Advances in Gastrointestinal Malignancies

Edward J. Kim MD, PhD

UCDAVIS
COMPREHENSIVE
CANCER CENTER

EDWARD KIM, MD, PHD

ADVANCES IN GASTROINTESTINAL MALIGNANCIES

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

GRANT/RESEARCH SUPPORT: MERCK, ONCOMED, CELGENE, HALOZYME, BOSTON BIOMEDICAL, EPICENTRX, BRISTOL-MYERS SQUIBB
CONSULTANT: VICUS, ARMO

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

Topics

- Pancreatic Cancer
  - adjuvant therapy
- Hepatocellular Carcinoma
  - Lenvatinib, cabozantinib, regorafenib, ramucirumab
  - Nivolumab
- Gastric Cancer
  - pembrolizumab
- Colorectal Cancer
  - Regorafenib

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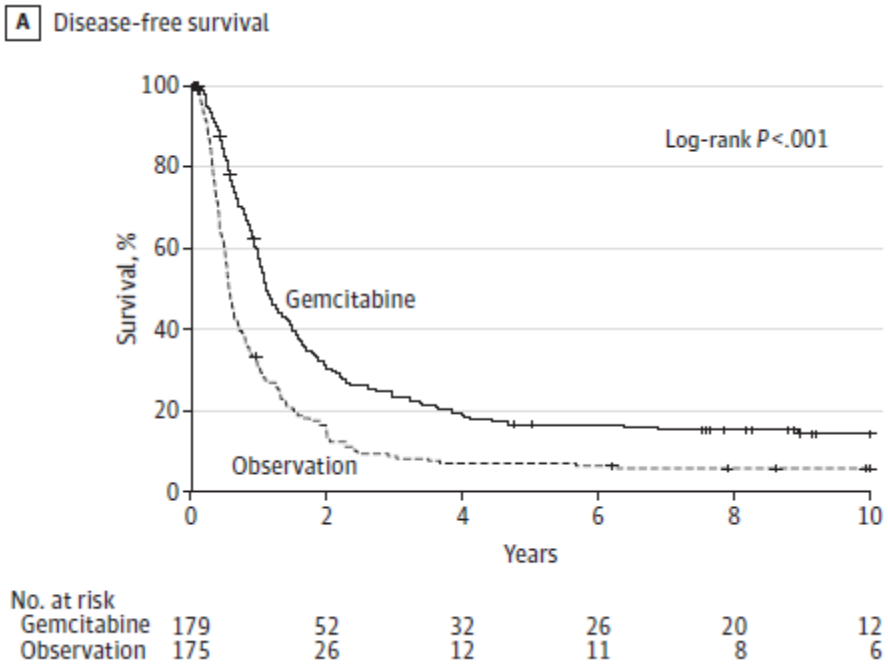
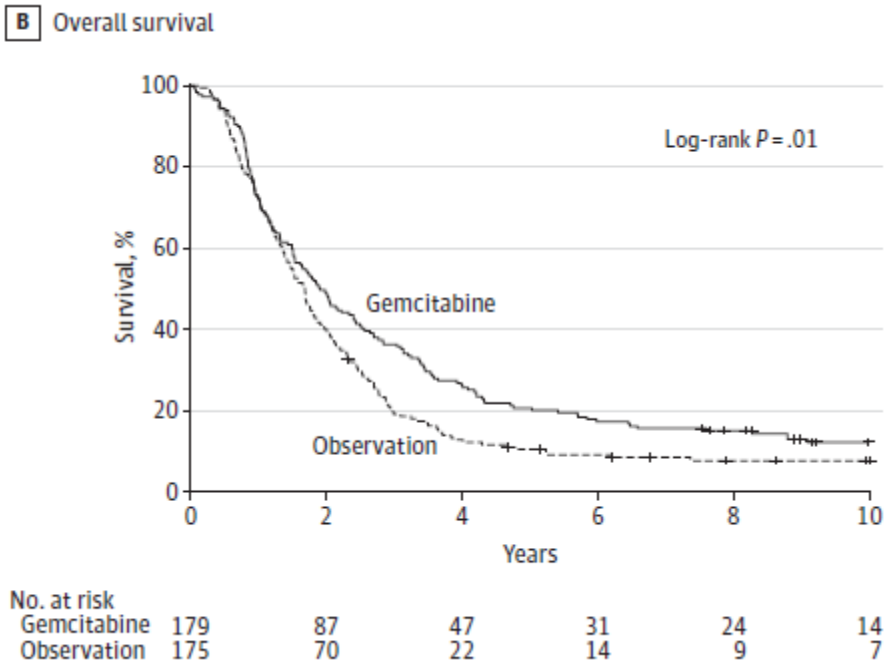
Conko-001





Oettle et al. JAMA 2013 Oct 9:1473-81

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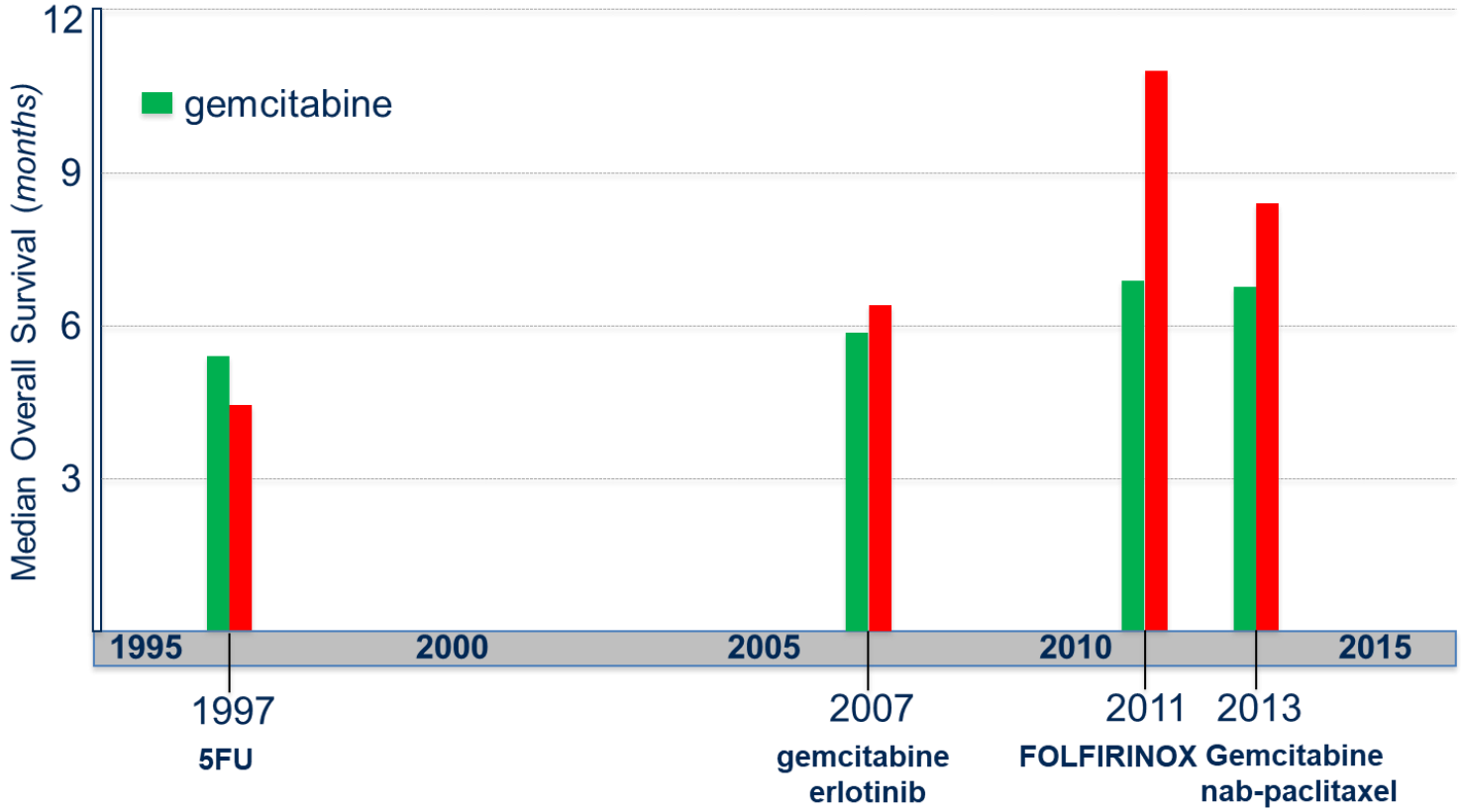
New drugs? New strategies?

- Looking for inspiration from the metastatic disease setting…



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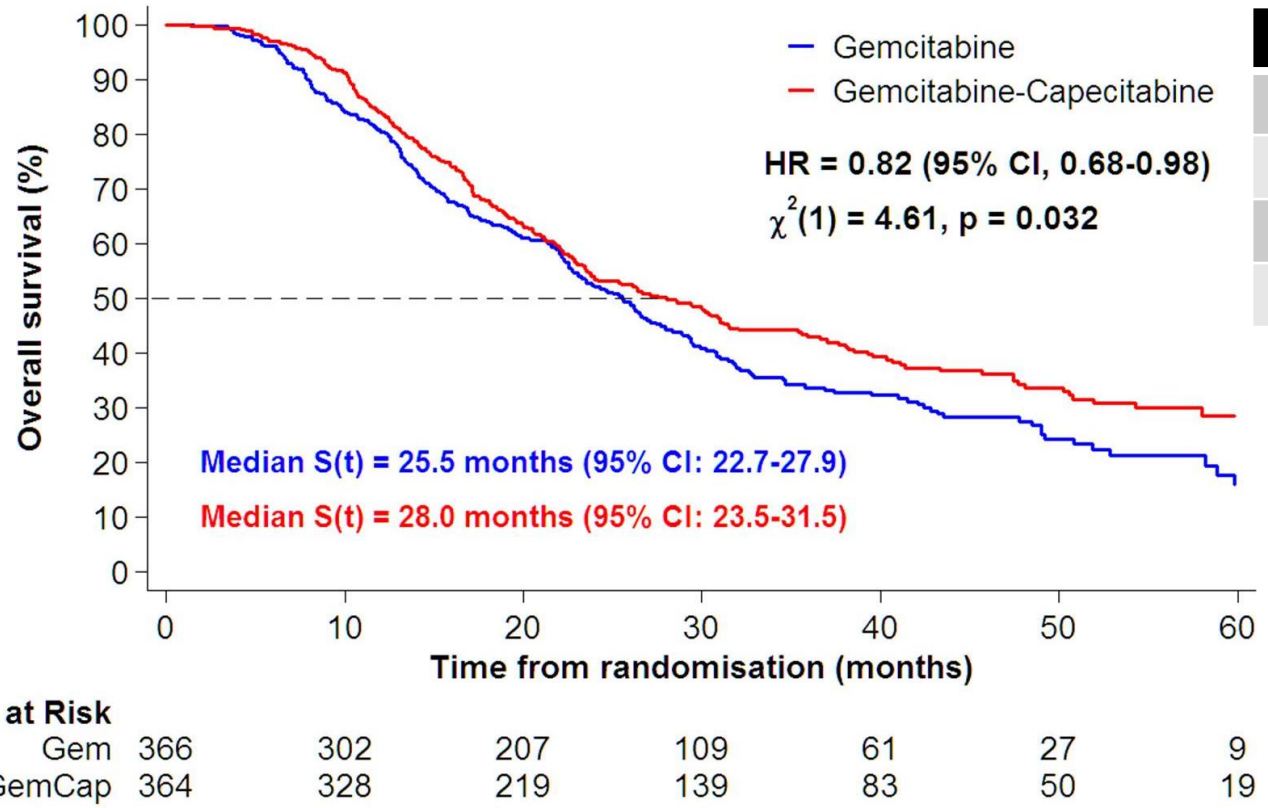
ESPAC-4 – gem vs gem/capecitabine



Gr 3/4	Gem	Gem-Cap
SAE's	26%	24%
ANC	24%	38%
Hand Foot	0	7%
Diarrhea	2%	5%

Presented By John Neoptolemos at 2016 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

No bolus 5FU

mFolfirinox 247 patients

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 246 patients

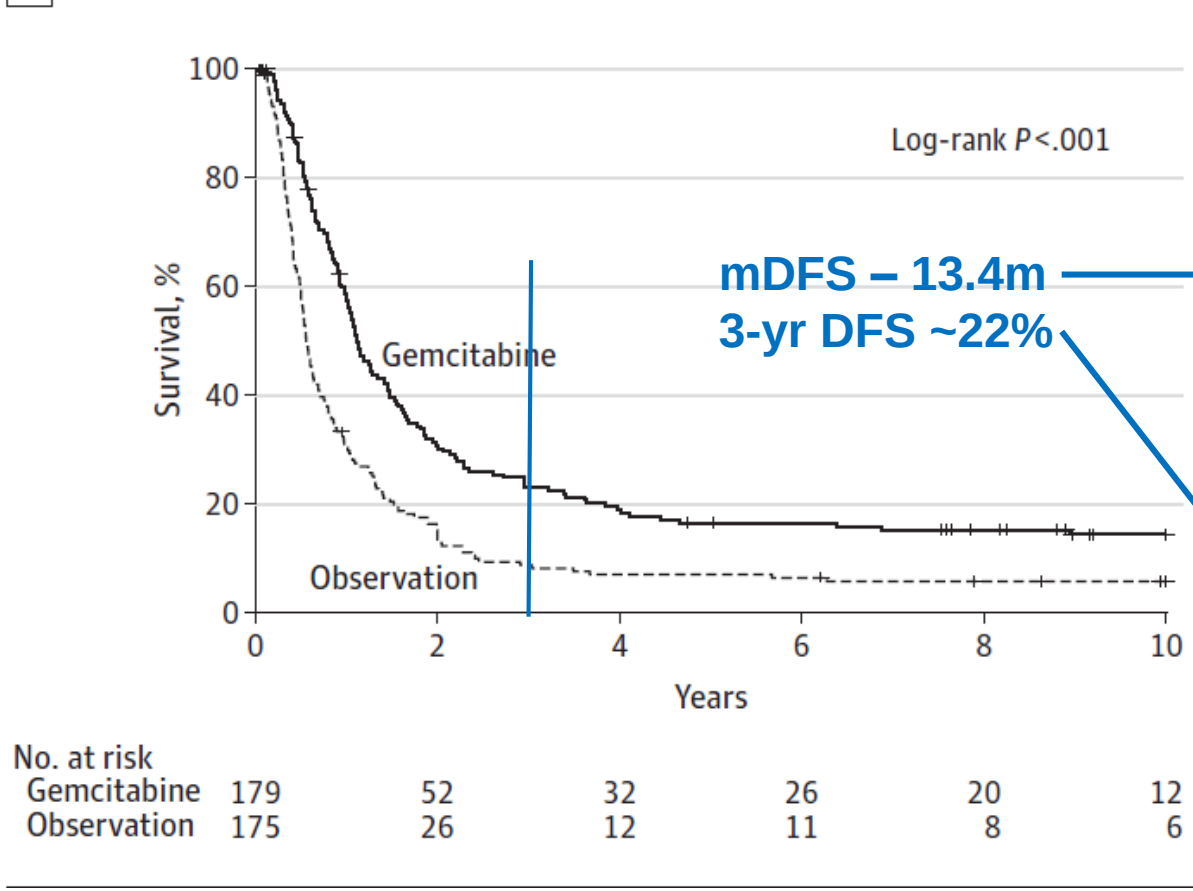
1000 mg/m², qw 3/4 *weeks;*
6 cycles

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

Primary Endpoint

Disease-Free Survival

CONKO-001



mDFS – 13.4m
3-yr DFS ~22%

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

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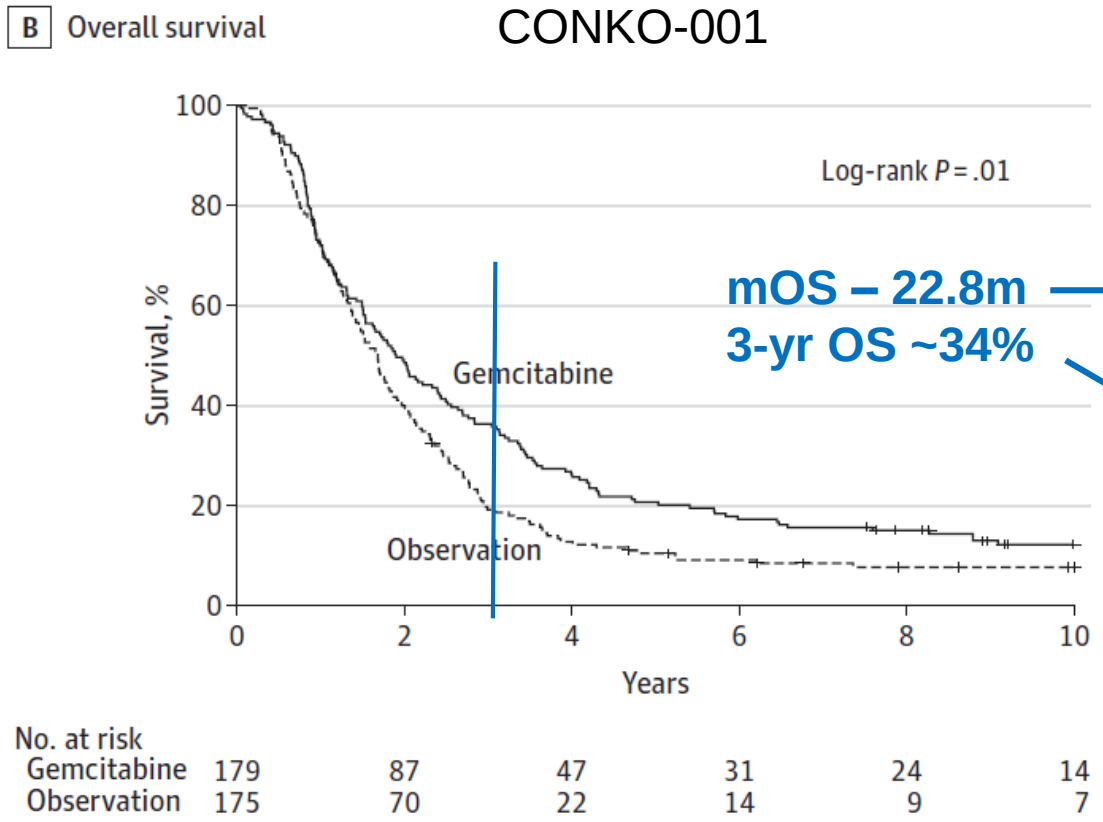
Overall Survival



mOS – 22.8m
3-yr OS ~34%

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)**

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.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Thierry Conroy

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%)	

Discussion

Strengths

- Well designed and executed prospective randomized phase III study
- Meaningful margin of benefit
- “Manageable” toxicity profile

Limitations

- “Real world” tolerability
- Very select patient population
- Overall impact to pancreatic cancer survival

Practice Changing?

- Yes, confirms role of combination adjuvant therapy
- Yes, for super-fit patients

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Key Unanswered Questions

- Impact of dose intensity
- Subsequent treatment at recurrence
- Other combination therapies
  - Gem/nab-paclitaxel: APACT study
  - Multiple options, no head-to-head, same problem as metastatic
- Role for radiation
  - RTOG 0848
- Neoadjuvant vs adjuvant

Topics

- Pancreatic Cancer
  - adjuvant therapy
- Hepatocellular Carcinoma
  - Lenvatinib, cabozantinib, regorafenib, ramucirumab
  - Nivolumab
- Gastric Cancer
  - pembrolizumab
- Colorectal Cancer
  - Regorafenib

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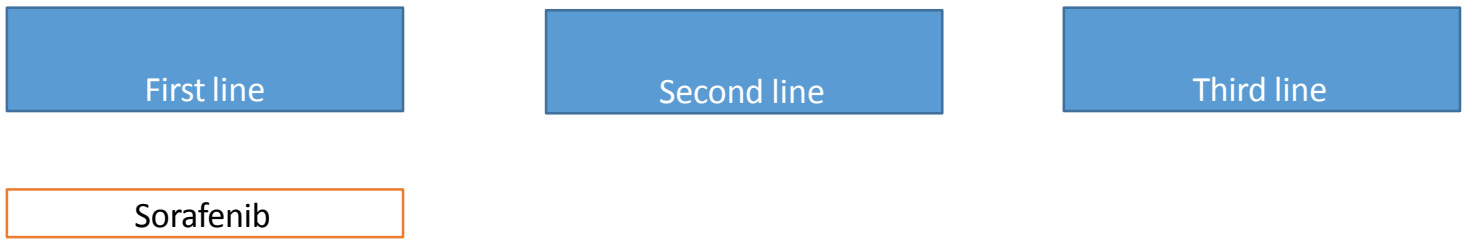
Until recently this was the reality for patients with advanced HCC



First-line Lenvatinib vs Sorafenib in Pts With Unresectable HCC: Background

- Sorafenib is the only FDA-approved systemic agent for unresectable HCC, a leading cause of cancer death in need of new therapies[1,2]
  - Sunitinib, brivanib, linifanib, and erlotinib + sorafenib each failed to demonstrate noninferior or superior OS vs sorafenib in pts with advanced HCC in phase III trials

- Lenvatinib: multikinase inhibitor of VEGF1-3, FGF1-4, PDGFRα, RET, and KIT[8]

REFLECT: Study Design

- Multicenter, randomized, open-label phase III **noninferiority** study

Pts with unresectable HCC, no prior systemic therapy, and adequate organ function
(N = 954)

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

Sorafenib
400 mg BID
(n = 476)

- Primary endpoint: **OS**
  - Noninferiority margin **1.08**; criteria met if upper limit of 2-sided 95% CI for HR < 1.08
- Secondary endpoints: PFS, TTP, ORR, QoL, lenvatinib PK
- Other endpoints: DCR, CBR, exploratory biomarker analysis

Slide credit: clinicaloptions.com

Cheng AL, et al. ASCO 2017. Abstract 4001.

REFLECT: Baseline Characteristics

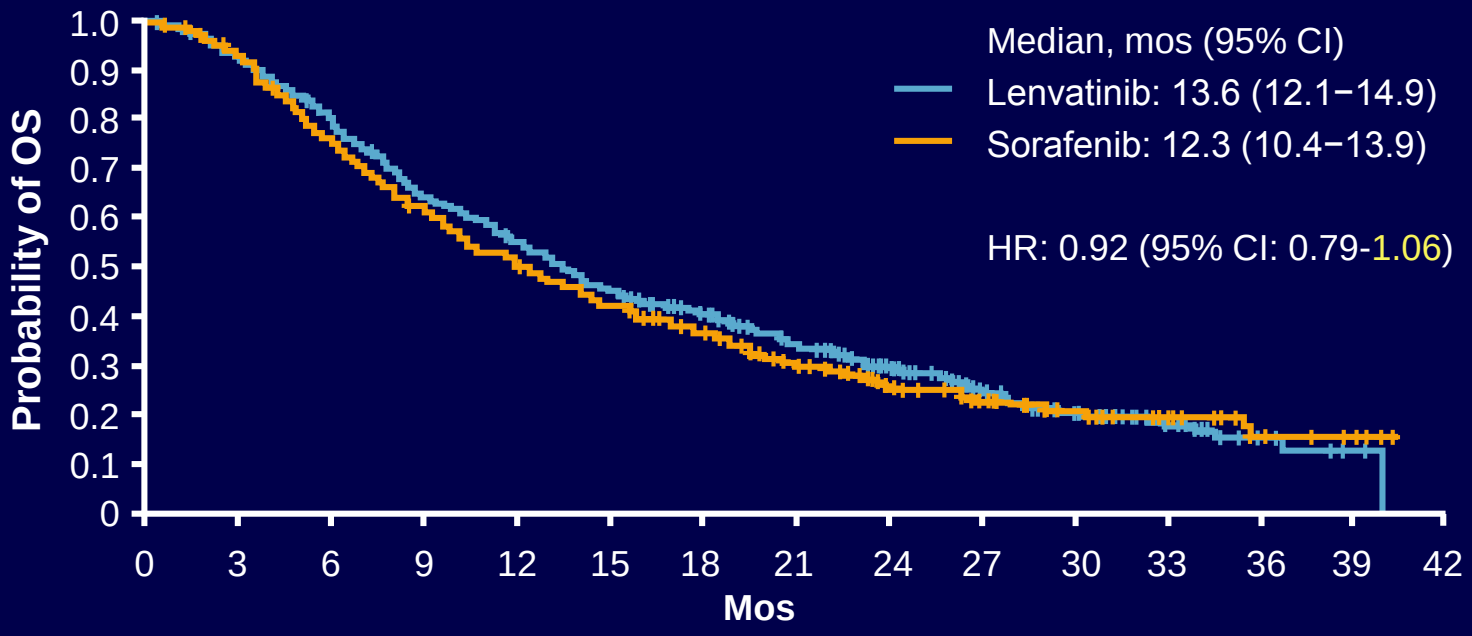
Characteristic	Lenvatinib (n = 478)	Sorafenib (n = 476)
Mean age, yrs	61.3	61.2
Male, n (%)	405 (85)	401 (84)
Region, n (%)		
▪ Western	157 (33)	157 (33)
▪ Asia-Pacific	321 (67)	319 (67)
Body weight, n (%)		
▪ < 60 kg	153 (32)	146 (31)
▪ ≥ 60 kg	325 (68)	330 (69)
ECOG PS, n (%)		
▪ 0	304 (64)	301 (63)
▪ 1	174 (36)	175 (37)
MVI and/or EHS diagnosis, n (%)	329 (69)	336 (71)
BL AFP level, n (%)		
▪ < 200 ng/mL	255 (53)	286 (60)
▪ ≥ 200 ng/mL	222 (46)	187 (39)
Median BL AFP level, ng/mL	133.1	71.2

Characteristic, n (%)	Lenvatinib (n = 478)	Sorafenib (n = 476)
Child-Pugh class		
▪ A	475 (99)	471 (99)
▪ B	3 (1)	5 (1)
BCLC stage		
▪ B (intermediate)	104 (22)	92 (19)
▪ C (advanced)	374 (78)	384 (81)
Involved disease sites per pt		
▪ 1	207 (43)	207 (44)
▪ 2	167 (35)	183 (38)
▪ ≥ 3	103 (22)	86 (18)
Etiology of chronic liver disease		
▪ HBV	251 (53)	228 (48)
▪ HCV	91 (19)	126 (27)
▪ Alcohol	36 (8)	21 (4)
▪ Other	38 (8)	32 (7)
▪ Unknown	62 (13)	69 (15)
Concomitant HBV/HCV therapy	163 (34)	149 (31)

Slide credit: clinicaloptions.com

Cheng AL, et al. ASCO 2017. Abstract 4001.

REFLECT: OS (Primary Endpoint)



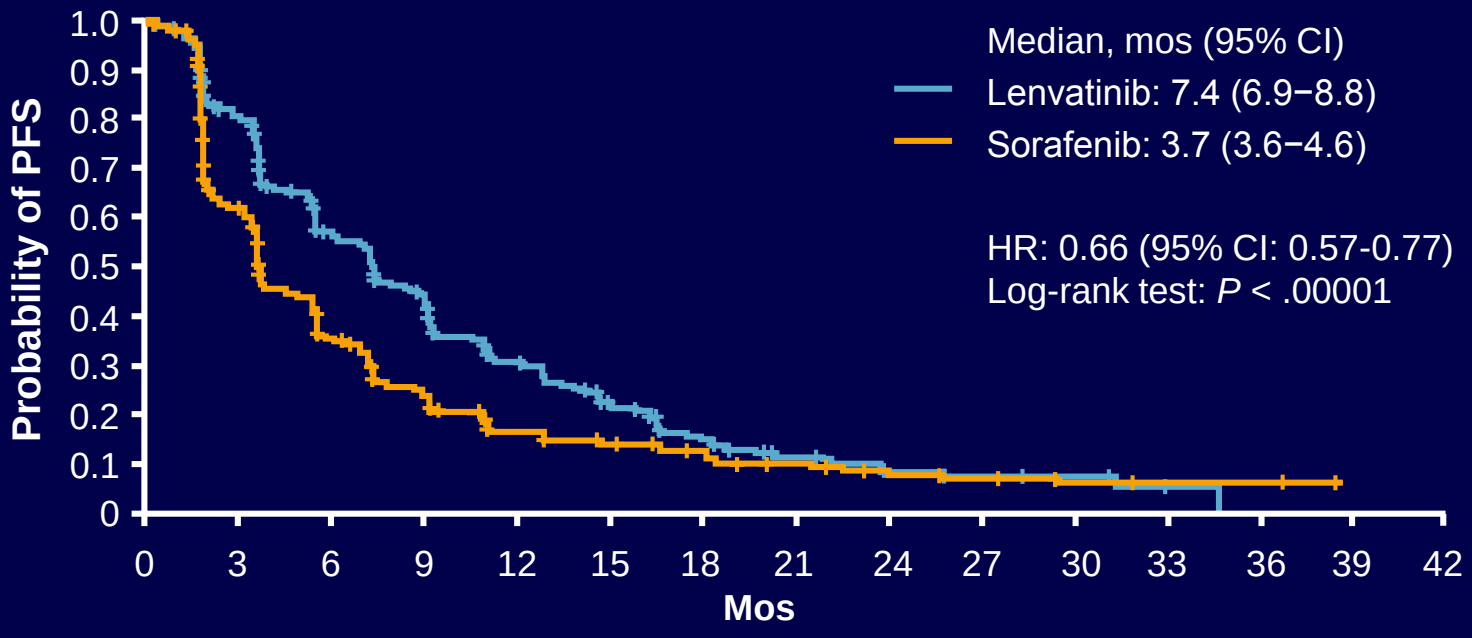
Pts at Risk, n

	47	43	37	29	25	20	17	14	10	67	40	21	8	2	0
	8	6	4	7	3	7	8	0	2	57	33	16	8	4	0
	47	44	34	28	23	19	15	116	83						
	6	0	8	2	0	2	6								

Slide credit: clinicaloptions.com

Cheng AL, et al. ASCO 2017. Abstract 4001. Reproduced with permission.

REFLECT: PFS by mRECIST



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REFLECT: Other Efficacy Outcomes

Outcome,* Mos (95% CI)	Lenvatinib (n = 478)	Sorafenib (n = 476)	OR (95% CI)	*P* Value
ORR, % (95% CI)	**24.1** (20.2-27.9)	**9.2** (6.6-11.8)	3.13 (2.15-4.56)	< .00001
▪ CR, n (%)	6 (1.3)	2 (0.4)		
▪ PR, n (%)	109 (22.8)	42 (8.8)		
▪ SD, n (%)	246 (51.5)	244 (51.3)		
• Durable SD, n (%)	167 (34.9)	139 (29.2)		
▪ PD, n (%)	71 (14.9)	147 (30.9)		
▪ Unknown/NE, n (%)	46 (9.6)	41 (8.6)		
DCR, % (95% CI)	75.5 (71.7-79.4)	60.5 (56.1-64.9)		
Median TTP	**8.9** (7.4-9.2)	**3.7** (3.6-5.4)	0.63 (0.53-0.73)	< .00001

*Tumor assessments according to mRECIST by investigator.

Slide credit: clinicaloptions.com

Cheng AL, et al. ASCO 2017. Abstract 4001.

REFLECT: Most Common TEAEs

TEAEs Occurring in ≥ 15% of Pts, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any	Grade 3/4	Any	Grade 3/4
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Hand-foot syndrome	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (< 1)	57 (12)	0
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0	8 (2)	0
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0
Elevated AST	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0	76 (16)	2 (< 1)
Alopecia	14 (3)	0	119 (25)	0

Cheng AL, et al. ASCO 2017. Abstract 4001.

Slide credit: clinicaloptions.com

Conclusions

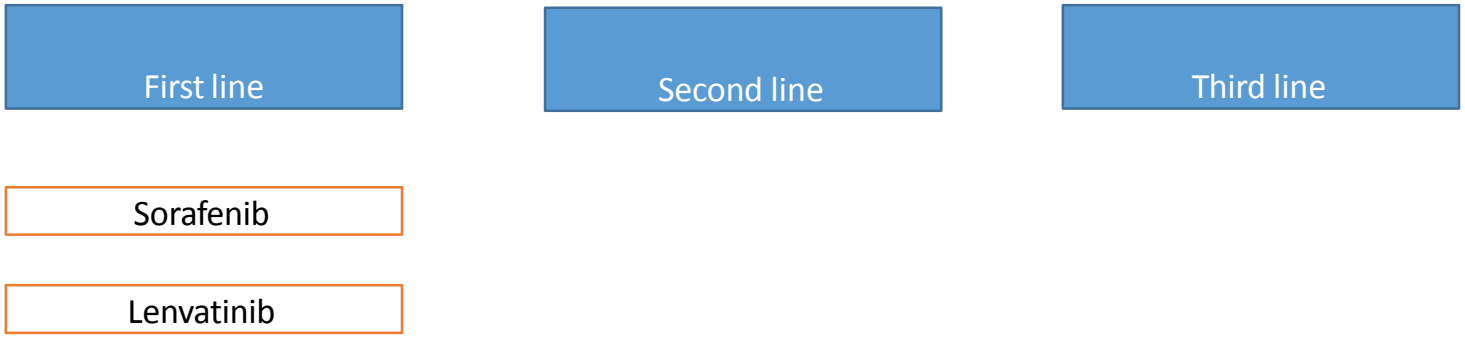
- In pts with unresectable HCC and no prior systemic therapy for HCC, lenvatinib demonstrated noninferior OS vs sorafenib

- Lenvatinib significantly increased PFS, TTP, and ORR vs sorafenib

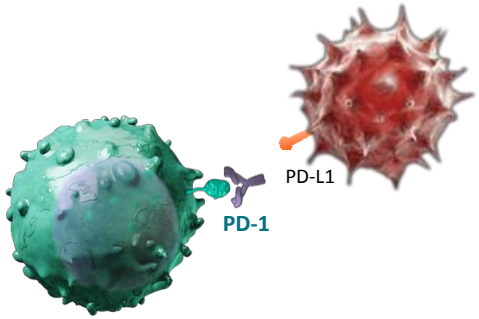
Slide credit: clinicaloptions.com

Cheng AL, et al. ASCO 2017. Abstract 4001.

A new reality for patients with advanced HCC



CHECKMATE-459: Phase III trial of nivolumab vs sorafenib in first-line advanced HCC patients[1]



Adapted from Mellman I et al 2011.[2]

Start Date: November 2015

Primary Endpoints: TTP, OS

Other Endpoints: ORR, PFS, biomarkers

Key Eligibility Criteria

N=726

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

R

Nivolumab

Sorafenib

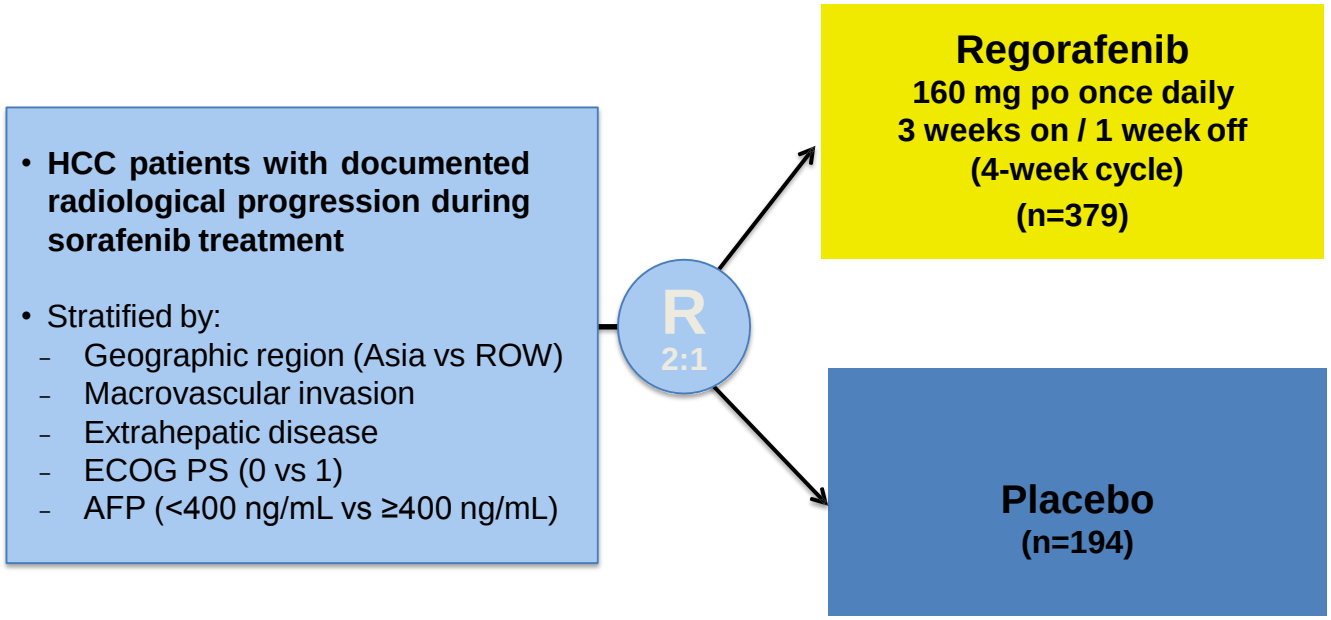
. Mellman I et al. *Nature*. 2011;480(7378):480-489.

A new reality for patients with advanced HCC

First line	Second line	Third line
Sorafenib		
Lenvatinib		

Regorafenib

RESORCE trial design



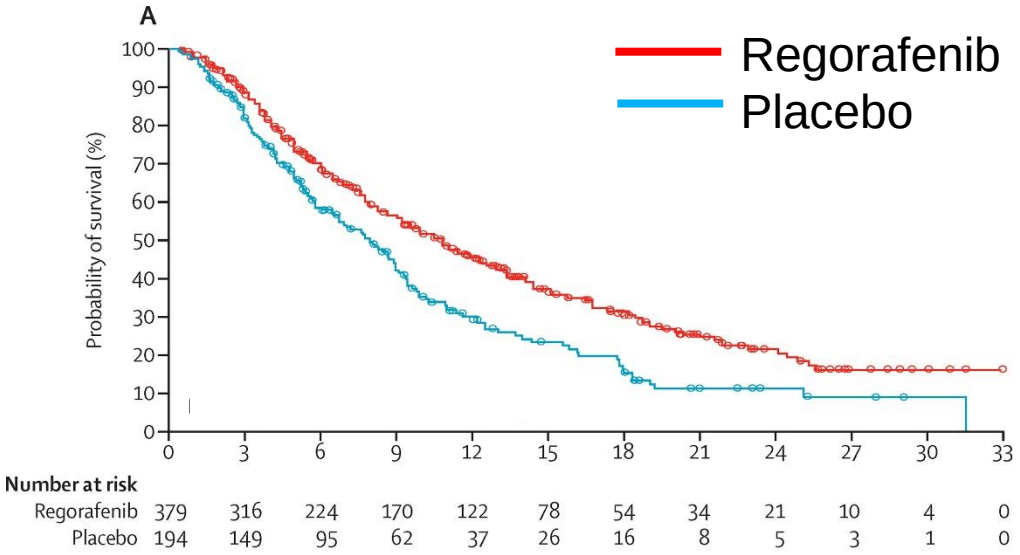
- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

Bruix J et al, Lancet 2017; 389: 56–66

Key inclusion criteria

- HCC confirmed by histological or cytological analysis, or diagnosed by non-invasive assessment per AASLD criteria in a patient with confirmed cirrhosis
- BCLC stage B or C patients who could not benefit from resection, local ablation, or chemoembolization
- Documented radiological progression during sorafenib
- Randomization within 10 weeks after the last sorafenib dose
- Tolerability of prior sorafenib, defined as receiving sorafenib ≥400 mg daily for at least 20 of the last 28 days of treatment
- ECOG PS 0/1
- Child-Pugh A liver function

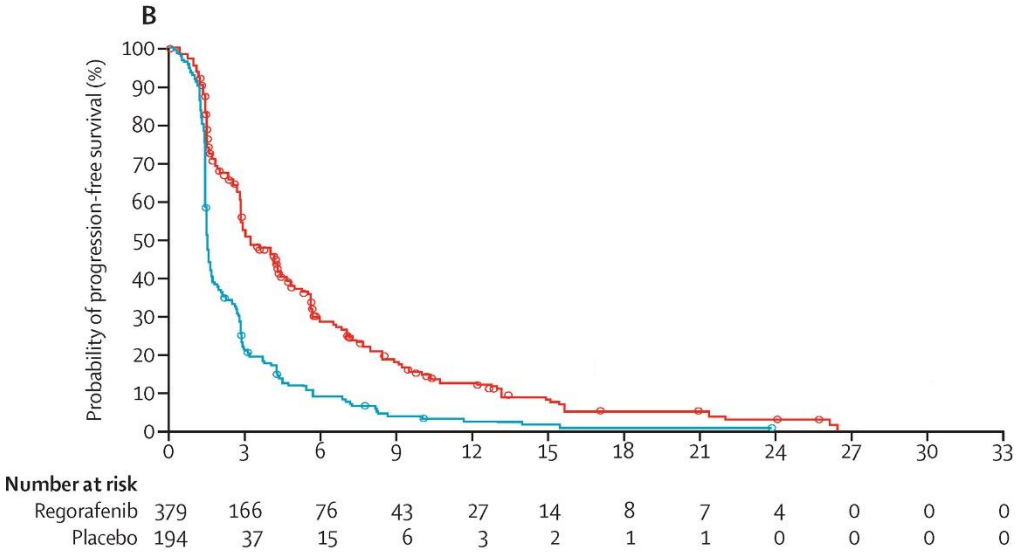
Efficacy



	Regorafenib n=379	**Placebo** n=194
Median OS (95% CI)	**10.6 m (9.1, 12.1)**	7.8 m (6.3, 8.8)

HR 0.62 (95% CI: 0.50, 0.78)

P<0.001 (2-sided)

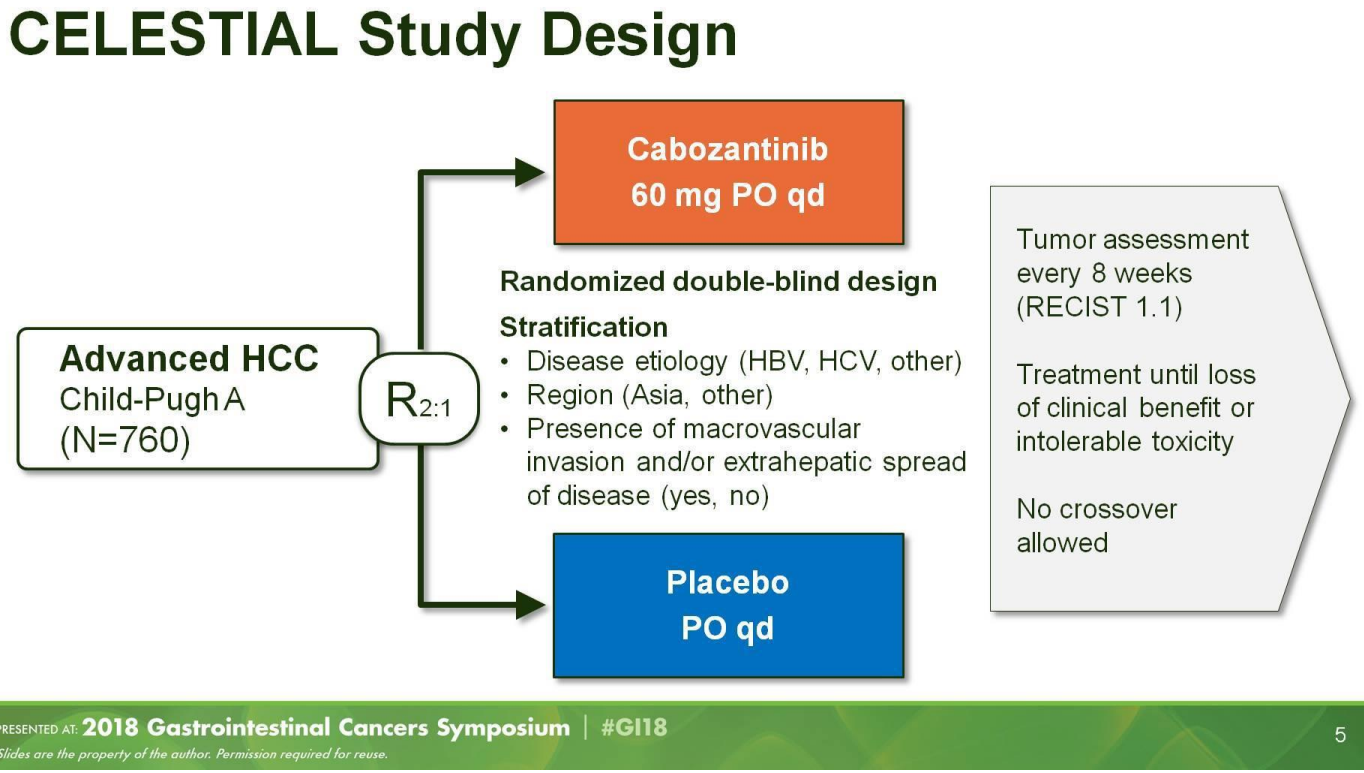


	Regorafenib n=379	**Placebo** n=194
Median PFS (95% CI)	**3.1 m (2.8, 4.2)**	1.5 m (1.4, 1.6)

HR 0.46 (95% CI: 0.37, 0.56)

P<0.001 (2-sided)

Cabozantinib



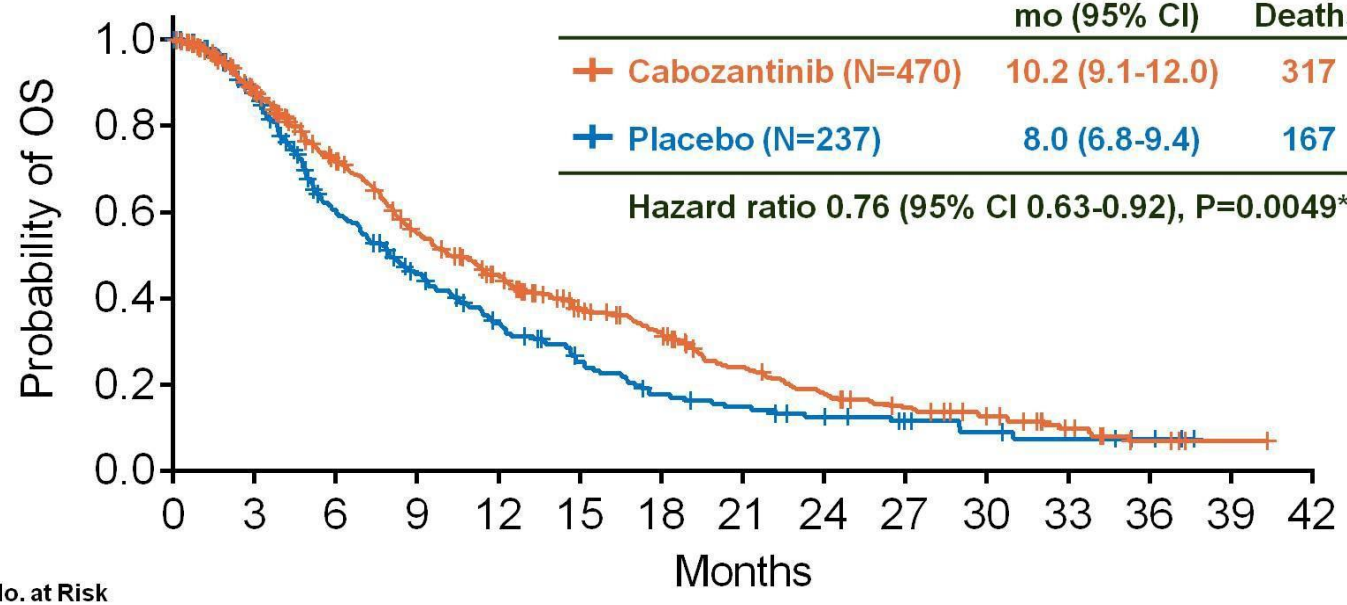
Abou Alfa G et al, NEJM 2018

Key Eligibility Criteria

- Pathologic diagnosis of HCC not amenable to curative treatment
- Child-Pugh score A
- Received prior sorafenib
- Progressed following at least one prior systemic treatment for HCC
- Received up to two prior systemic regimens for advanced HCC
- ECOG performance status 0 or 1
- No uncontrolled hypertension, defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment

Efficacy

Overall Survival



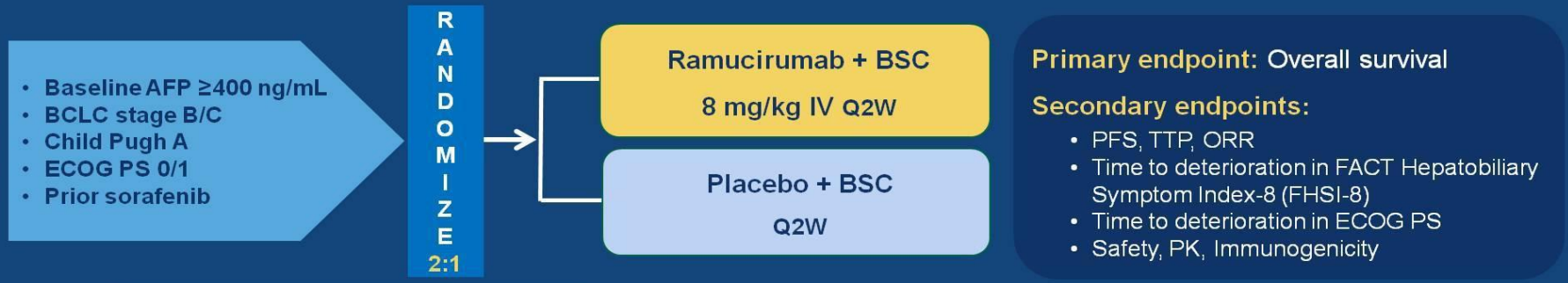
No. at Risk

Cabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

*Critical p-value ≤ 0.021 for second interim analysis

Ramucirumab

REACH 2: Study Design



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

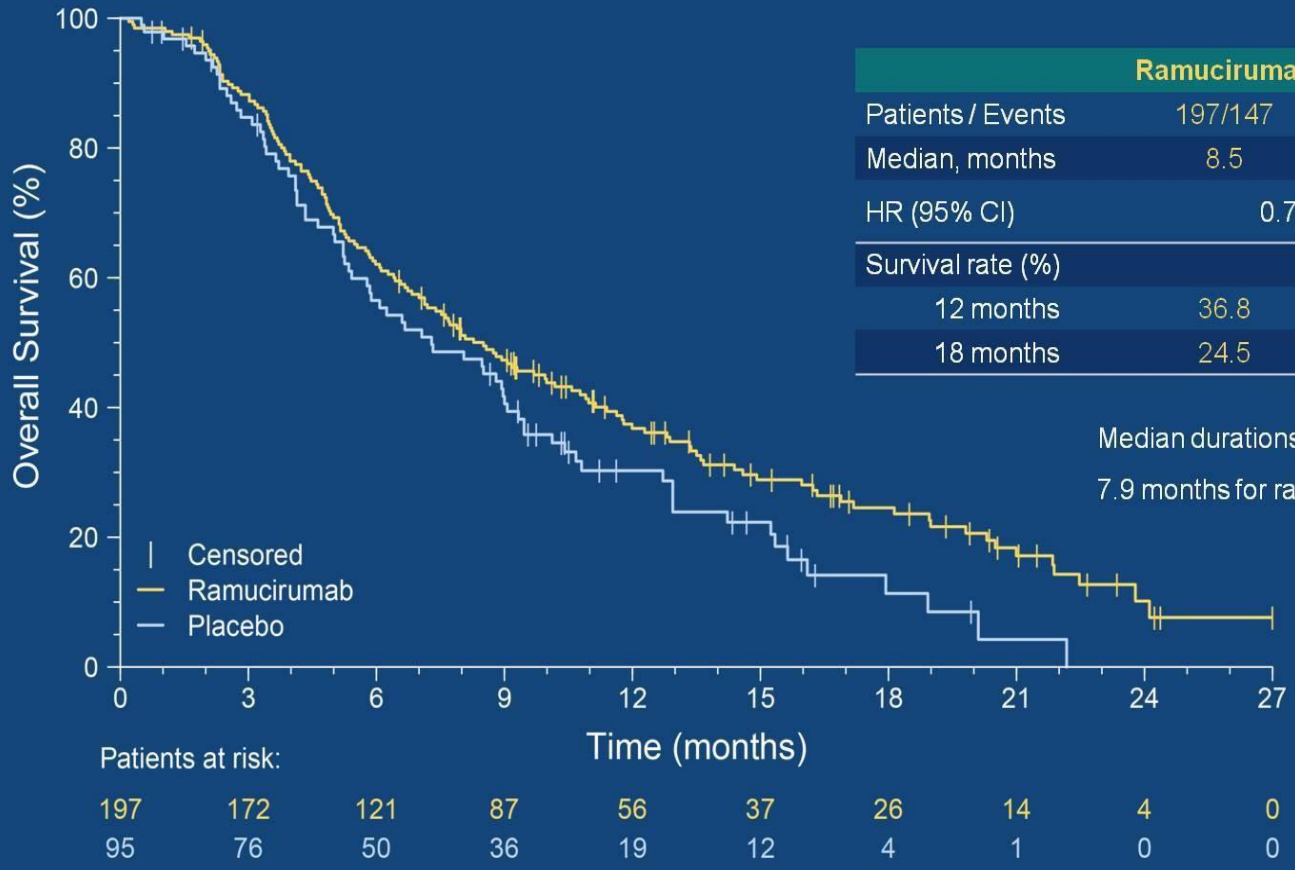
- 80% power, alpha 0.05
- HR 0.67
- mOS 6.7 months ramucirumab vs. 4.5 months placebo
- N=279 (2:1 randomization, ramucirumab vs placebo)
- 221 events

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

Efficacy

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

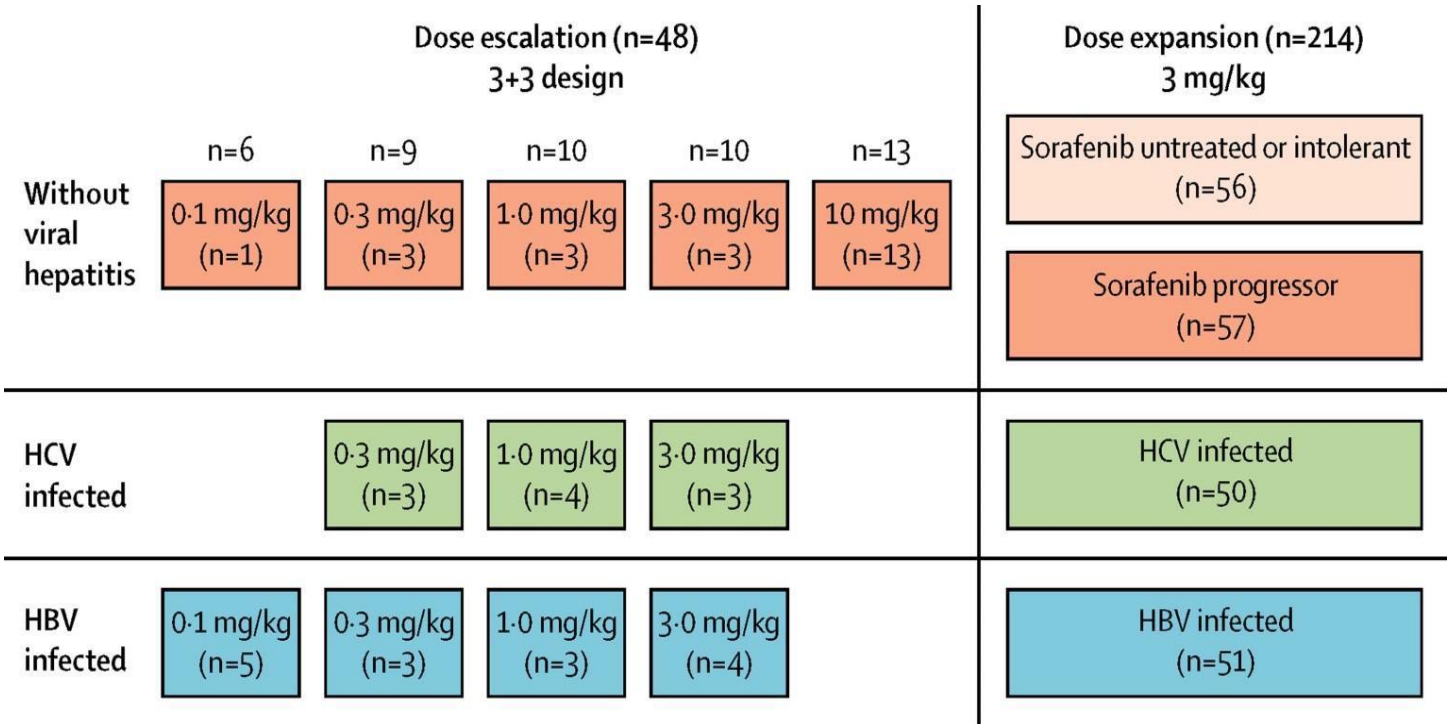
Median durations of follow-up were

7.9 months for ramucirumab, 6.6 months for placebo

Nivolumab

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*



El-Khoueiry A et al, Lancet, online April 2017

Efficacy

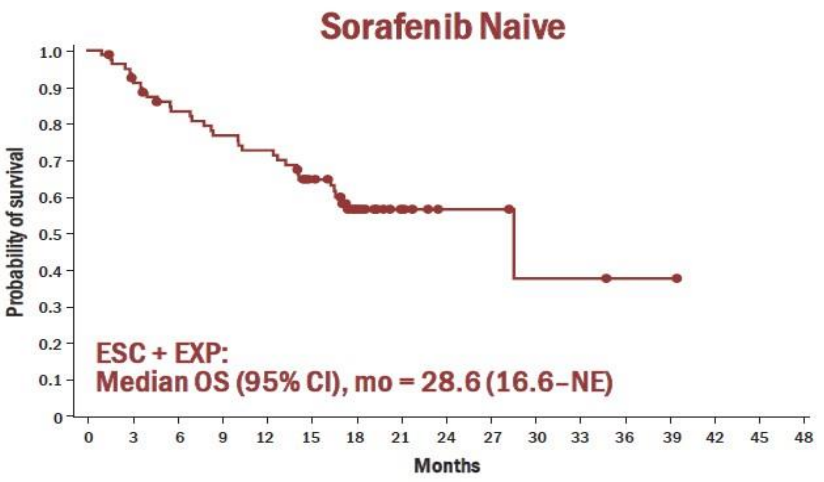
	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

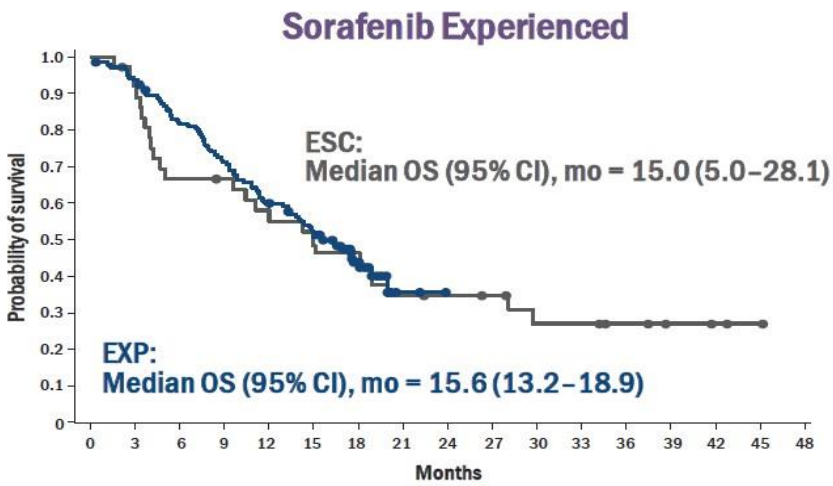
***Table 4*: Nivolumab efficacy in the dose-expansion phase**

Survival update based on sorafenib exposure

Figure 4. Overall Survival



OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

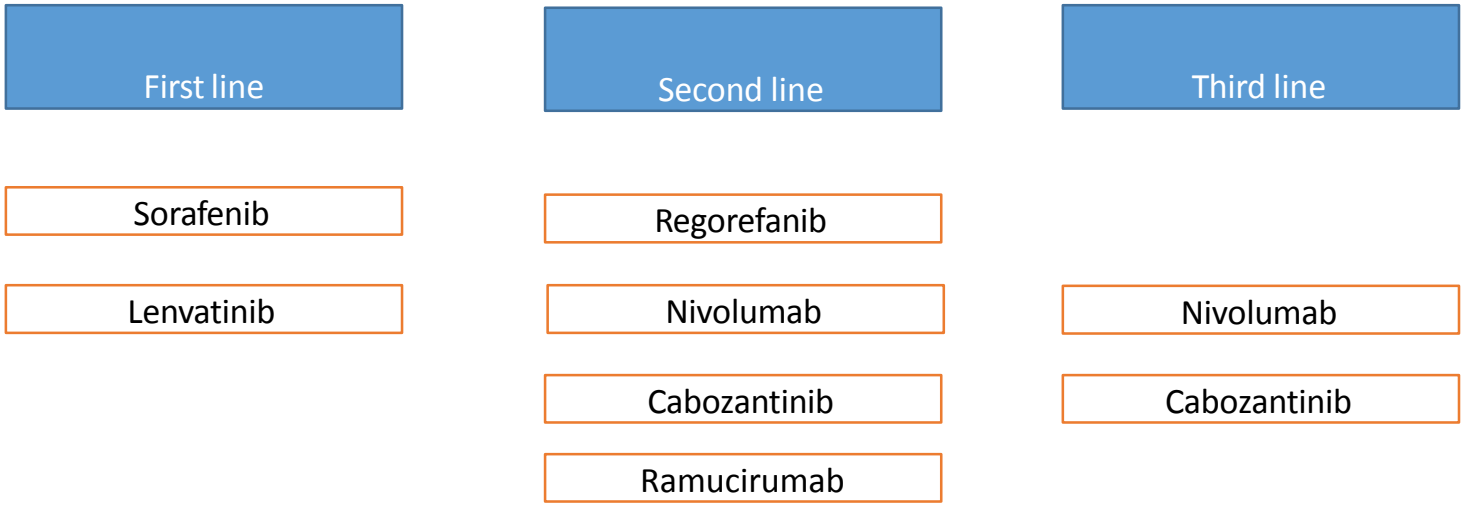


OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

Crocenzi T et al, J Clin Oncol 35, 2017 (suppl; abstr 4013)

A new reality for patients with advanced HCC



Topics

- Pancreatic Cancer
  - adjuvant therapy
- Hepatocellular Carcinoma
  - Lenvatinib, cabozantinib, regorafenib, ramucirumab
  - Nivolumab
- Gastric Cancer
  - pembrolizumab
- Colorectal Cancer
  - Regorafenib

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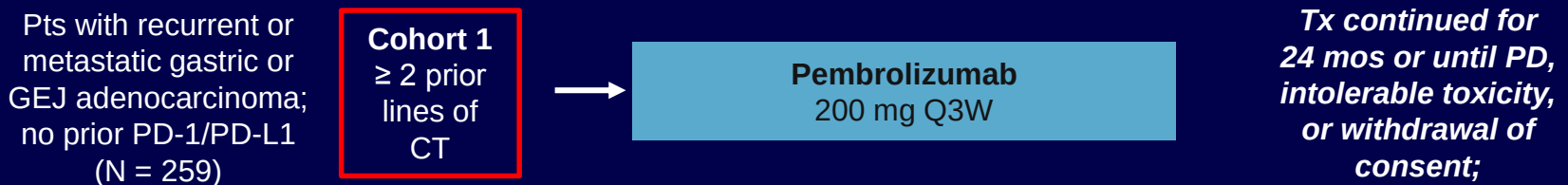
KEYNOTE-059: Study Design

- Open-label, multi-cohort phase II study



**HER2/neu* positive allowed in cohort 1 if prior trastuzumab administered.

- **Primary endpoints:** ORR, safety; **secondary endpoints:** DoR, PFS, OS
- Exploratory biomarker endpoints: efficacy by MSI, GEP

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-059 (Cohort 1): Response

Confirmed Response, % (95% CI)	All Pts (N = 259)
ORR	**11.6 (8.0-16.1)**
CR	2.3 (0.9-5.0)
PR	9.3 (6.0-13.5)
SD	16.2 (11.9-21.3)
PD	56.0 (49.7-62.1)
DCR*	27.0 (21.7-32.9)

*CR + PR + SD ≥ 2 mos.

Median follow-up: 5.8 mos (range: 0.5-21.6 mos)

Fuchs CS, et al. ASCO 2017. Abstract 4003.

KEYNOTE-059 (Cohort 1): Response by PD-L1 Expression and Line of Therapy

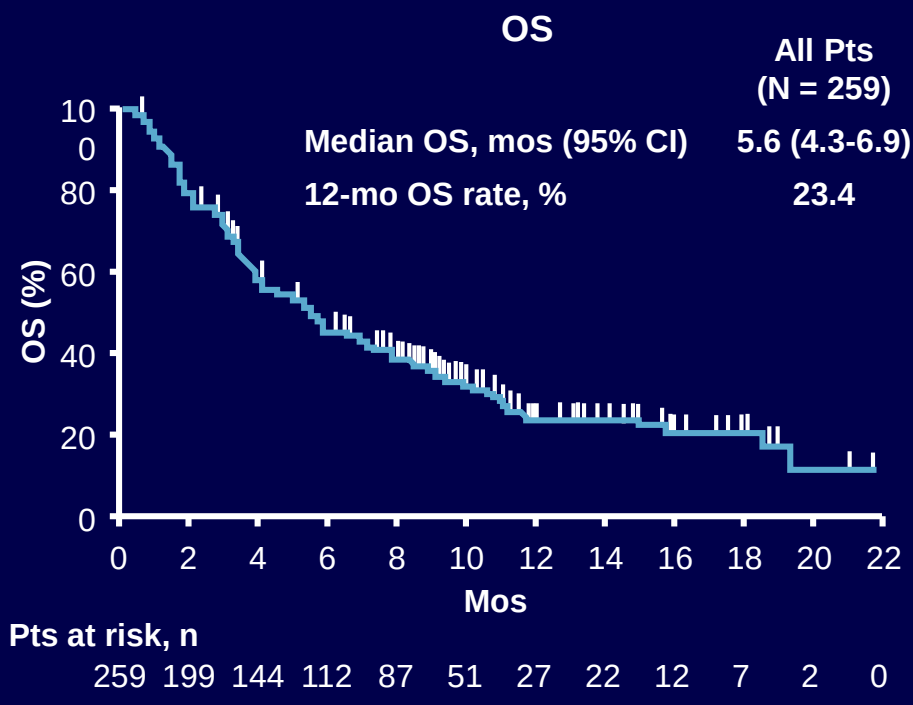
Confirmed Response, % (95% CI)	PD-L1		Line of Therapy		PD-L1 and Third Line of Therapy	
	Positive (n = 148)	Negative (n = 109)	Third (n = 134)	≥ Fourth (n = 125)	Positive (n = 75)	Negative (n = 58)
ORR	**15.5** (10.1-22.4)	**6.4** (2.6-12.8)	**16.4** (10.6-23.8)	**6.4** (2.8-12.2)	**22.7** (13.8-33.8)	**8.6** (2.9-19.0)
CR	2.0 (0.4-5.8)	2.8 (0.6-7.8)	3.0 (0.8-7.5)	1.6 (0.2-5.7)	2.7 (0.3-9.3)	3.4 (0.4-11.9)
PR	13.5 (8.5-20.1)	3.7 (1.0-9.1)	13.4 (8.2-20.4)	4.8 (1.8-10.2)	20.0 (11.6-30.8)	5.2 (1.1-14.4)
DCR*	33.1 (25.6-41.3)	19.3 (12.3-27.9)	31.3 (23.6-39.9)	22.4 (15.4-30.7)	38.7 (27.6-50.6)	22.4 (12.5-35.3)

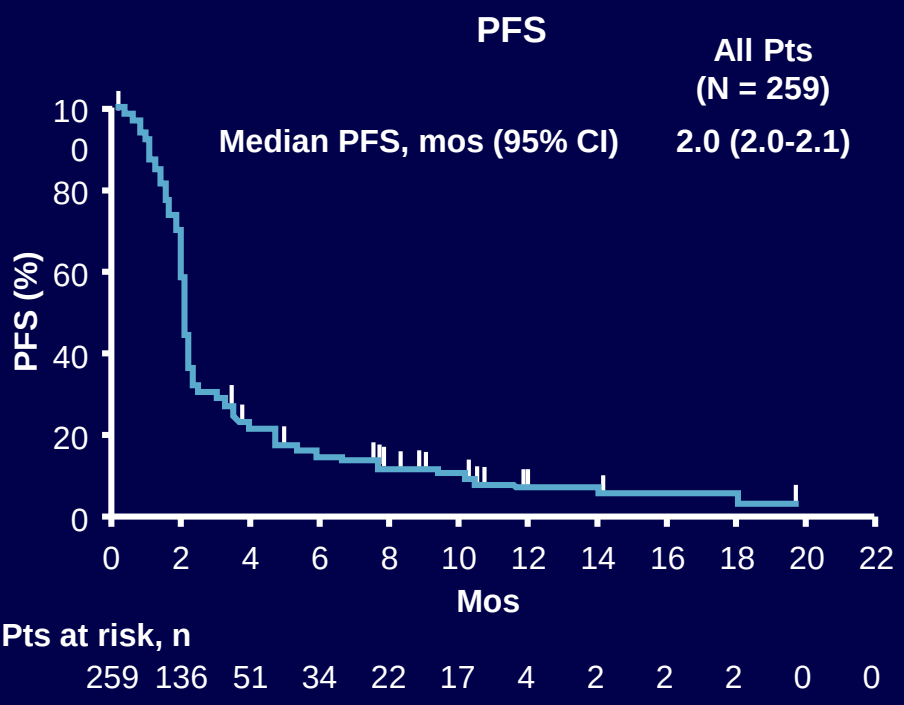
*CR + PR + SD ≥ 2 mos.

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-059 (Cohort 1): Survival





Fuchs CS, et al. ASCO 2017. Abstract 4003. Reproduced with permission.

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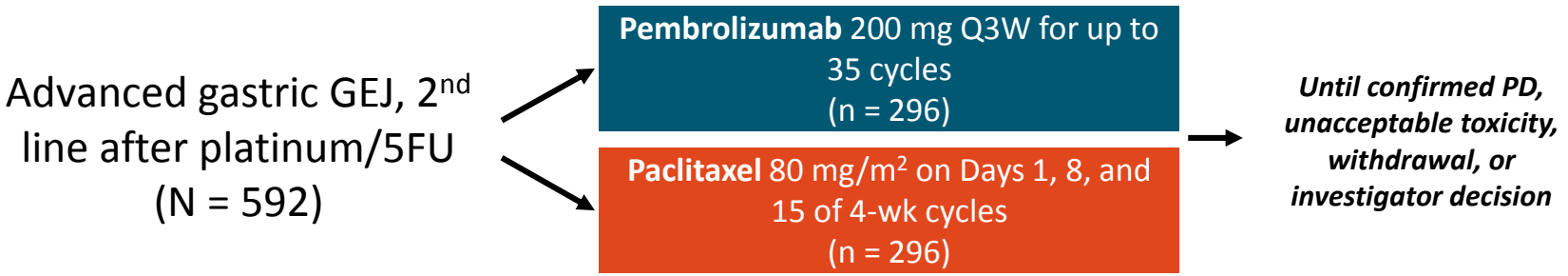
KEYNOTE-061: Study Design

- International, randomized, open-label phase III trial



- Primary endpoints: OS and PFS in CPS ≥ 1 population
- Secondary endpoints: ORR and DoR in CPS ≥ 1 population, safety in all treated patients

Slide credit: clinicaloptions.com

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

Stratified by region (Europe/Israel/N. America/Australia vs Asia vs rest of world), ECOG PS (0 vs 1), TTP on first-line tx (< 6 vs ≥ 6 mos), PD-L1 CPS (< 1 vs ≥ 1)*

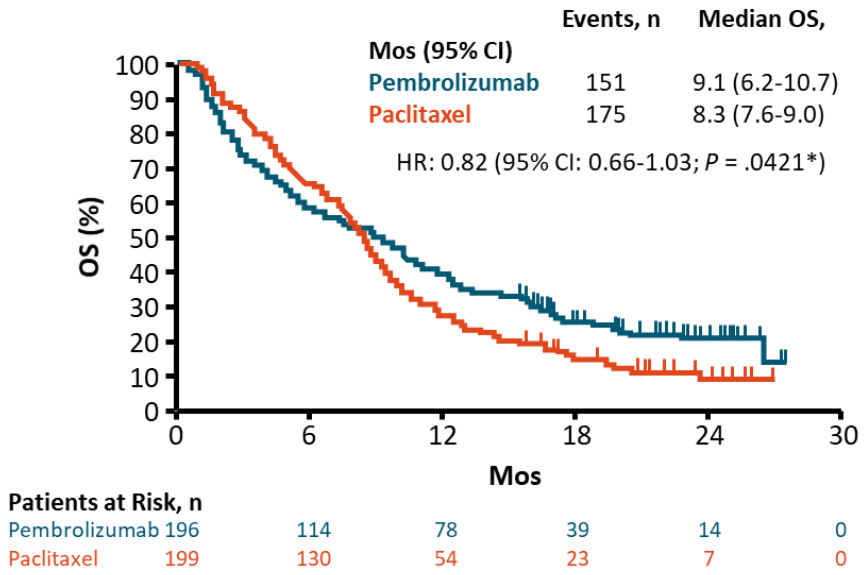
KEYNOTE-061: Baseline Characteristics

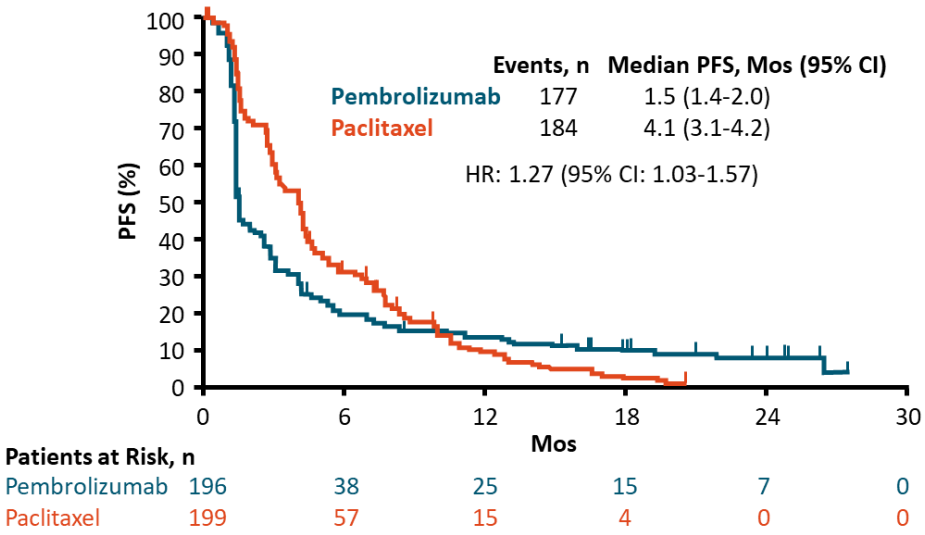
Characteristic	All Patients		PD-L1 CPS ≥ 1	
	Pembrolizumab (n = 296)	Paclitaxel (n = 296)	Pembrolizumab (n = 196)	Paclitaxel (n = 199)
Median age, yrs (IQR)	62.5 (54-70)	60.0 (53-68)	64.0 (57-70.5)	61.0 (54-68)
Male, n (%)	202 (68)	208 (70)	146 (74)	140 (70)
Enrolled in Asia, n (%)	88 (30)	89 (30)	52 (27)	52 (26)
ECOG PS 1, n (%)	169 (57)	158 (53)	108 (55)	106 (53)
Primary tumor in stomach, n (%)	207 (70)	200 (68)	134 (68)	126 (63)
PD-L1 CPS ≥ 1, n (%)	196 (66)	199 (67)	196 (100)	199 (100)
TTP < 6 mos on first-line tx, n (%)	186 (63)	182 (61)	126 (64)	129 (65)
Peritoneal metastasis, n (%)	82 (28)	84 (28)	50 (26)	49 (25)
Ascites present, n (%)	47 (16)	43 (15)	20 (10)	26 (13)

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

Slide credit: clinicaloptions.com

KEYNOTE-061: OS and PFS in PD-L1 CPS ≥ 1 Population



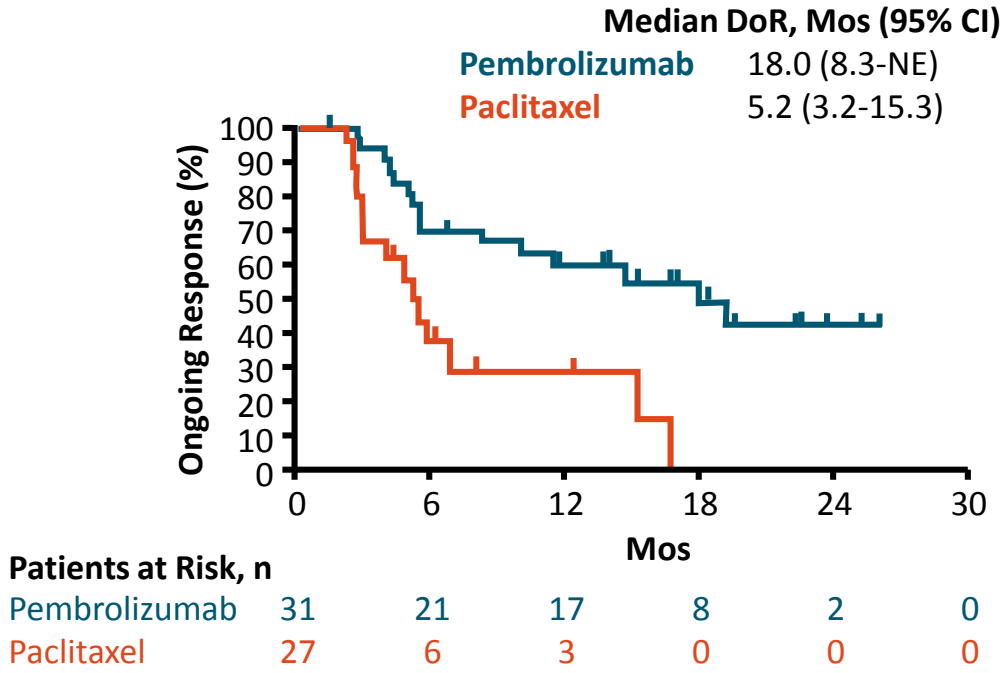


Slide credit: clinicaloptions.com

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

KEYNOTE-061: Response in PD-L1 CPS ≥ 1 Population

- Responses more durable with pembrolizumab
- In post hoc analysis of subgroup with MSI-H tumors, ORR:
  - 47% with pembrolizumab
  - 17% with paclitaxel



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

Slide credit: clinicaloptions.com

KEYNOTE-061: Conclusions

- **Second-line** pembrolizumab did not significantly improve OS vs paclitaxel for advanced/metastatic gastric/GEJ cancer with PD-L1 CPS ≥ 1
  - HR for OS in PD-L1 CPS ≥ 1 population: 0.82 (95% CI: 0.66-1.03)
  - Pembrolizumab improved OS in subgroups with ECOG PS 0, primary tumor in GEJ, PD-L1 CPS ≥ 10, and MSI-H tumors
- Pembrolizumab was not associated with improved PFS or ORR
  - Responses to pembrolizumab more durable than to paclitaxel (median DoR: 18.0 vs 5.2 mos)

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

Topics

- Pancreatic Cancer
  - adjuvant therapy
- Hepatocellular Carcinoma
  - Lenvatinib, cabozantinib, regorafenib, ramucirumab
  - Nivolumab
- Gastric Cancer
  - pembrolizumab
- Colorectal Cancer
  - Regorafenib

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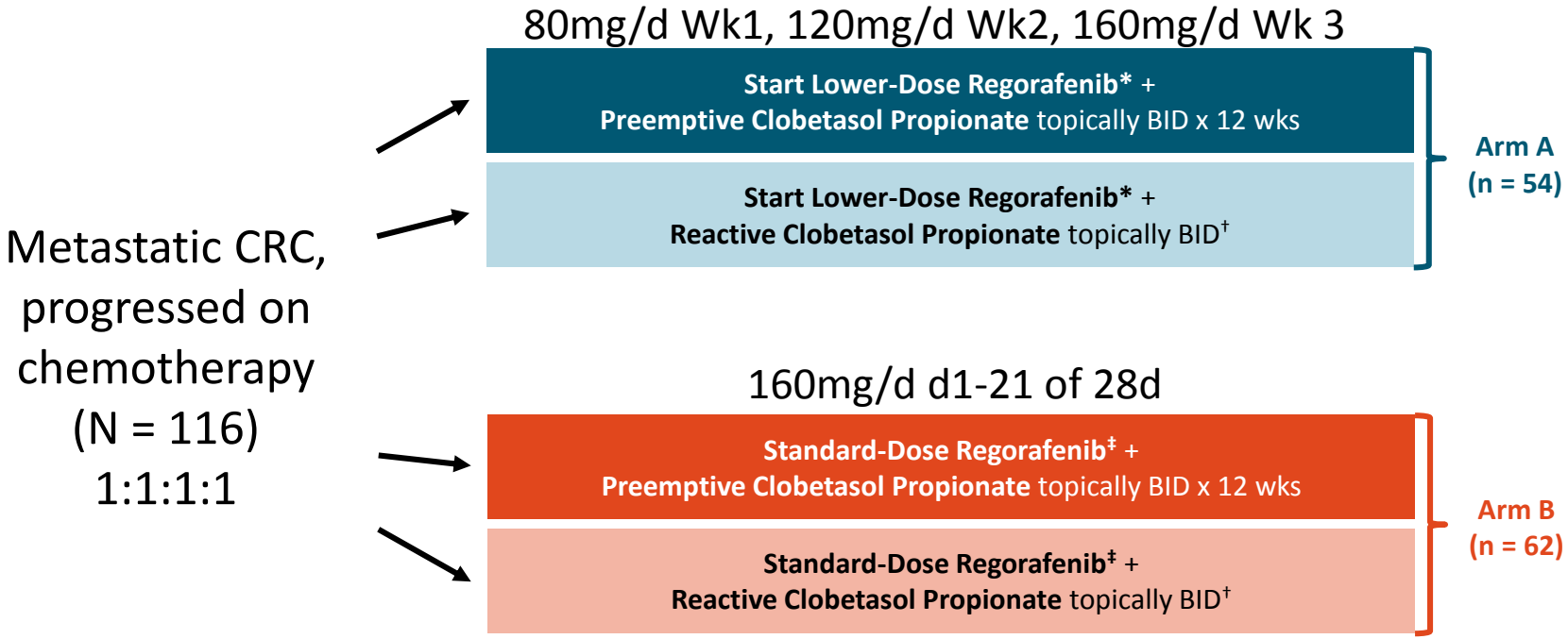
ReDOS: Phase II Study Design



Primary endpoint: proportion of patients completing 2 cycles and initiating cycle 3 in arms A and B

Secondary endpoints: OS, PFS, TTP

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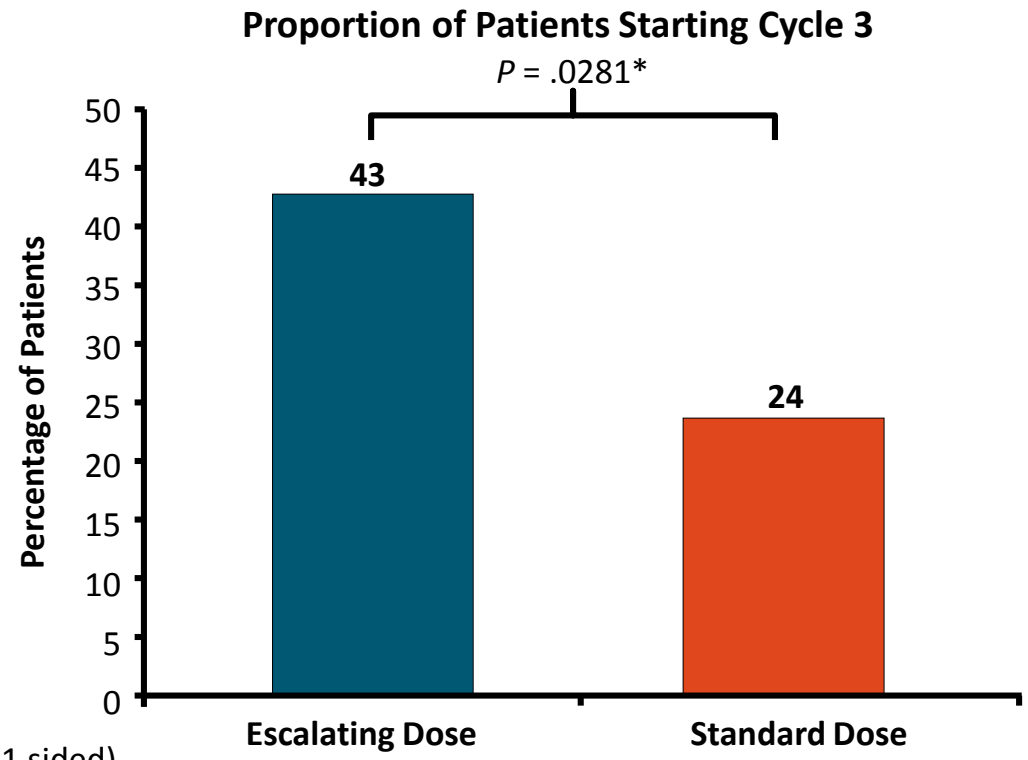
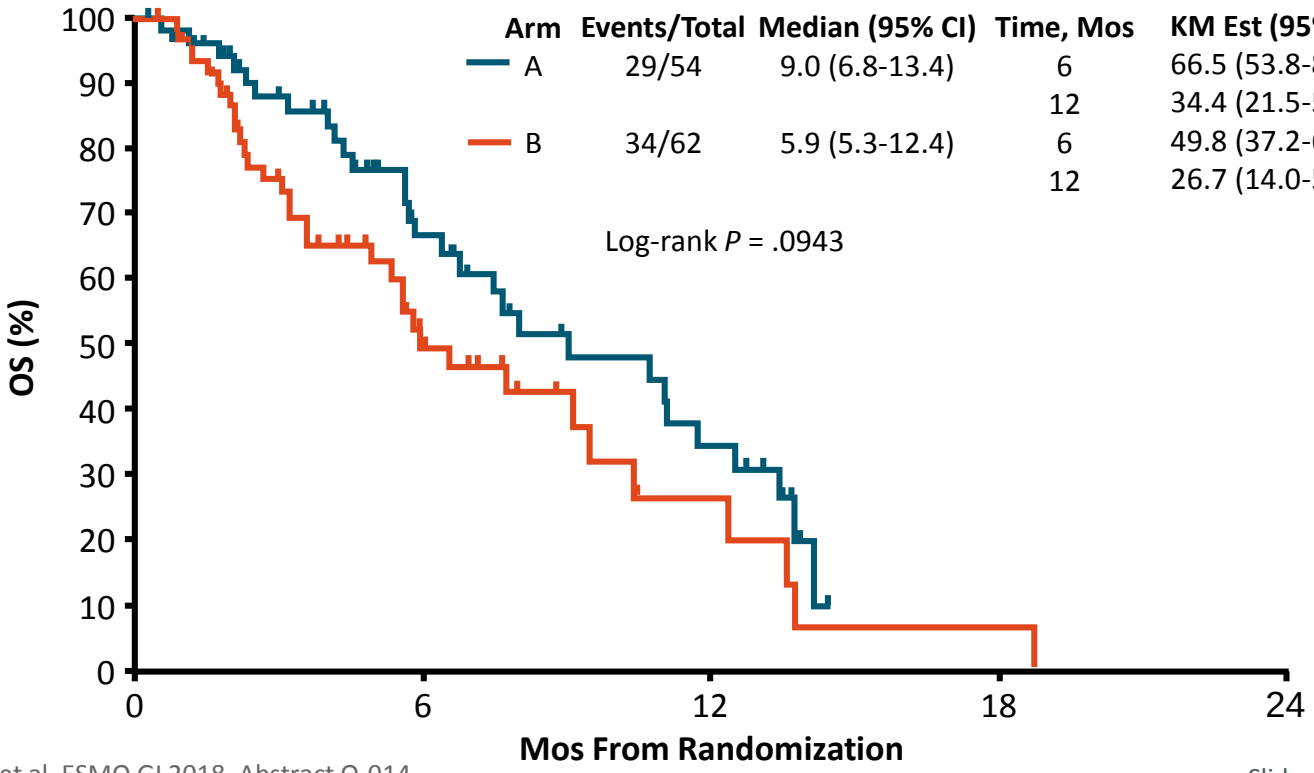
ReDOS: Primary Endpoint



*Fisher's exact test (1 sided).

Bekaii-Saab T, et al. ESMO GI 2018. Abstract O-014.

ReDOS: Overall Survival

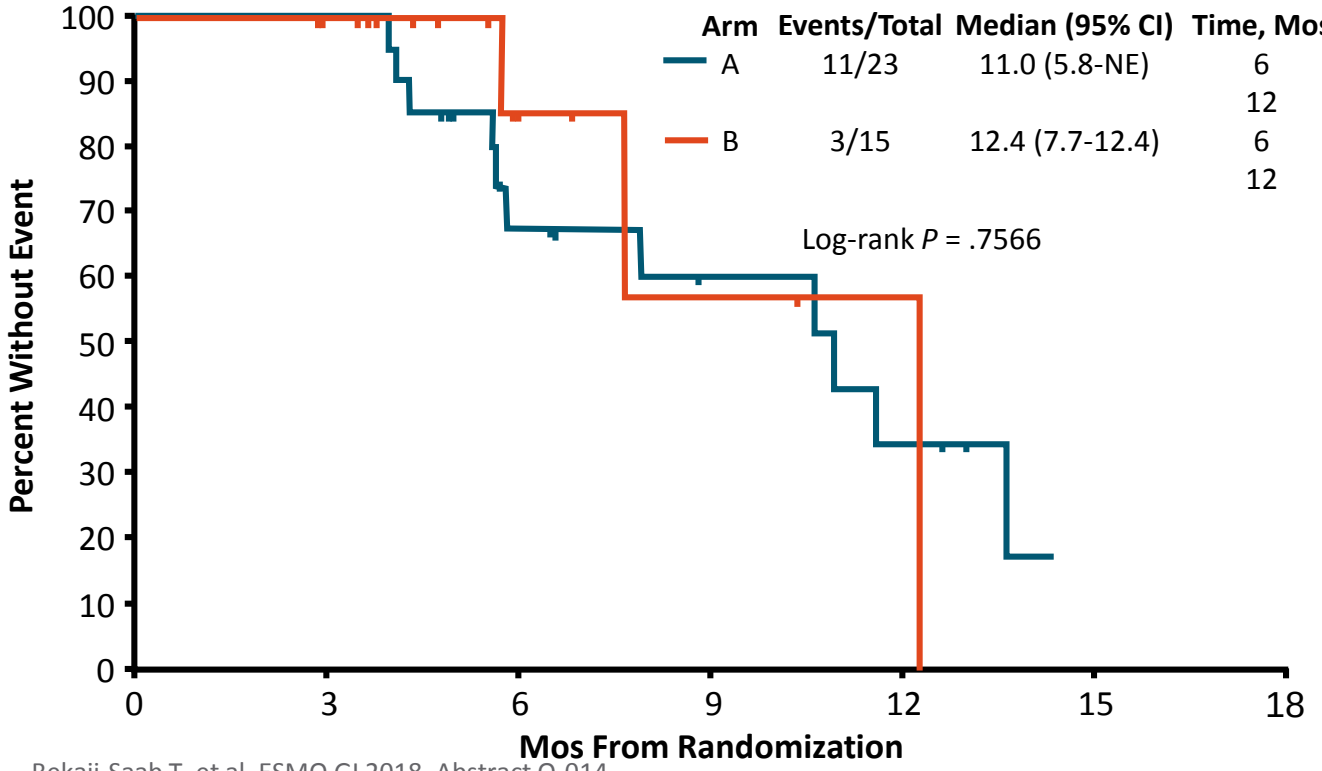


Arm	Events/Total	Median (95% CI)	Time, Mos	KM Est (95% CI)	HR (95% CI)
A	29/54	9.0 (6.8-13.4)	6	66.5 (53.8-82.2)	0.65 (0.39-1.08)
			12	34.4 (21.5-55.2)	
B	34/62	5.9 (5.3-12.4)	6	49.8 (37.2-66.8)	Reference
			12	26.7 (14.0-51.1)	

Bekaii-Saab T, et al. ESMO GI 2018. Abstract O-014.

Slide credit: clinicaloptions.com

ReDOS: OS in Patients Able to Initiate Cycle 3

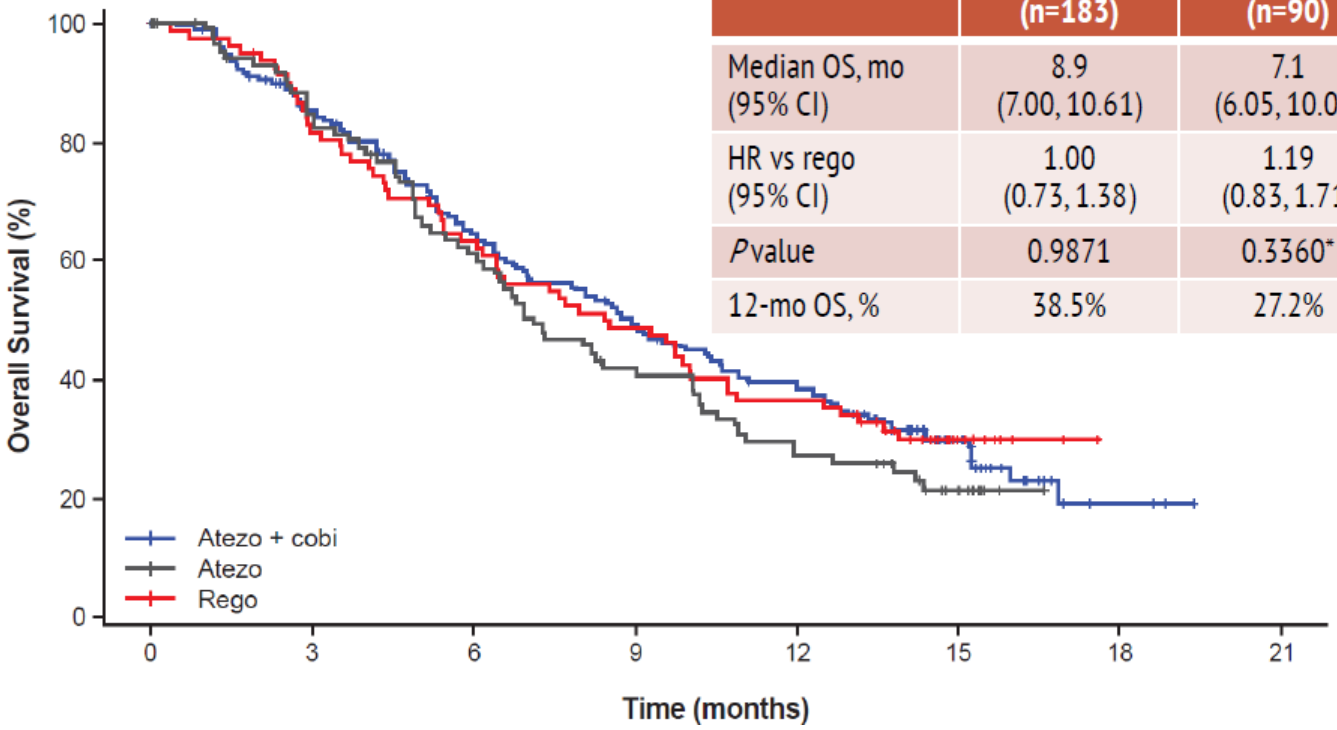


Arm	Events/Total	Median (95% CI)	Time, Mos	KM Est (95% CI)	HR (95% CI)
A	11/23	11.0 (5.8-NE)	6	68.1 (49.7-93.3)	1.23 (0.33-4.58)
			12	34.6 (16.3-73.3)	
B	3/15	12.4 (7.7-12.4)	6	85.7 (63.3-100)	Reference
			12	57.1 (24.3-100)	

Bekaii-Saab T, et al. ESMO GI 2018. Abstract O-014.

Slide credit: clinicaloptions.com

IMblaze370: OS (Primary Endpoint)



	Atezo + cobi (n=183)	Atezo (n=90)	Rego (n=90)
Median OS, mo (95% CI)	8.9 (7.00, 10.61)	7.1 (6.05, 10.05)	8.5 (6.41, 10.71)
HR vs rego (95% CI)	1.00 (0.73, 1.38)	1.19 (0.83, 1.71)	N/A
P value	0.9871	0.3360*	N/A
12-mo OS, %	38.5%	27.2%	36.6%

Bendell J, et al. ESMO GI 2018. Abstract LBA-004.

Discussion

Strengths

- Answers clinically relevant question
- Provides additional clinical trial experience

Limitations

- Confirms approach that was an already generally adopted practice pattern

Practice Changing?

- Yes – potentially for those hesitant based on initial experience with full dose

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Thank you

Questions?

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