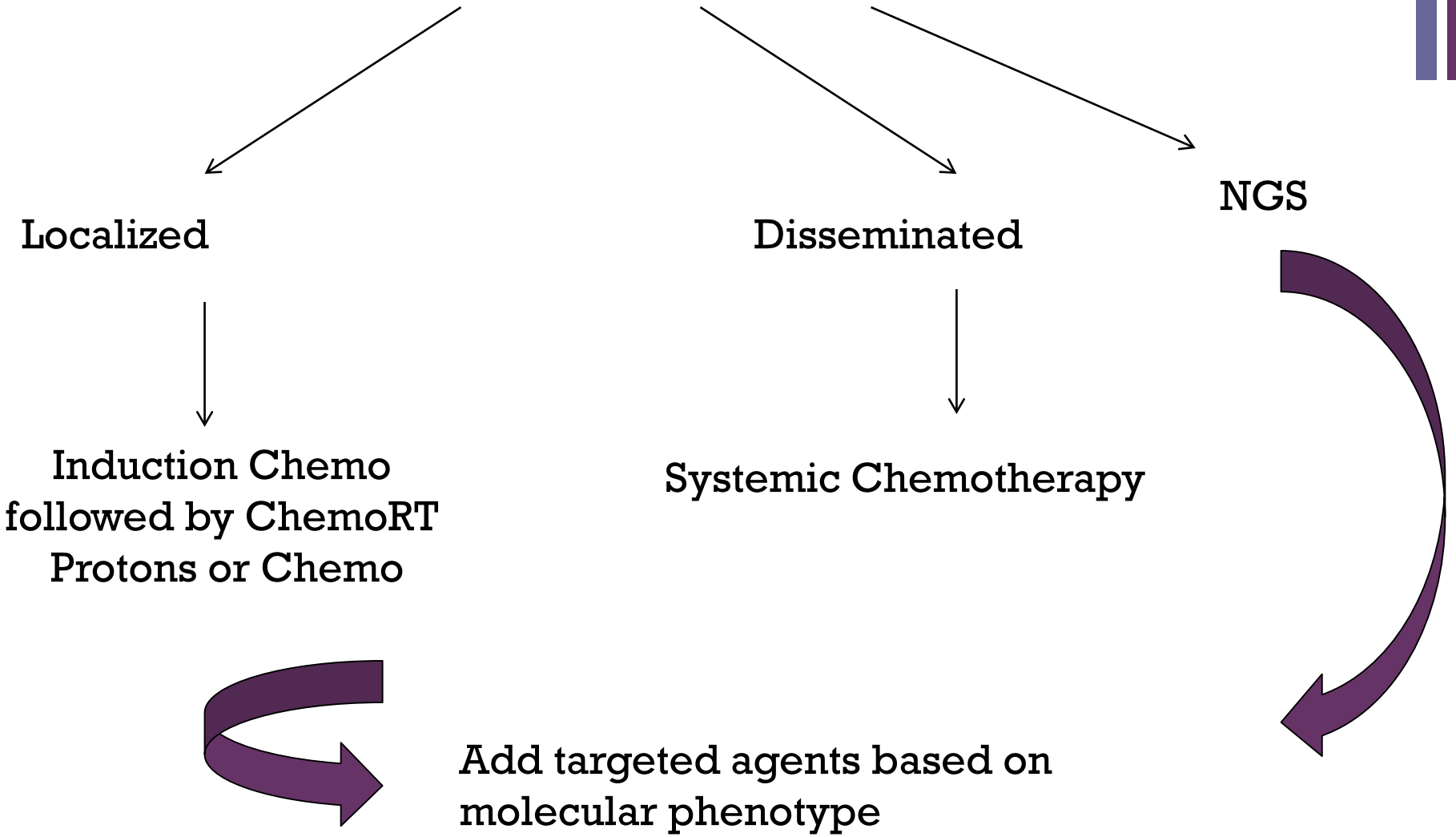
Biliary Cancer ASCO

Kelley et al. (Abs 4087)
Phase 2 pembrolizumab /GM-CSF
27 pts, median 6 cycles, PR 19%, 1 MSI, 33% SD> 6 mos,
PFS 6 mos 35%, median OS-NR

Mizrahi et al. (Abs 4081)
Phase 2 ramucirumab
42 pts, ICC 23%, ORR 0%, PFS 2.73 mos, OS 6.31 mos
Gr 3- 21%, HTN, proteinuria, hypo Na, vomiting, anorexia

Kim et al. (Abs 4082)
Phase 2 regorafenib
39 pts, ICC 69%, PFS 3.7 mos, OS 9.9 mos, PR 2 pts (6%), SD 18 pts (56%), DCR of 62.4%, 49% required dose mods

Unresectable Intrahepatic Cholangiocarcinoma

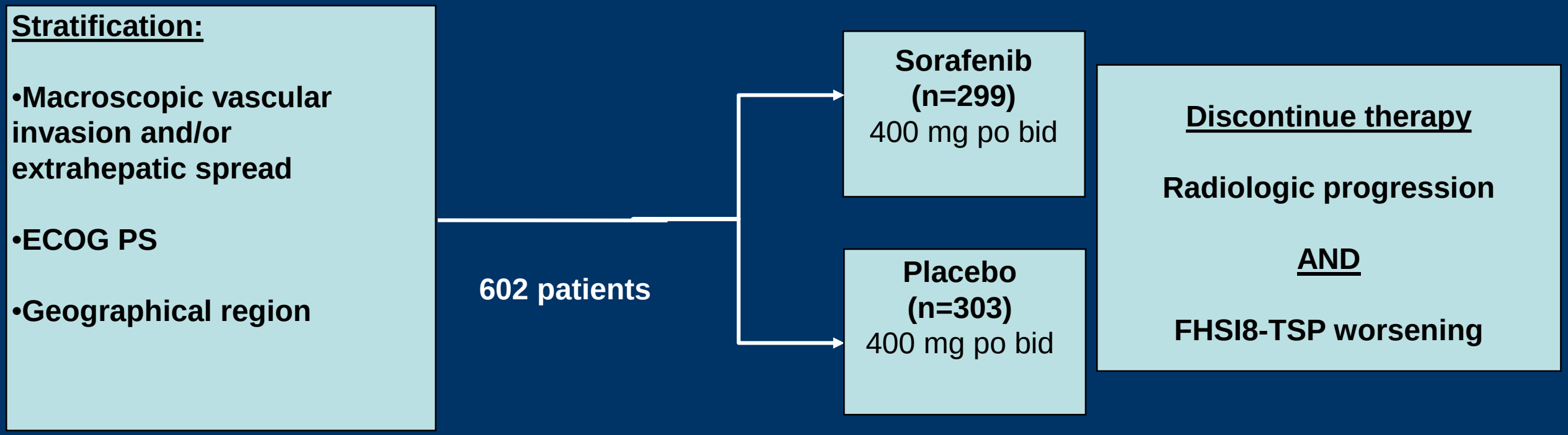


Hepatocellular Cancer

Phase III SHARP Trial Study Design

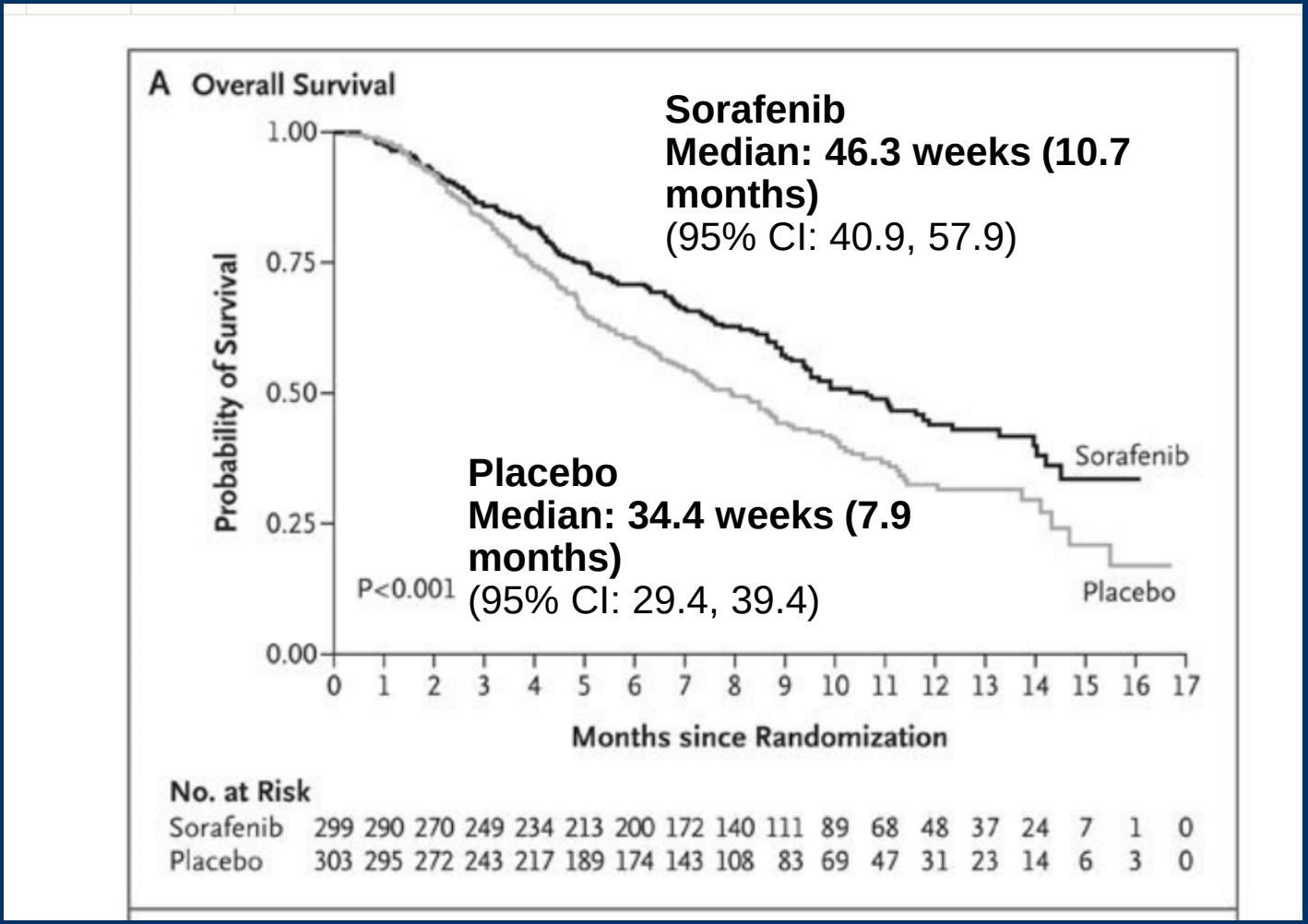
- Primary end-points: Overall survival
  Time to symptomatic progression (FHSI8-TSP)

- Secondary end-points: Time to progression (independent review)



Llovet JM, et al. *N Engl J Med.* 2008;359: 378-390

SHARP Overall Survival (ITT)



Hazard ratio 0.69
(95% CI: 0.55, 0.87)
P*<0.001

**O'Brien-Fleming threshold for statistical significance was P=0.0077.*

Llovet JM, et al. *N Engl J Med.* 2008;359: 378-390

RESORCE trial design

- HCC patients with documented radiological progression during sorafenib treatment

- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R
2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

N= 573

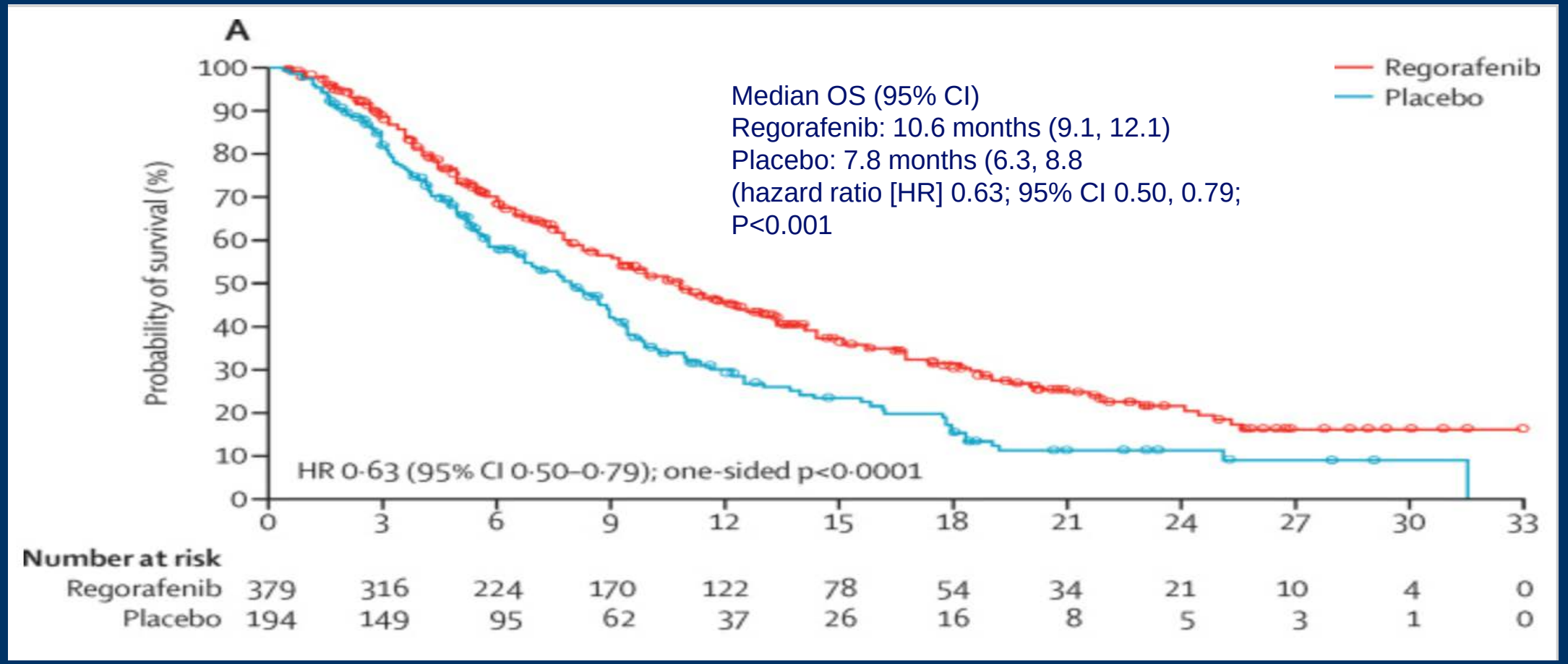
Placebo
(n=194)

- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein

Bruix, J. et al. The Lancet Volume 389, No. 10064, p56–66, 7 January 2017

Regorafenib vs. Placebo Overall Survival



Bruix, J. et al. The Lancet Volume 389, No. 10064, p56–66, 7 January 2017

Lenvatinib vs Sorafenib Phase III

Global, randomized, open-label, phase 3 noninferiority study (N=954)

- No prior systemic therapy
- ≥1 measurable target lesion by mRECIST
- BCLC stage B or C
- Child-Pugh A
- ECOG PS ≤1
- Patients with ≥50% liver occupation, clear bile duct invasion, or portal vein invasion at the main portal vein were excluded

Stratification
- Region: (Asia-Pacific or Western)
- MVI and/or EHS: (yes or no)
- ECOG PS: (0 or 1)
- Body weight: (< 60 kg ≥60 kg)

Randomization 1:1

Lenvatinib (n=478)
8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) once daily

Sorafenib (n=476)
400 mg twice daily

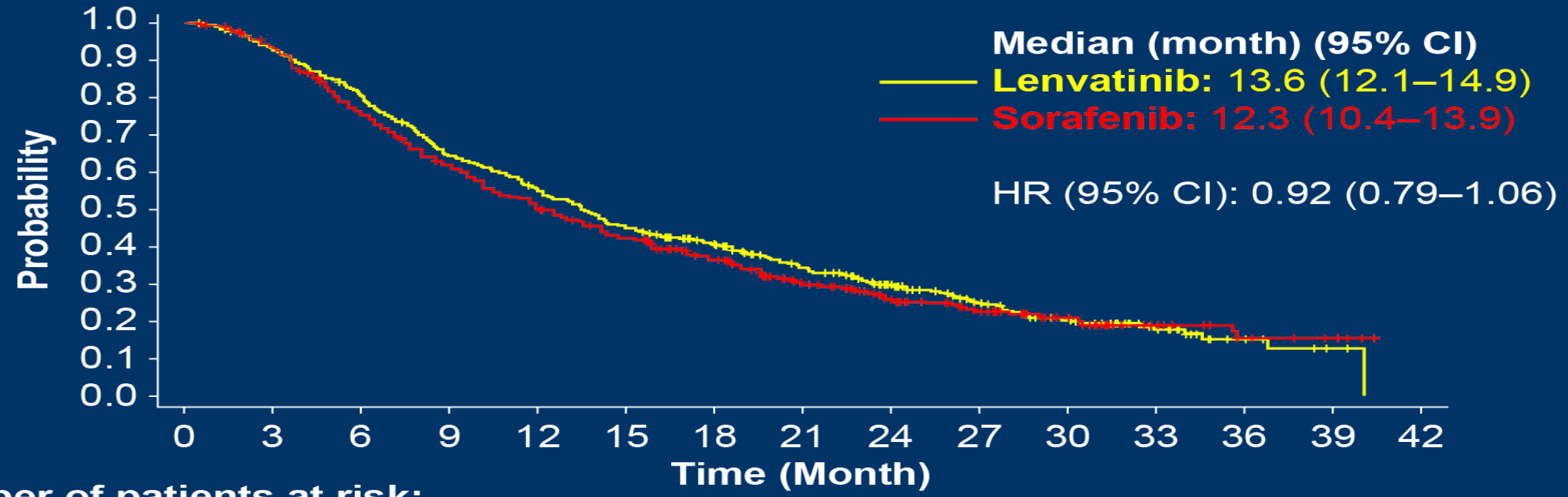
Primary endpoint:
- OS

Secondary endpoints:
- PFS
- TTP
- ORR
- Quality of Life
- PK lenvatinib exposure parameters

mRECIST by the investigator

Ann-Lii Cheng, etal. J Clin Oncol 35, 2017 (suppl; abstr 4001)

Lenvatinib vs Sorafenib
Primary Endpoint: OS

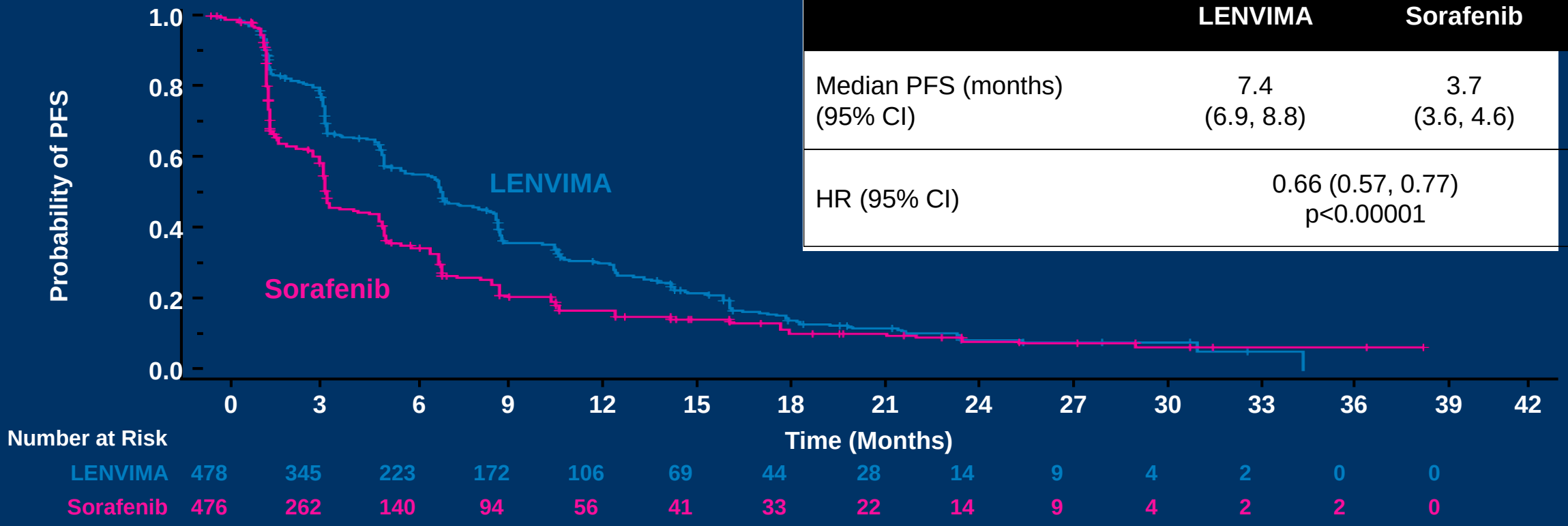


Number of patients at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Ann-Lii Cheng, etal. J Clin Oncol 35, 2017 (suppl; abstr 4001)

PFS Statistically Significant Improvement



	LENVIMA	Sorafenib
Median PFS (months) (95% CI)	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)
HR (95% CI)	0.66 (0.57, 0.77) p<0.00001	

Levatinib Response Rates

	Investigator Assessment (mRECIST)		Independent Review			
			mRECIST		RECIST v1.1	
	Lenvatinib	Sorafenib	Lenvatinib	Sorafenib	Lenvatinib	Sorafenib
ORR (CR + PR), %	24.1	9.2	40.6	12.4	18.8	6.5
(95% CI)	(20.2, 27.9)	(6.6, 11.8)	(36.2, 45.0)	(9.4, 15.4)	(15.3, 22.3)	(4.3, 8.7)
Difference,% (95% CI)	14.8 (10.2, 19.4)		28.2 (22.9, 33.5)		12.3 (8.2, 16.5)	
Odds ratio (95% CI)	3.13 (2.15, 4.56)		5.01 (3.59, 7.01)		3.34 (2.17, 5.14)	
P-value	$P < 0.00001$		$P < 0.00001$		$P < 0.00001$	

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

Andrew X. Zhu[1], Yoon-Koo Kang[2], Chia-Jui Yen[3], Richard S. Finn[4], Peter R. Galle[5], Josep M. Llovet[6], Eric Assenat[7], Giovanni Brandi[8], Ho Yeong Lim[9], Marc Pracht[10], Kun-Ming Rau[11], Philippe Merle[12], Kenta Motomura[13], Izumi Ohno[14], Bruno Daniele[15], Dong Bok Shin[16], Guido Gerken[17], Paolo B. Abada[18], Yanzhi Hsu[19], Masatoshi Kudo[20], for the REACH-2 study investigators

PRESENTED BY: Andrew Zhu, MD, PhD
Massachusetts General Hospital Cancer Center, Harvard Medical School

Background

- HCC is the second most common cause of cancer-related mortality globally with high unmet need[1]
- Elevated AFP has been associated with poor prognosis and aggressive disease[2]
- Sorafenib (1L) and regorafenib (2L) are the only globally approved drugs for treatment of HCC.[3,4,5] Nivolumab (2L) is approved in the US based on a single arm phase 2 study.[6] Lenvatinib (1L) and cabozantinib (2L) have demonstrated benefits in phase 3 studies[7,8]
- Ramucirumab, a humanized IgG1 mAb, inhibits activation of VEGFR2[9]
- In the prior REACH study that evaluated ramucirumab in patients with advanced HCC, improvement of overall survival in the intent-to-treat population was not significant.[10] However, a survival benefit with ramucirumab was observed in the pre-specified population with baseline AFP ≥400 ng/mL (HR 0.674, P=0.006) and was well tolerated
- REACH-2 aimed to confirm the survival benefit of ramucirumab in patients with baseline AFP ≥400 ng/mL

1. WHO Cancer Fact sheet No. 297, 2015; 2. Tangkijvanich P et al. J Clin Gastroenterol 2000, 31:302-8.3. Llovet JM et al. *N Engl J Med* 2008, 359:378-90; 4. Cheng AL et al. *Lancet Oncol* 2009, 10:25-34
5. Bruix J et al. *Lancet* 2017, 389: 56-66; 6. El-Khoueiry AB et al. *Lancet* 2017, 389:2492-502. 7. Kudo M et al. *Lancet* 2018, 391:1163-73; 8. Abou-Alfa GKM et al. *J Clin Oncol* 2018, 36:(suppl 4S; abstr 207);
9. Spratlin JL et al. *J Clin Oncol* 2010, 28(5):780-7; 10. Zhu AX et al. *Lancet Oncol* 2015,16:859-70

Study Design

- Baseline AFP ≥400 ng/mL
- BCLC stage B/C
- Child Pugh A
- ECOG PS 0/1
- Prior sorafenib

RANDOMIZE 2:1

Ramucirumab + BSC
8 mg/kg IV Q2W

Placebo + BSC
Q2W

Primary endpoint: Overall survival

Secondary endpoints:
- PFS, TTP, ORR
- Time to deterioration in FACT Hepatobiliary Symptom Index-8 (FHSI-8)
- Time to deterioration in ECOG PS
- Safety, PK, Immunogenicity

Stratification factors
- Macrovascular invasion (yes vs. no)
- ECOG PS (0 vs. 1)
- Geographic region
  - Americas, Europe, Israel and Australia
  - Asia (except Japan)
  - Japan

Statistical assumptions and analysis
- 80% power, alpha 0.05
- HR 0.67
- mOS 6.7 months ramucirumab vs. 4.5 months placebo
- N=279 (2:1 randomization, ramucirumab vs placebo)
- 221 events

Abbreviations: AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; BSC=best supportive care; ECOG PS=Eastern Cooperative Oncology Group performance status; FACT=Functional Assessment of Cancer Therapy; mOS= median overall survival; ORR=objective response rate; PFS=progression-free survival; PK=pharmacokinetics; Q2W=every 2 weeks; TTP=time to progression.

ClinicalTrials.gov NCT02435433

Eligibility Criteria

Key Inclusion Criteria

- Diagnosis of HCC (histological or radiological imaging confirmation)
- BCLC stage C or B refractory or not amenable to locoregional therapy
- Child-Pugh Class A
- ECOG PS score of 0 or 1
- Baseline AFP ≥400 ng/mL
- Prior sorafenib treatment (discontinued due to progression or intolerance)
- Adequate hematologic and biochemical parameters

Key Exclusion Criteria

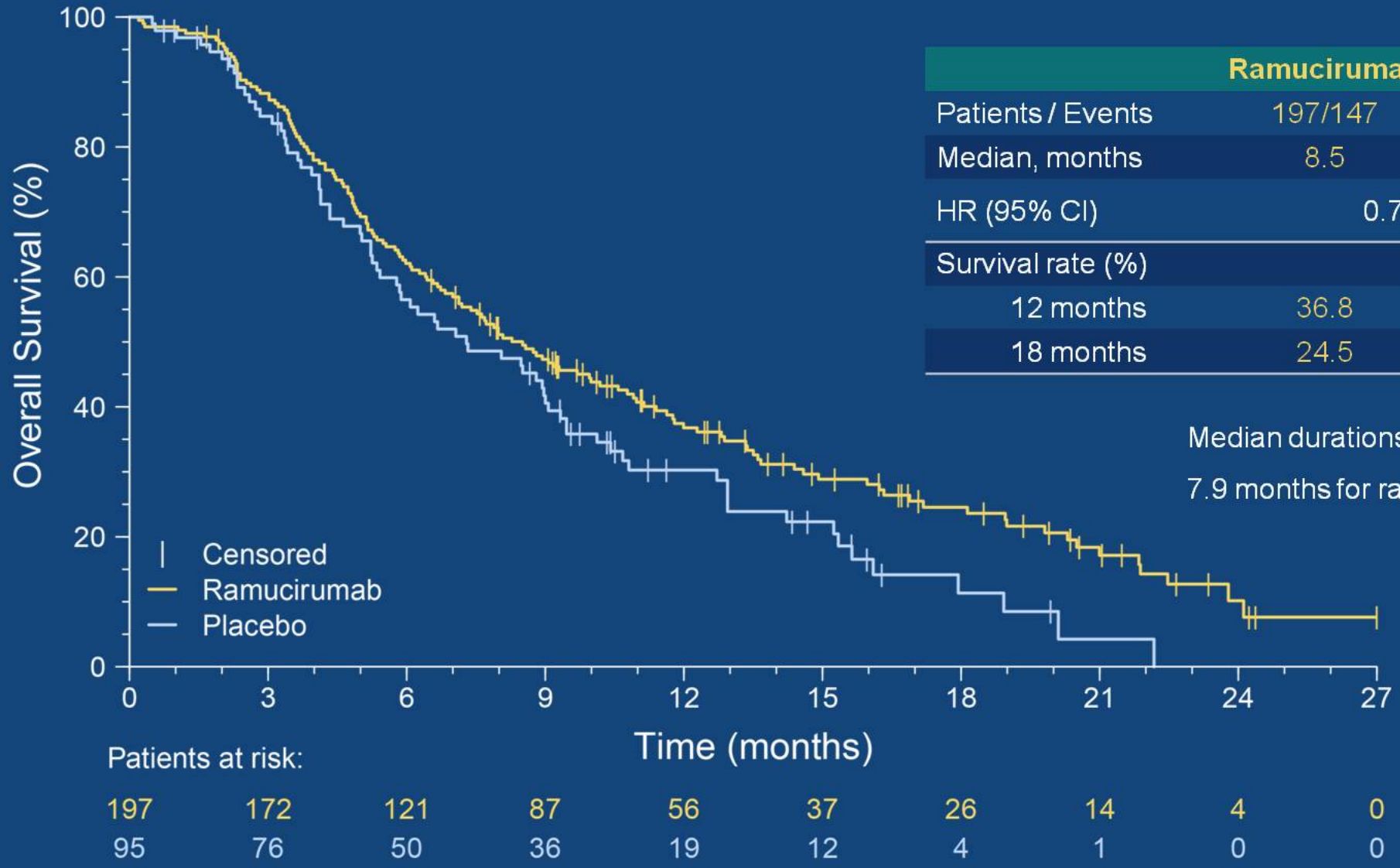
- Uncontrolled hypertension
- Esophageal or gastric varices requiring immediate intervention
- Prior anti-VEGF pathway therapy other than sorafenib
- Arterial thrombotic event within 6 months
- Therapeutic anticoagulation or chronic antiplatelet agents including NSAIDs
- History of or current hepatic encephalopathy (any grade) or ascites grade ≥2

Baseline Demographics and Characteristics

n, (%) except where indicated		Ramucirumab n=197	Placebo n=95	Total N=292
Sex	Male	154 (78.2)	79 (83.2)	233 (79.8)
Age	Median, years	64	64	64
ECOG PS	0	113 (57.4)	55 (57.9)	168 (57.5)
Geographic region	Americas, Europe, Israel, Australia	101 (51.3)	50 (52.6)	151 (51.7)
	Asia (excluding Japan)	55 (27.9)	27 (28.4)	82 (28.1)
	Japan	41 (20.8)	18 (18.9)	59 (20.2)
Child Pugh score	A-5	123 (62.4)	54 (56.8)	177 (60.6)
Baseline BCLC Stage	C	163 (82.7)	75 (78.9)	238 (81.5)
Etiology of liver disease	Hepatitis B	71 (36.0)	36 (37.9)	107 (36.6)
	Hepatitis C	48 (24.4)	28 (29.5)	76 (26.0)
	Significant Alcohol Use	48 (24.4)	21 (22.1)	69 (23.6)
	Steatohepatitis (NASH, Fatty Liver)	19 (9.6)	4 (4.2)	23 (7.9)
	Cryptogenic Cirrhosis	12 (6.1)	4 (4.2)	16 (5.5)
	Others	17 (8.6)	7 (7.4)	24 (8.2)
Macrovascular Invasion	Present	70 (35.5)	33 (34.7)	103 (35.3)
Extrahepatic Spread	Present	141 (71.6)	70 (73.7)	211 (72.3)
Baseline AFP (ng/mL)	Median	3920	2741	3394
	Min-Max	408 - 230500	419 - 473163	408 - 473163

Presented By Andrew Zhu at 2018 ASCO Annual Meeting

Overall Survival



	Ramucirumab	Placebo	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.5	7.3	1.2	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199
Survival rate (%)				
12 months	36.8	30.3	6.5	0.2930
18 months	24.5	11.3	13.2	0.0187

Median durations of follow-up were

7.9 months for ramucirumab, 6.6 months for placebo

Adverse Events of Special Interest

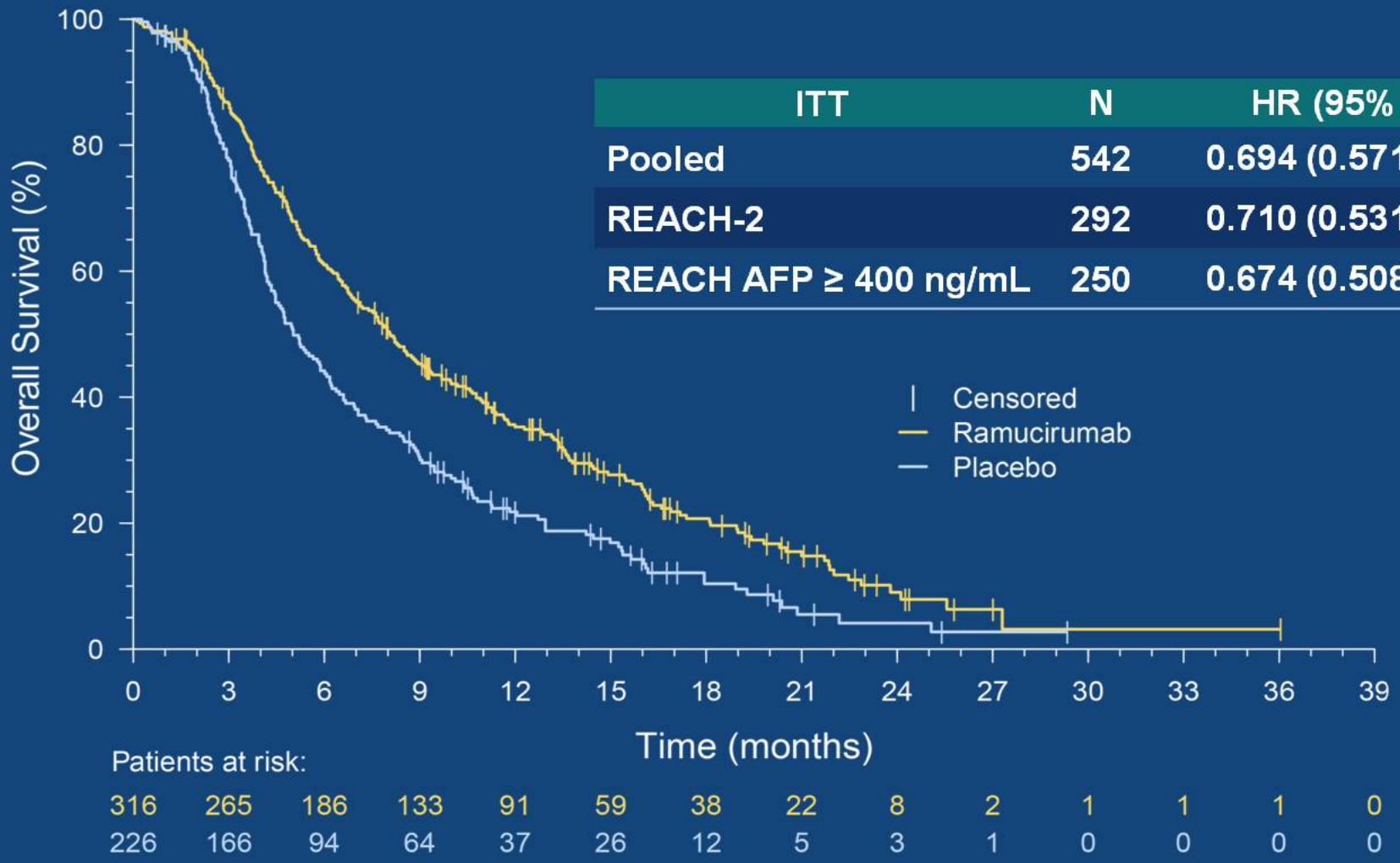
	Ramucirumab n=197		Placebo n=95	
n[a] (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypertension	49 (24.9)	25 (12.7)	12 (12.6)	5 (5.3)
Bleeding / Hemorrhage events	48 (24.4)	10 (5.1)	12 (12.6)	3 (3.2)
GI Hemorrhage events	12 (6.1)	7 (3.6)	5 (5.3)	2 (2.1)
Epistaxis	27 (13.7)	1 (0.5)	3 (3.2)	0
Proteinuria	40 (20.3)	4 (2.0)	4 (4.2)	0
Arterial thromboembolic events	5 (2.5)	3 (1.5)	1 (1.1)	1 (1.1)
Venous thromboembolic events	2 (1.0)	0	2 (2.1)	1 (1.1)
Gastrointestinal perforation	2 (1.0)	2 (1.0)	2 (2.1)	2 (2.1)
Congestive heart failure	1 (0.5)	1 (0.5)	1 (1.1)	1 (1.1)
Fistula	1 (0.5)	0	0	0
Liver injury / liver failure	78 (39.6)	36 (18.3)	28 (29.5)	15 (15.8)
Ascites	35 (17.8)	8 (4.1)	7 (7.4)	2 (2.1)
Hepatic encephalopathy	8 (4.1)	6 (3.0)	0	0
Infusion-related reactions[b]	17 (8.6)	0	3 (3.2)	0

[a]Adverse events of special interest according to either MEDRA preferred terms or consolidated categories, [b]Infusion-related reactions occurring within 24 hours of infusion

CONCLUSIONS

- REACH-2 met its primary endpoint showing a significant survival benefit of ramucirumab treatment in patients with HCC and AFP ≥400 ng/mL who progressed on or were intolerant to sorafenib
- Clinically meaningful benefits were demonstrated in secondary endpoints, including PFS and DCR
- Ramucirumab was well tolerated, with a safety profile consistent with monotherapy ramucirumab treatment
- REACH-2 is the first positive study in a biomarker-selected patient population, demonstrating a significant and meaningful OS benefit and favorable safety profile in HCC patients with baseline AFP ≥400 ng/mL, a population associated with poor prognosis
- REACH-2 confirms the efficacy and safety observed in the pre-specified group of patients from REACH with AFP ≥400 ng/mL

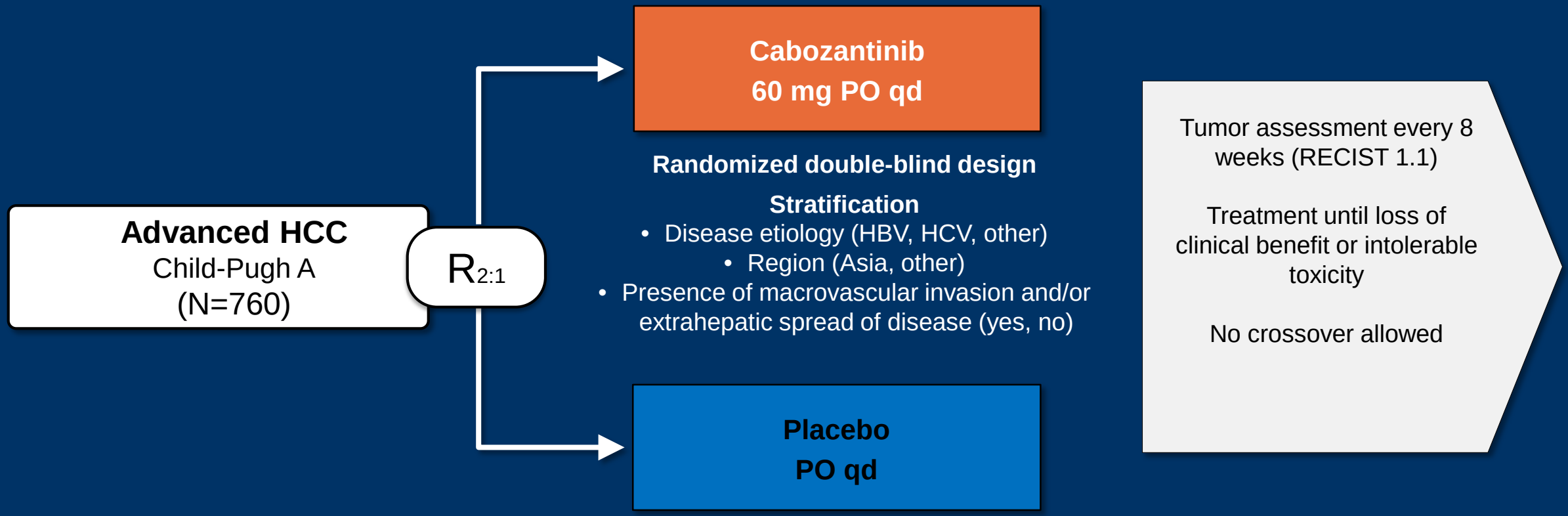
Overall Survival in Pooled Population



ITT	N	HR (95% CI)	mOS	P-value
Pooled	542	0.694 (0.571, 0.842)	Δ=+3.1 (8.1 vs. 5.0)	0.0002
REACH-2	292	0.710 (0.531, 0.949)	Δ=+1.2 (8.5 vs. 7.3)	0.0199
REACH AFP ≥ 400 ng/mL	250	0.674 (0.508, 0.895)	Δ=+3.6 (7.8 vs. 4.2)	0.0059

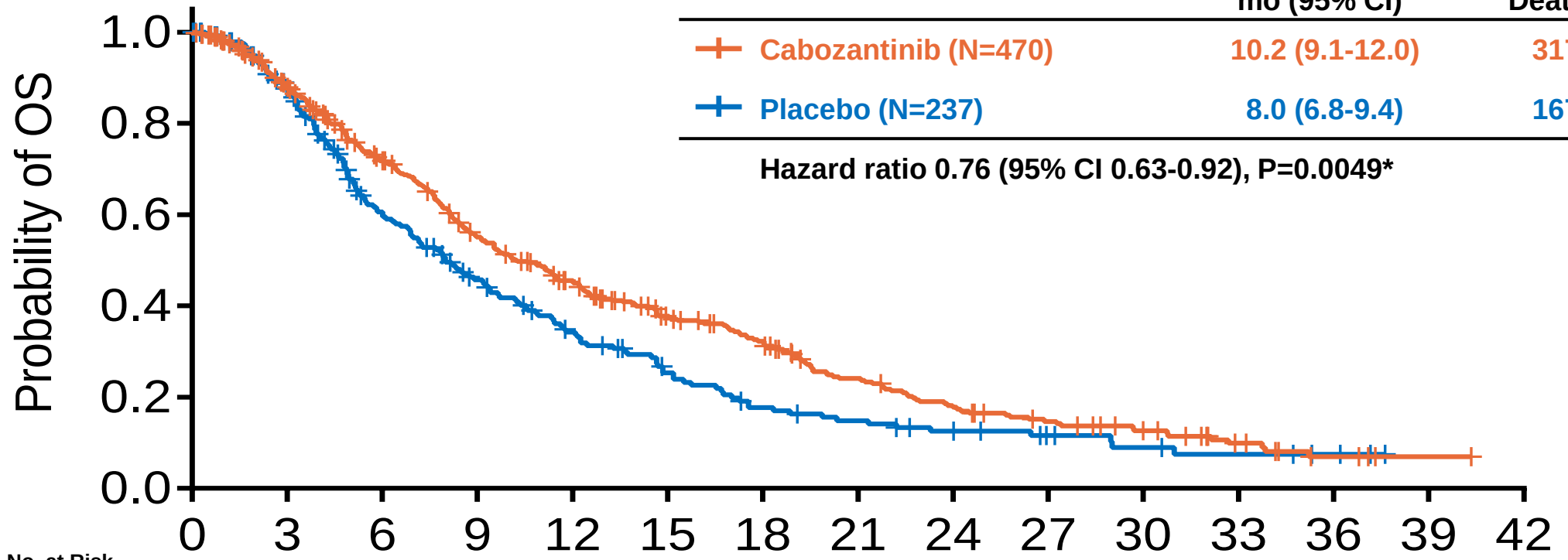
Presented By Andrew Zhu at 2018 ASCO Annual Meeting

CELESTIAL Study Design



Abou-Alfa, GK Journal of Clinical Oncology 32, no. 15_suppl

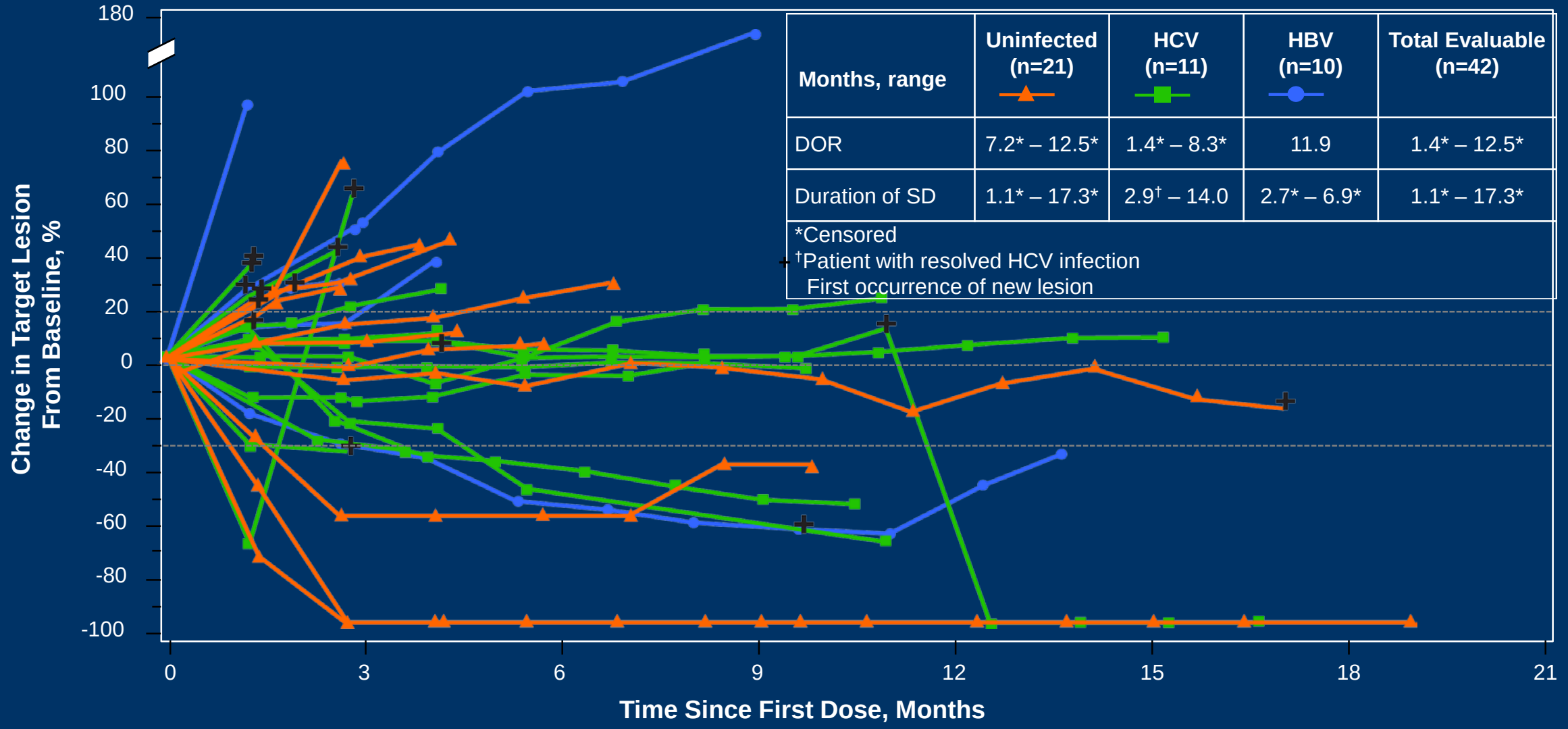
CELESTIAL Overall Survival



*Critical p-value ≤ 0.021 for second interim analysis

Abou-Alfa, GK Journal of Clinical Oncology 32, no. 15_suppl

Nivolumab Response Kinetics in HCC

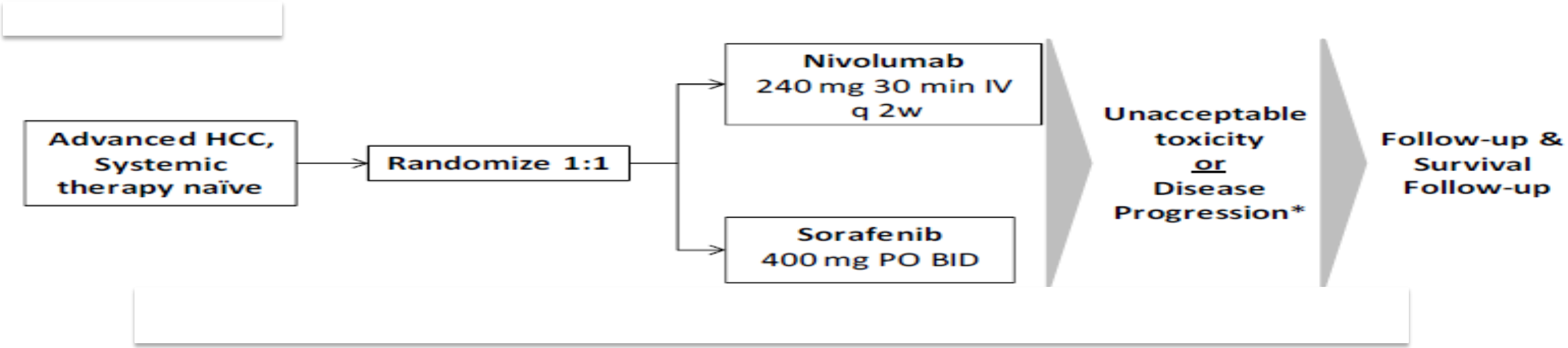


Months, range	Uninfected (n=21)	HCV (n=11)	HBV (n=10)	Total Evaluable (n=42)
DOR	7.2* – 12.5*	1.4* – 8.3*	11.9	1.4* – 12.5*
Duration of SD	1.1* – 17.3*	2.9† – 14.0	2.7* – 6.9*	1.1* – 17.3*

*Censored
†Patient with resolved HCV infection
First occurrence of new lesion

El-Khoueiri, A, ASCO 2015

CheckMate-459: Nivolumab vs Sorafenib as First-line Treatment in Advanced HCC

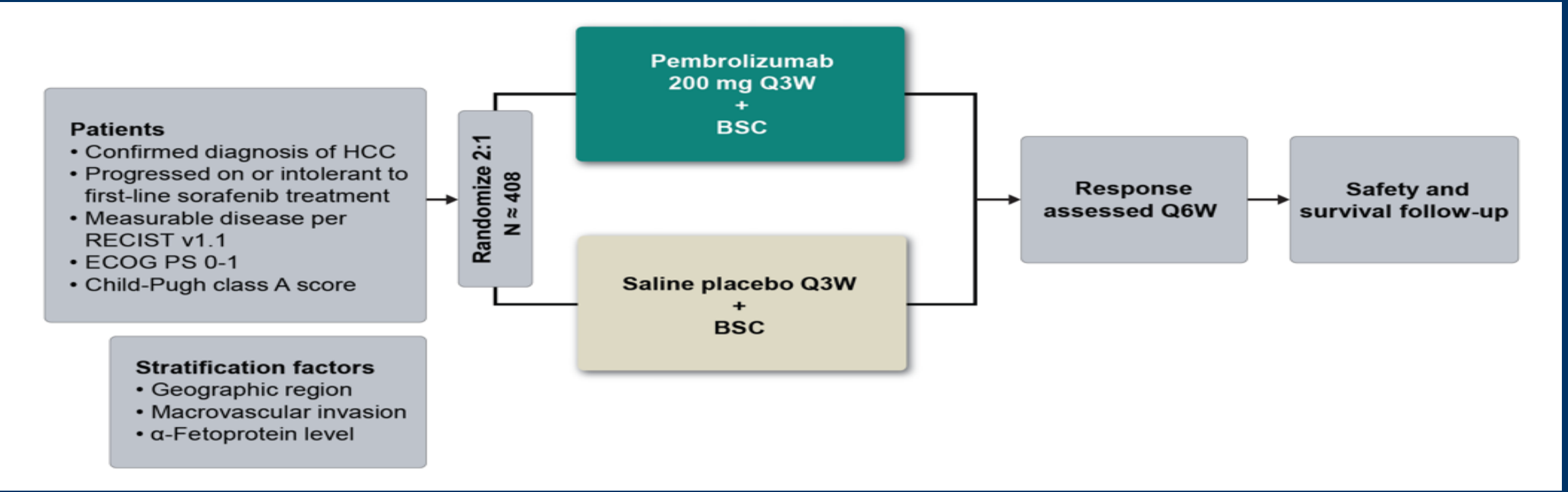


Stratification factors:

- Etiology (HCV vs. non-HCV [ie, HBV- and HCC with no history of hepatitis virus infection])
- Vascular invasion &/or extrahepatic spread (present or absent),
- Geography (Asia vs Non-Asia).

Sangro B, et al. ASCO 2016. Abstract TPS4147. ClinicalTrials.gov. NCT02576509

Pembrolizumab versus Placebo in HCC



R Finn, et al. Annals of Oncology 11 October, 2016

Second Line HCC Therapies

	RESORCE	CELESTIAL	REACH-2
Patients	573	760	292
CP A/BCLC B/C	98/B14/C86	100/NS	100/B17/C83
AFP >400	43	41	100
Asia-Pacific/Western	38/62	25/75	49/51
Extrahep/MacroVI	70/29/80	79/27/85	71/35/NS
Response Rate, %	11 vs. 4	4 vs. 0.4	4.6 vs. 1.1
Progression free survival	3.1 vs. 1.5	5.2 vs. 1.9	2.8 vs. 1.6
Overall Survival	10.6 vs. 7.8 HR 0.63	10.2 vs.8.0 (11.3) HR 0.76	8.5 vs. 7.3 HR 0.71
Toxicities>Gr 3 (%)	HFSR (12), fatigue (10), HTN (15), (diarrhea- 3)	HFSR (17) HTN (16), diarrhea, fatigue (10) *60% of planned dose	HTN, bleeding- GI 3.6, liver injury 18%

Thank you!!

Ghassan Abou-Alfa
Milind Javle

gmrpkim@gmail.com