PANCREATIC, BILIARY TRACT AND HEPATOCELLULAR CARCINOMA

MITESH J. BORAD, M.D.
Associate Professor, Mayo Clinic College of Medicine and Science

16TH ANNUAL MIAMI CANCER MEETING
Miami, FL
March 29-31, 2019

CONFLICTS OF INTEREST

RESEARCH FUNDING

Boston Biomedical
Mirna
Sunbiopharma
Senhwa
Medimmune
Arqule/Basilea
Agios
Halozyme
Threshold
Celgene
Toray
Novartis/QED
Sillajen
Eisai
Taiho
Ionis
EMD Serono
Incyte
ARIAD
Imclone

CONSULTANT

G1 Therapeutics
TD2
Fujifilm
Insys
Novartis
Arqule
Celgene
Inspyr
Halozyme

EDUCATIONAL OBJECTIVES

- **Review clinical and translational data in the precision medicine space in HPB cancers (hepato-pancreato-biliary)**

- **Review recent studies of importance in HPB cancer using cytotoxic therapies**

- **Review data on DNA repair targeting in pancreatic cancer**

- **Review immunotherapy approaches in HPB cancer**

PANCREATIC CANCER
THE PROBLEM AND CHALLENGES

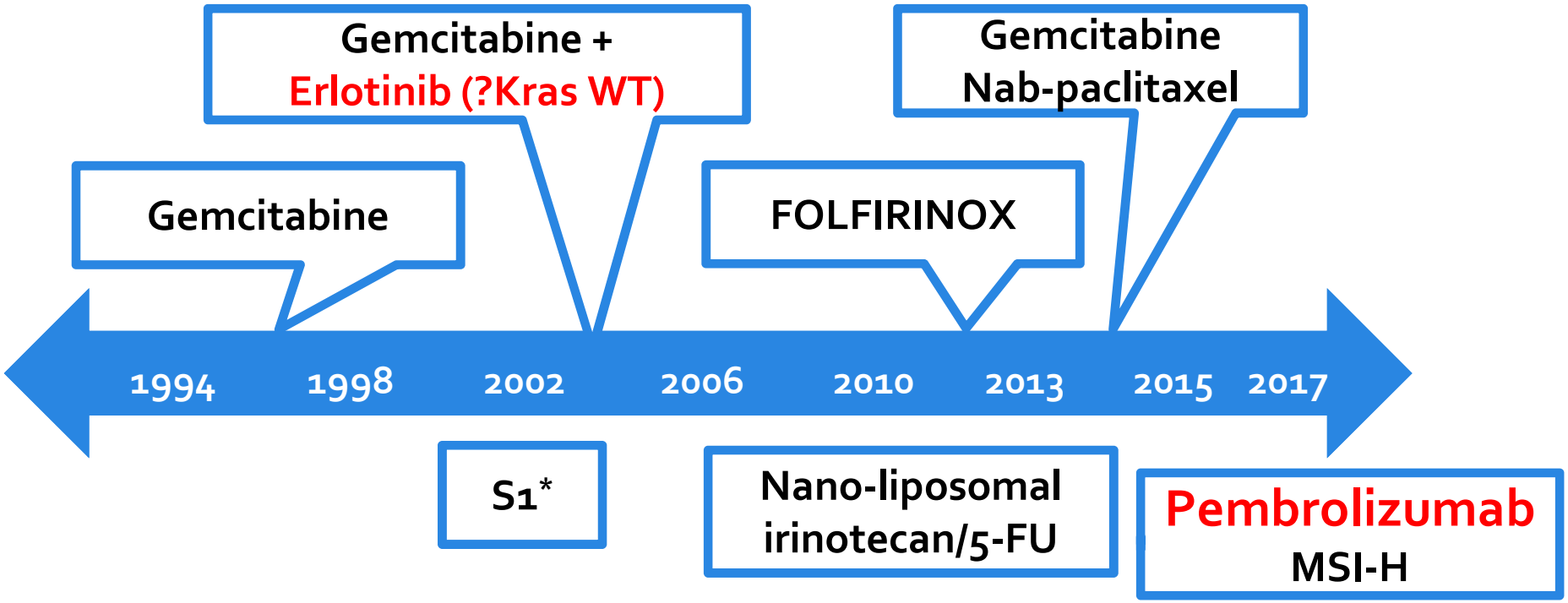
- New diagnoses – US 2017: 53,670
- Mortality – US 2017: 43,090
- 9^{th}–10^{th} most common cancer (3% new cancers)
- 1.2% increase/yr → 2^{nd} cause-related deaths by 2020
- Fourth-leading cause of cancer mortality (8%)

American Cancer Society, 2017. www.cancer.org; SEER Cancer Statistics Review, 1975-2006. NCI. www.surveillance.cancer.gov; Hoos WA. J Clin Oncol, 2013; Siegel R. Ca Cancer J Clin, 2014

PDAC: CHALLENGING BIOLOGY

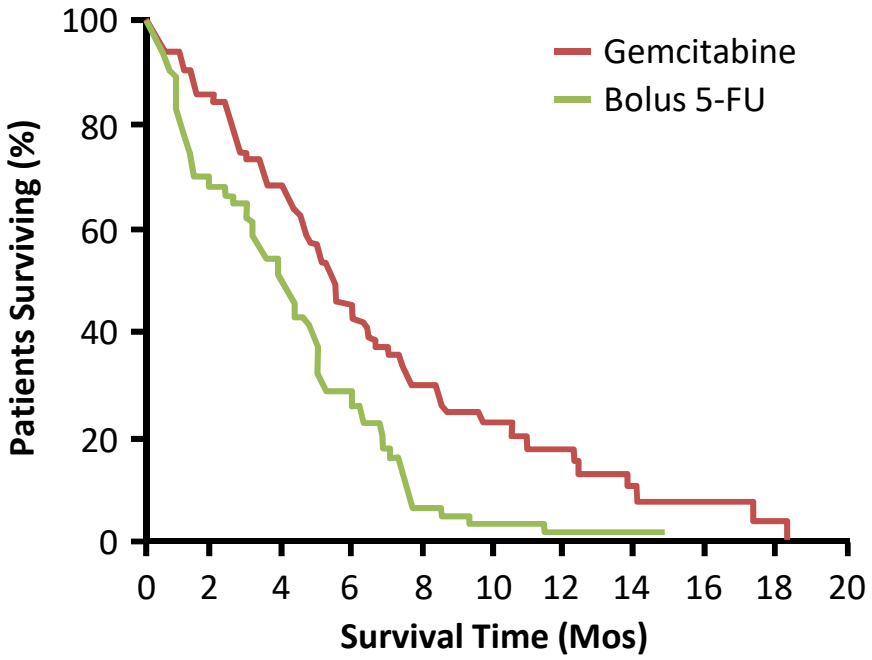
- Drug resistance
- Stroma as a barrier to drug delivery
- Complex and poorly understood microenvironment
- Multiple gene mutations
- Non-druggable tumor suppressor genes
- Few validated biomarkers

APPROVED THERAPIES IN ADVANCED PANCREATIC ADENOCARCINOMA (PDAC)



GEMCITABINE VS 5-FLUOROURACIL ADVANCED PDAC

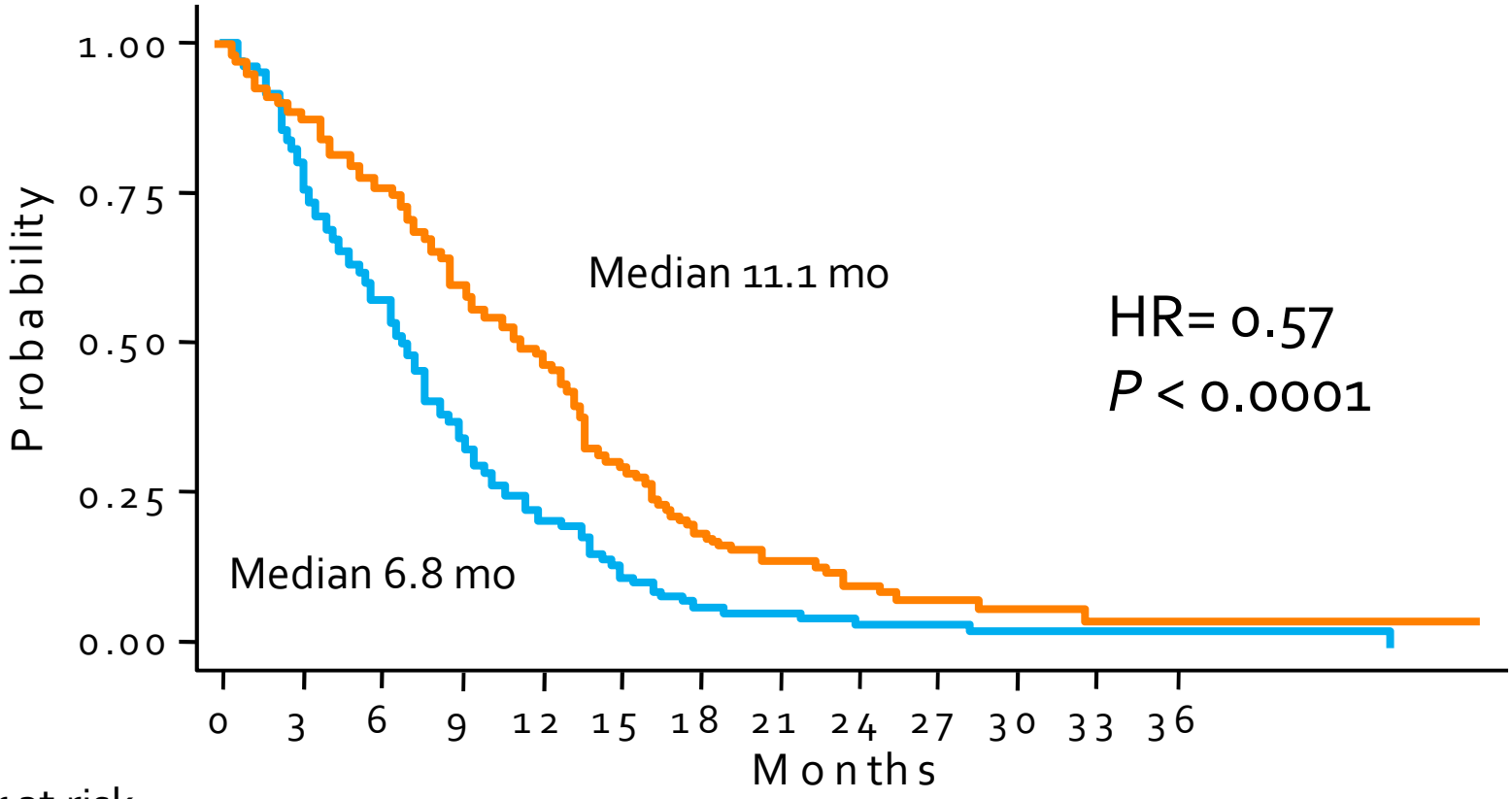
- Median survival
  5.65 vs 4.41 mo (*P* = .0025)
- 1-year survival
  18% vs 2%
- Clinical benefit*
  23.8% vs 4.8% (*P* = .0022)
- Response rate:
  5.4% vs 0% (*P* = NS)



*Composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight

Burris HA. J Clin Oncol. 1997;15:2403-2413

FOLFIRINOX VS GEMCITABINE
OVERALL SURVIVAL

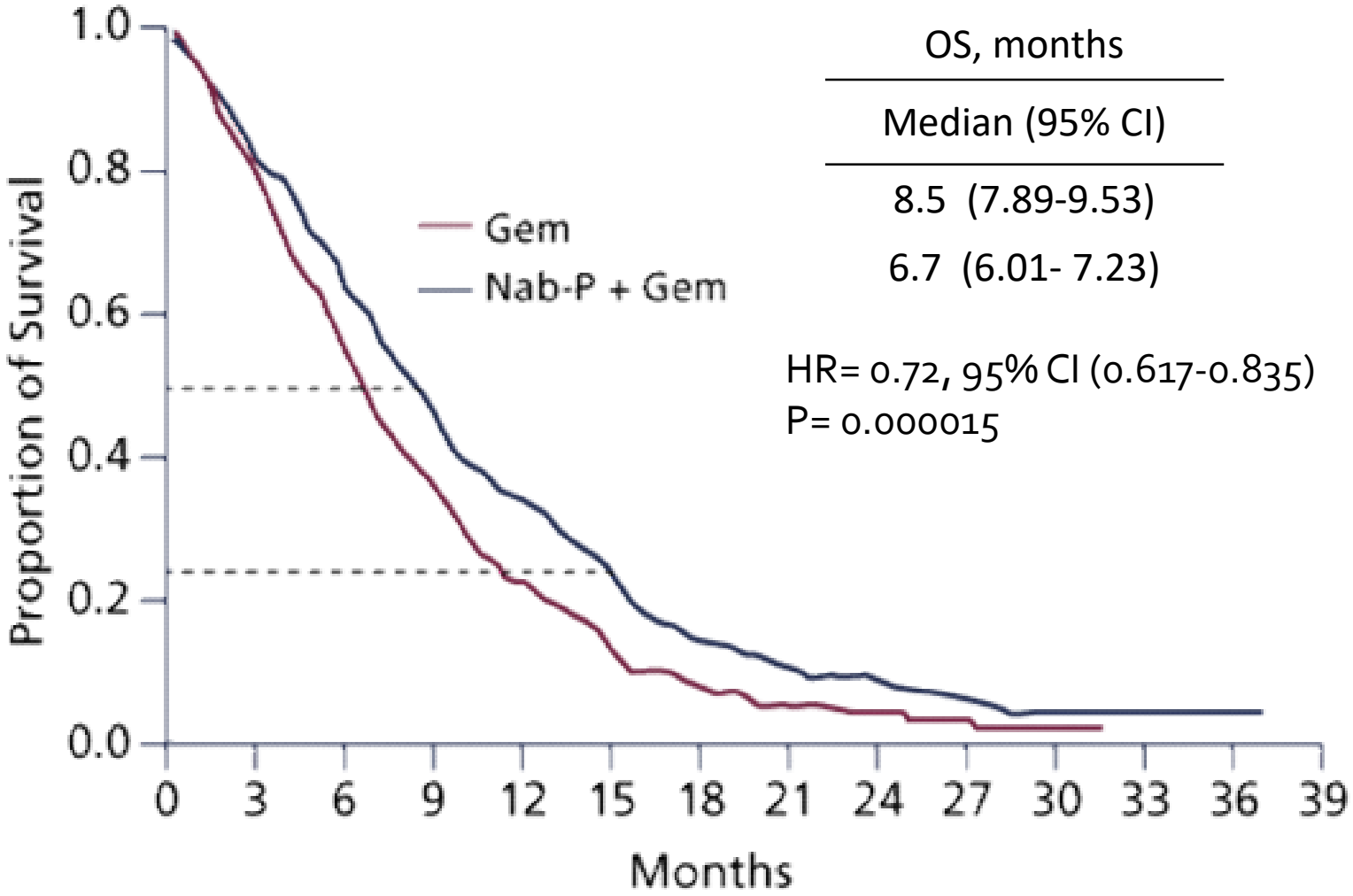


Number at risk

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

Conroy, T. NEJM, 2011

MPACT: OVERALL SURVIVAL

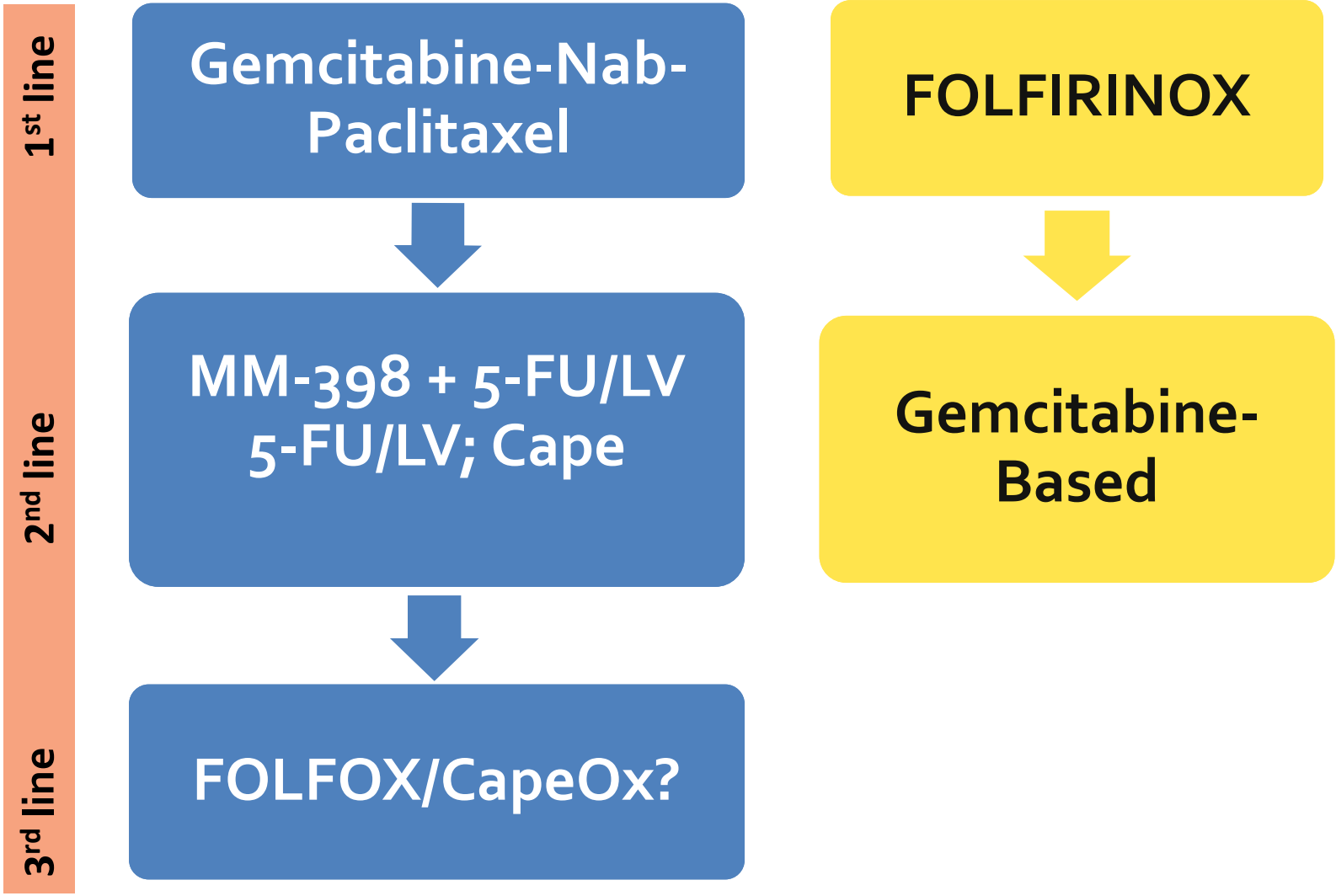


OS, months
Median (95% CI)
8.5 (7.89-9.53)
6.7 (6.01- 7.23)

HR= 0.72, 95% CI (0.617-0.835)
P= 0.000015

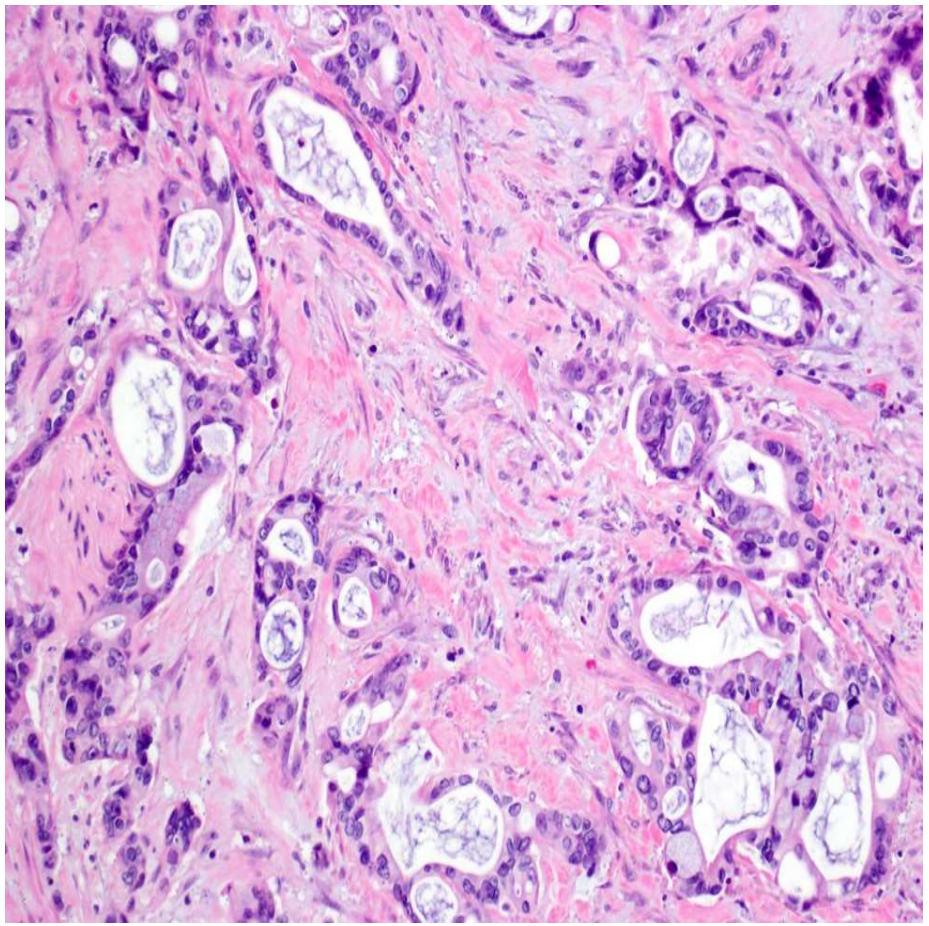
Von Hoff, D. N Engl J Med, 2013

CURRENT APPROACH TO TREATMENT SEQUENCING FOR ADVANCED PDAC



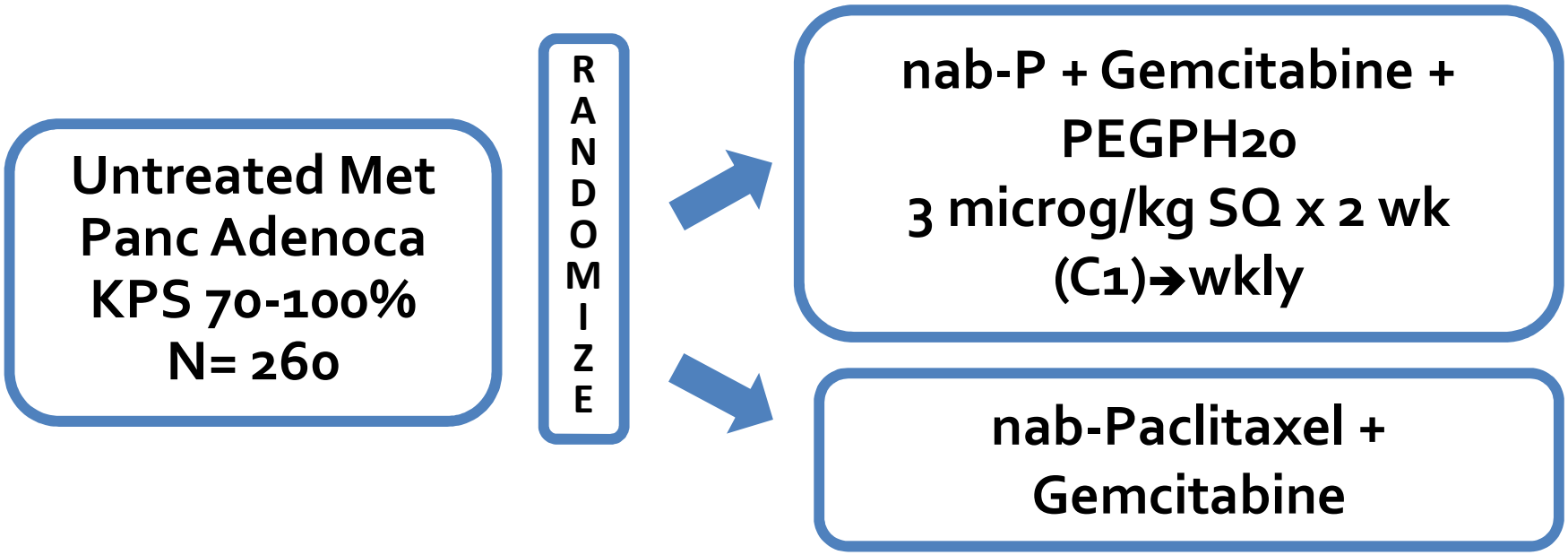
TUMOR MICROENVIRONMENT IN PDAC

- Hypovascular, hypoxic
- Physical stromal barrier
  - Hyaluronan (HA) glycosaminoglycans
  - Increased EMT, chemoresistance
- PEGPH20 rhuman hyaluronidase
  - Depletes HA in stroma
  - Improves drug delivery



Jaocobetz, et al. Gut, 2013. Provenzano, P. Cancer Cell, 2012. Courtesy: J. Shia (MSKCC)

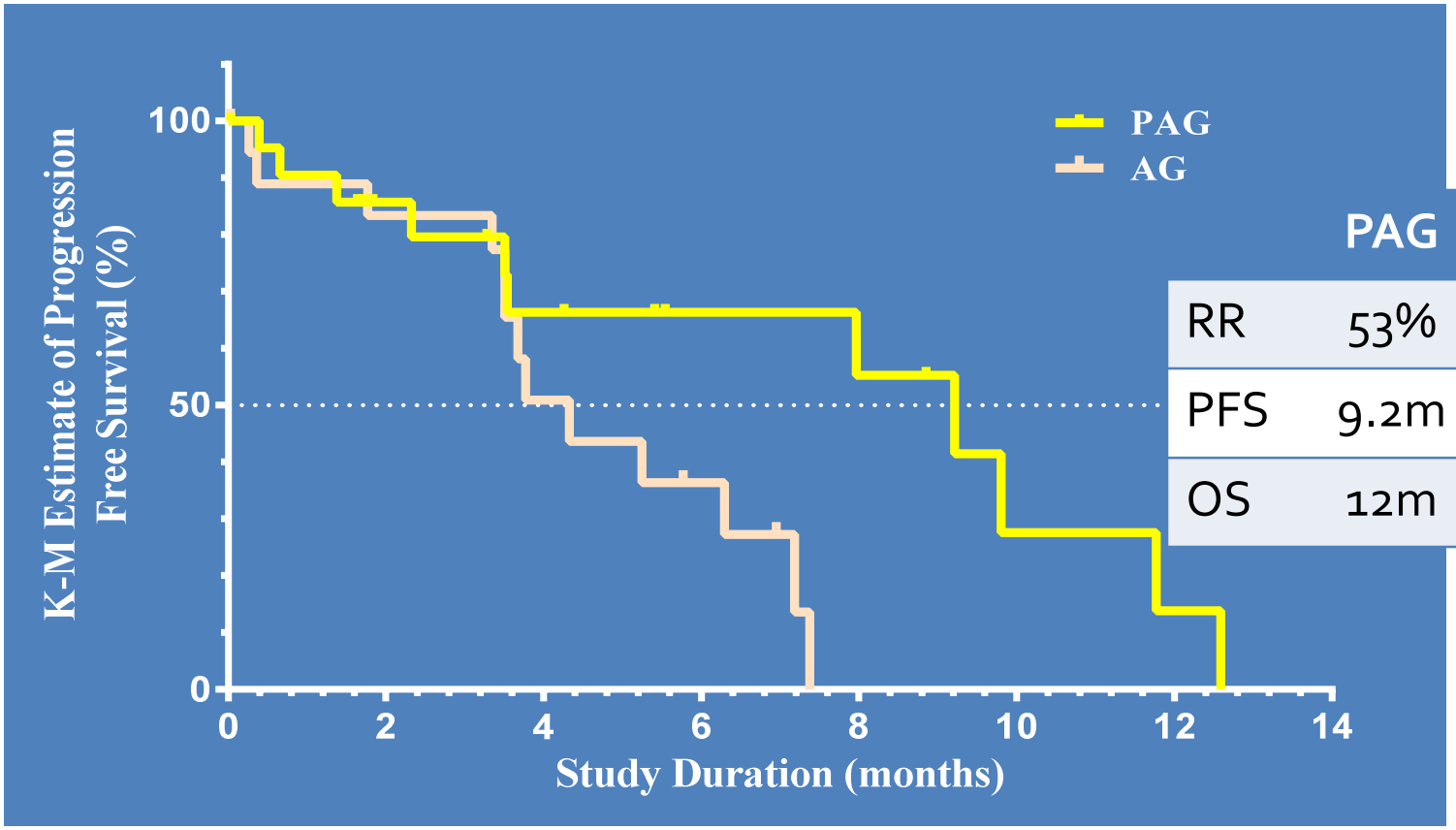
RANDOMIZED PHASE II NAB-P + GEM +/- PEGHPH20



Primary endpoint: Progression-free survival
Secondary endpoints: PFS by Hyaluronan, ORR, OS, Safety, Correlatives

Hingorani, S. J Clin Oncol 2017

RANDOMIZED PHASE II NAB-P + GEM +/- PEGHPH20



	PAG	AG
RR	53%	23.8%
PFS	9.2m	4.3m
OS	12m	9m

Subjects At Risk									
	PAG	23	14	10	6	5	2	1	0
	AG	21	14	7	4	0	0	0	0

Hingorani, S. J Clin Oncol 2017

TUMOR MICROENVIRONMENT IN PDAC

- Phase III trial underway
  - Nab-P + gemcitabine +/- PEGPH20 (HALO-301)
  - Biomarker selected: Hyaluronan-high
  - Primary endpoints: PFS, OS
  - N= 420

A Phase IB/II Randomized Study of mFOLFIRINOX (mFFOX) + Pegylated Recombinant Human Hyaluronidase (PEGPH20) versus mFFOX alone in Patients with Good Performance Status Metastatic Pancreatic Adenocarcinoma (mPC): SWOG- S1313 (NCT #01959139)

Ramesh K. Ramanathan, Shannon L. McDonough, Philip A. Philip, Sunil R. Hingorani, Jill Lacy, Jeremy S. Kortmansky, Jaykumar Thumar, E. Gabriela Chiorean, Anthony F. Shields, Deepti Behl, Paul T. Mehan, Rakesh Gaur, Tara Seery, Katherine A. Guthrie, Howard S. Hochster.

Mayo Clinic, Arizona, Phoenix, AZ; SWOG Statistical Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; Karmanos Cancer Institute/Wayne State University, Detroit, MI; Yale Cancer Center, New Haven, CT; Saint Francis Hospital & Medical Center, Enfield, MA; Sutter Cancer Research Consortium, Sacramento, CA; Heartland NCORP, Missouri Baptist Medical Center Cancer Center, St. Louis, MO; Kansas City NCORP, Prairie Village, KS; UC Irvine Medical Center, Orange, CA.

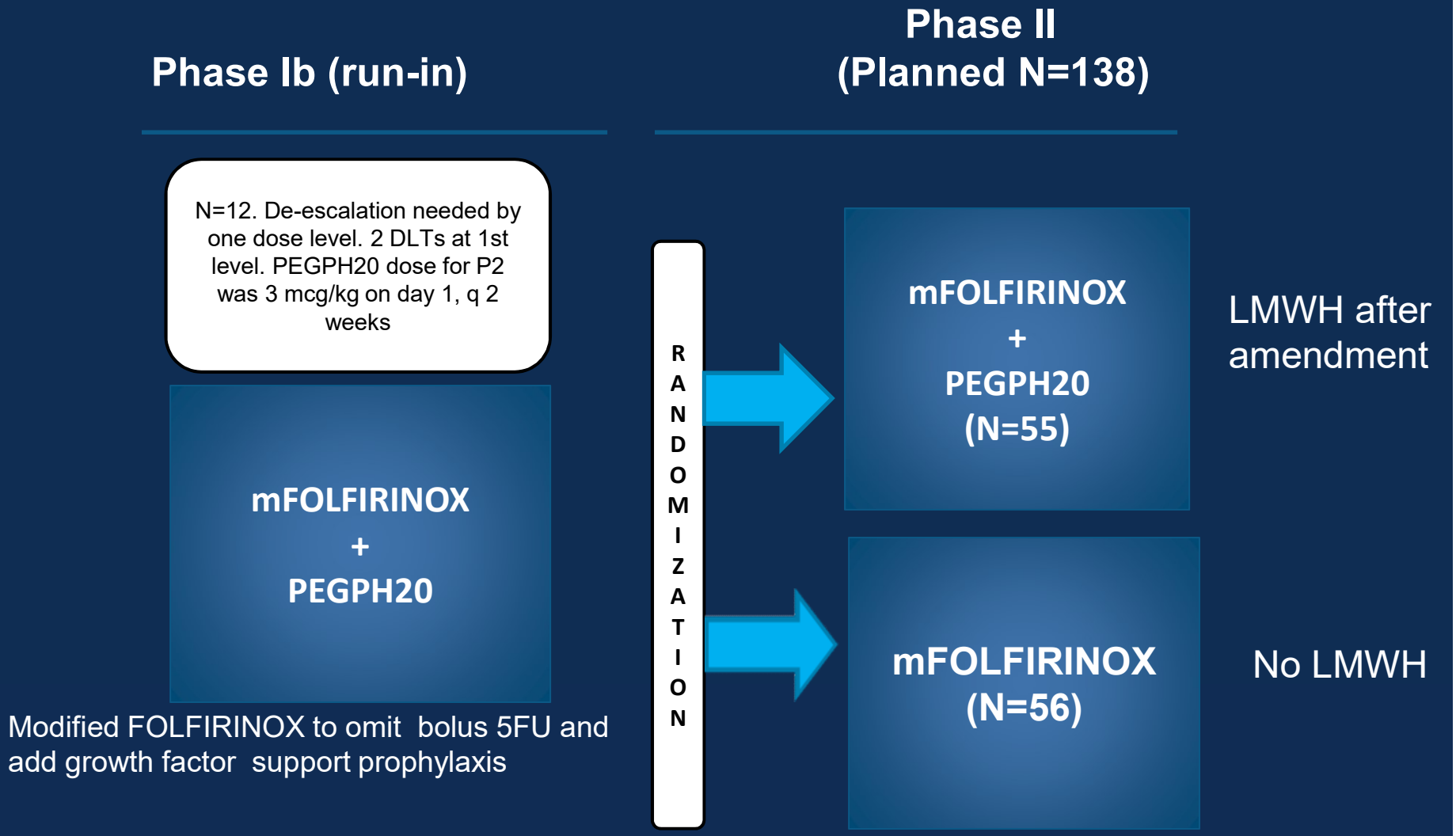
PRESENTED AT: 2018 Gastrointestinal Cancers Symposium | #GI18

SWOG NCI Community Oncology Research Program NCI National Clinical Trials Network

Study Design

- **Background:** PEGPH20 degrades hyaluronan (HA), a major component of the stroma, increases delivery of gemcitabine and prolongs survival in preclinical models. We evaluated the activity of PEGPH20 in combination with mFFOX in mPC, unselected for tumor HA.
- **Pertinent eligibility**: Untreated mPC, PS of 0-1 and adequate organ function. Standard FFOX was modified to add prophylactic growth factor support and omit bolus 5FU.
- **Study Conduct:** Following a dose finding cohort of mFFOX + PEGPH20, the Phase II study randomized patients (1:1) to the combination arm or mFFOX alone (n=138). The primary endpoint was overall survival (OS), with a null median OS of 10 mo and an alternative of 15 mo (1-sided type 1 error 0.1, 80% power).
- **Amendments:** Due to increased thromboembolic (TE) events with PEGPH20, an amendment instituted LMWH prophylaxis in the PEGPH20 arm only.
- **Planned interim analysis:** Occurred when 35 deaths noted (1/3rd of expected) in 113 patients enrolled and triggered a futility analysis on March 14, 2017.

S1313: Activated 01/2014. Terminated 3/2017 at Interim Futility Analysis

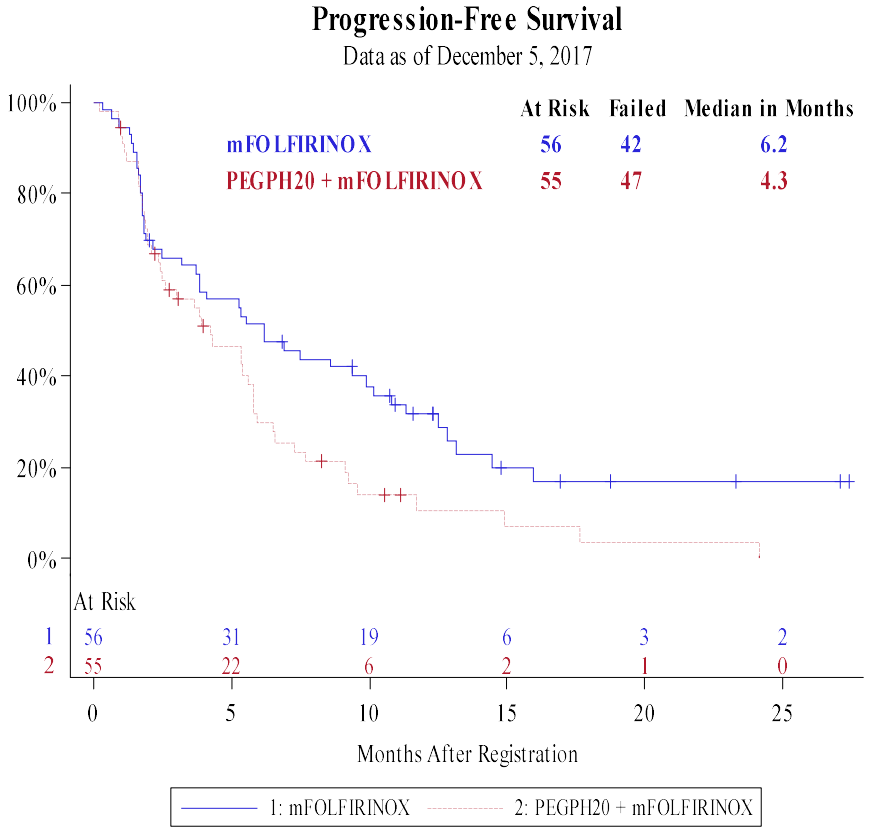


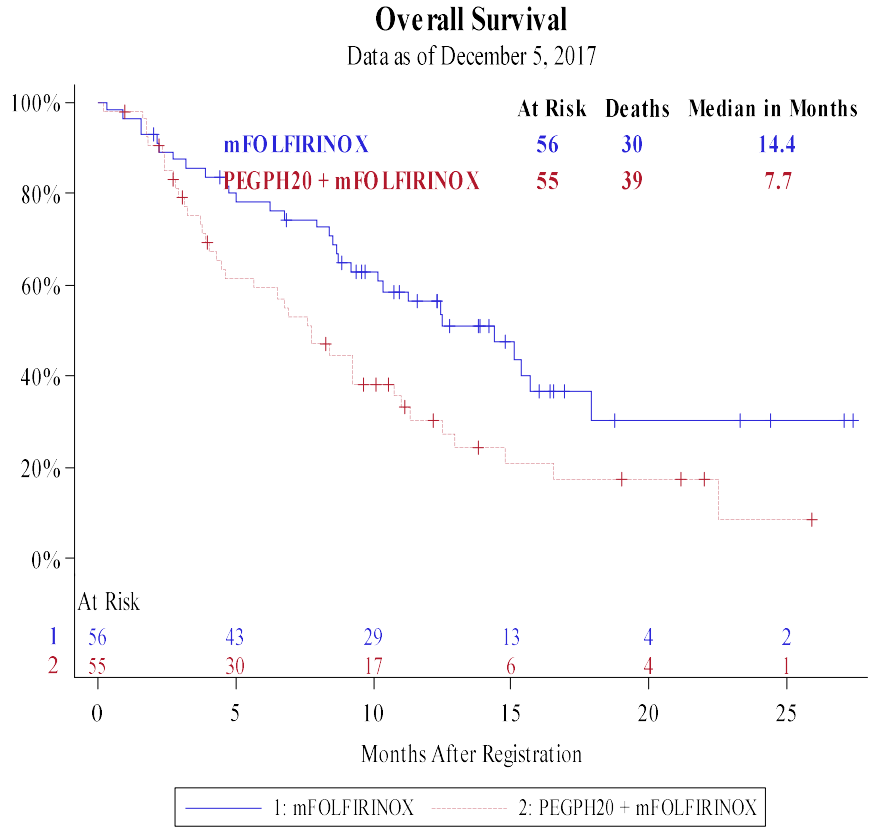
Patient Characteristics and Phase II Toxicities

Patient Characteristics	FFOX (N=56)	FFOX+PEGPH20 (N=55)
Age (median) Sex (M/F) Race Performance status (0/1)	60.5 yrs 55% / 45% 82% White 55% / 45%	63.9 yrs 44% / 56% 78% White 58% / 42%
Selected Gr 3/ 4 Toxicity	FFOX (N=54)	FFOX+PEGPH20 (N=51)
Diarrhea Dehydration Fatigue Nausea Vomiting TE Events (All grade) TE Events after LMWH	19% 13% 11% 15% 13% 4% 5%	24% 8% 20% 25% 22% 18% 9%
All Grade 3-5 Toxicity	Increased in PEGPH20 arm (P=0.02)	OR 2.7 (95% CI 1.1-7.1)
Response Rate	45% (95% CI 31-59%)	33% (95% CI 21-47%)
Treatment exposure	Median: 8 cycles (Range 0-37)	4 cycles (Range 0-43), P=0.05

One Gr 5 event occurred on FFOX arm due to sepsis.

Efficacy Data





HR 0.61
95% CI: 0.40-0.93, P=0.02

HR 0.50
95% CI: 0.31-0.81, P<0.01

Conclusions

- ***OS*** in the mFFOX control arm (14.4 mo) is longest yet reported. Addition of PEGPH20 to mFFOX resulted in increased toxicity and appears to be detrimental.
- ***Inferior*** results in this arm could be due to increased toxicity and less FFOX treatment exposure in the PEGPH20 arm, median 4 cycles versus 8 for FFOX alone.
- ***S1313*** results are in contrast to favorable results reported for the combination of gemcitabine/nab-paclitaxel + PEGPH20 (Hingorani S et al. JCO epub.2017.74.9564).
- ***Mechanistic*** effect on stroma needs study. Tumor HA content will be analyzed and preclinical studies are planned.

Funding: NIH/NCI grants CA180888, CA180819; and in part by Halozyme Inc.

TAKE HOME POINTS

- mFOLFIRINOX regimen can be safely administered in U.S. patients

- Median survival is in the range report in the original ACCORD 11 study

- In HA unselected patients, combining PEGPH20 with mFOLFIRINOX results in added toxicity and inferior efficacy

- Results of Phase III study with gemcitabine with PEGPH20 in HA selected patients are awaited

FAMILY HISTORY AND PDAC

- ~10% of PC related to genetic factors
- Several well-defined genetic syndromes (minority)
- Families with multiple individuals affected with PC, but no specific genetic abnormality identified (~70%)

DNA REPAIR DEFECTS COMMON IN HEREDITARY PDAC

Syndrome	Mutated Gene	Relative Risk	Reference
Peutz-Jegher	STK11 (19p13)	RR 132 x	Gastro 2000
Hereditary Pancreatitis	PRSSI (7q35) SPINK1 (5q31)	~ 50 x	Pancreat 2001 JNCI 1997
FAMMM	CDKN2A (9p21)	13- 22 x	NEJM 1995
FAP	APC (5q13)	RR 4.5 x	Gastro 2002
Hereditary Breast-Ovarian Syndrome	**BRCA1 (17q21)** **BRCA2 (13q12)**	RR 2.2 x RR 3.5 x	JNCI 1999, 2002 BJC, 2012
HNPCC	**MLHI (3p21)** **MSH2 (2p16)**	~ 9	Cancer 1996 JAMA 2009
Ataxia Telangiect	**ATM (11q23)**	Increased	Clin Gen 1999
Breast, Pancreas	**PALB2 (16p12.2)**	Increased	Science 2009

HIGH-RISK FAMILY RECOMMENDATIONS

- Young, sporadic, high-risk families
  - Smoking cessation (only reversible risk factor)
  - Healthy weight maintenance
  - Registry enrollment
  - Screening and prevention trials
  - IPMN – precursor lesion in FPC?

- Genetic counseling/ screening Therapeutic implications

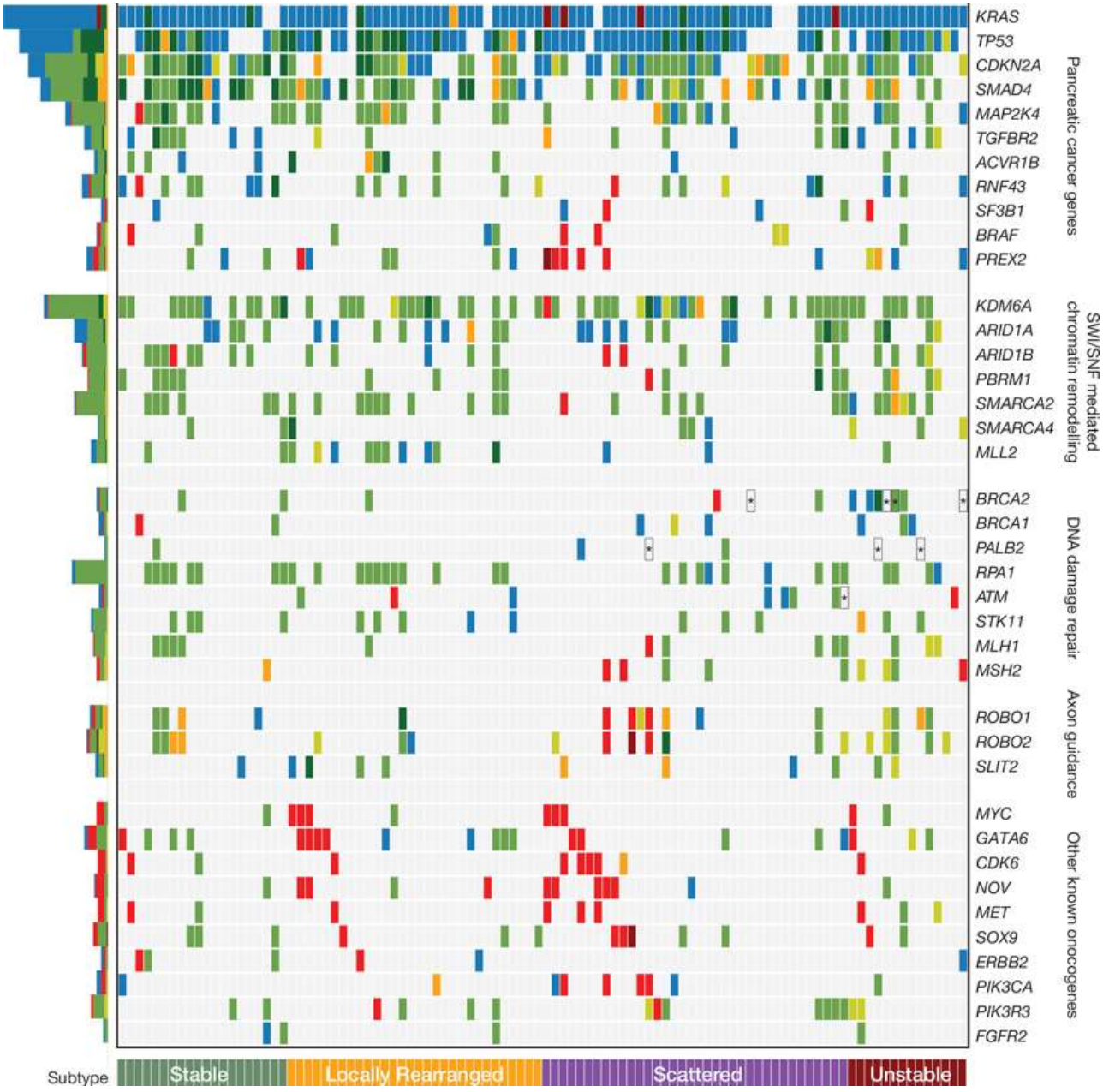
TARGETING DNA REPAIR : BRCA and PDAC

- 5-8% of PDAC patients germline BRCA 1 or 2 mutation
  - Ashkenazi Jewish 5-16%
  - Familial PDAC 5-19%
  - Familial breast/ovary cancer 5-10%

- BRCA Founder mutations in AJ descent (2-3%)
  - BRCA 1: 185delAG, 5382insC
  - BRCA 2: 6174delT

Hahn, SA. Gastro, 2003. Murphy, KM. Can Res, 2002. Ozcelik, H. Nat Genetics, 1997. Lal, G. Can Res, 2000. Lucas, AL. CCR, 2013. Ferrone, C. J Clin Oncol, 2009. Stadler, ZK. Can, 2012. Brose, MS. JNCI, 2002

GENOMIC LANDSCAPE PDAC



Waddell et al, Nature 2015

NCI P#8993: THREE TRIALS

- Phase IB cisplatin, gemcitabine + veliparib in PDAC **(completed)**

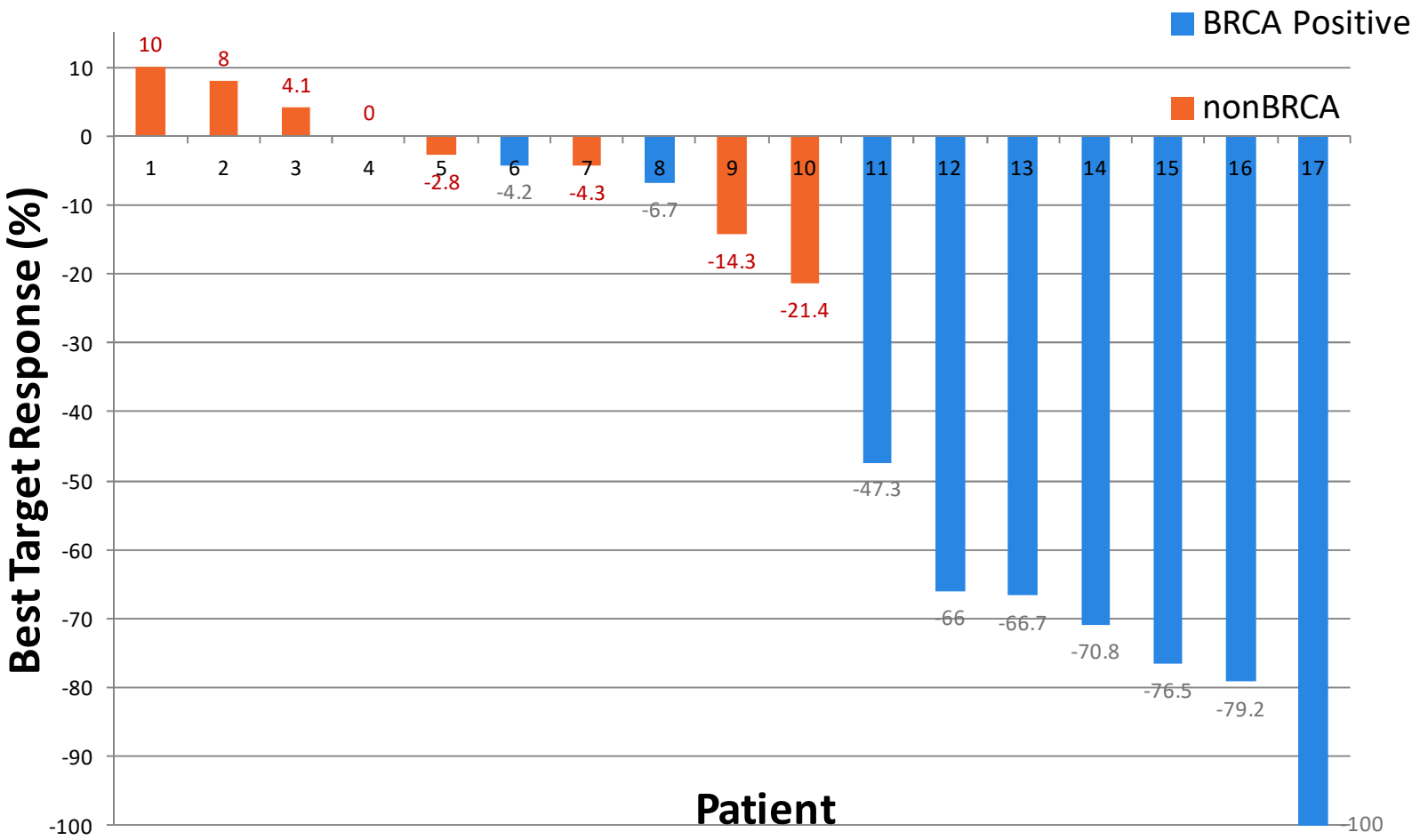
- Single-arm, non-randomized, phase II veliparib in previously-treated BRCA or PALB2 mutated PDAC **(completed)**

- Randomized phase II cisplatin, gem +/- veliparib in untreated BRCA/PALB2 mutated PDAC **(ongoing)**
  - Arm A: Gemcitabine, cisplatin, veliparib
  - Arm B: Gemcitabine, cisplatin

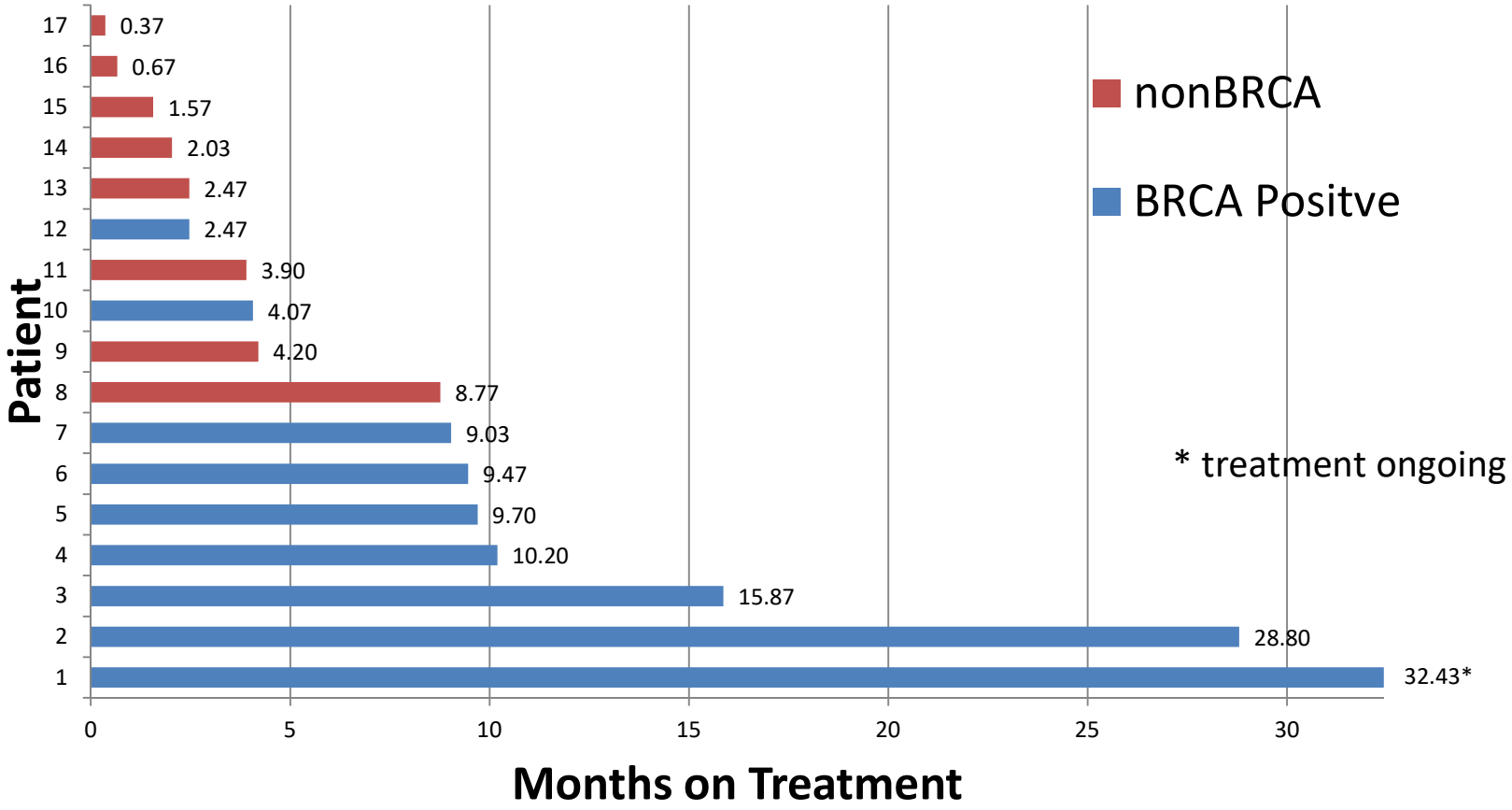
NCT01585805 O'Reilly, EM, Kelsen, DP, Lowery, MA

PHASE IB: CISPLATIN, GEM, VELIPARIB

RECIST RESPONSE: GBRCA(+) VS GBRCA(-)



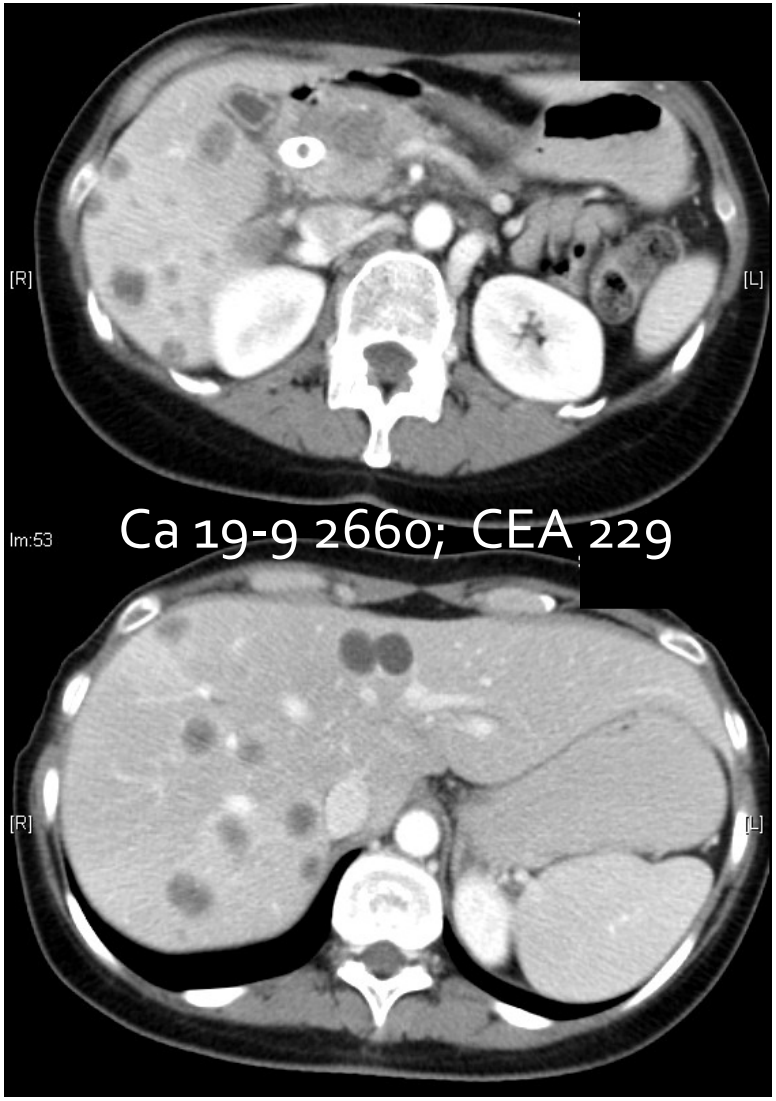
DURATION ON STUDY:
GBRCA(+) VS GBRCA(-)

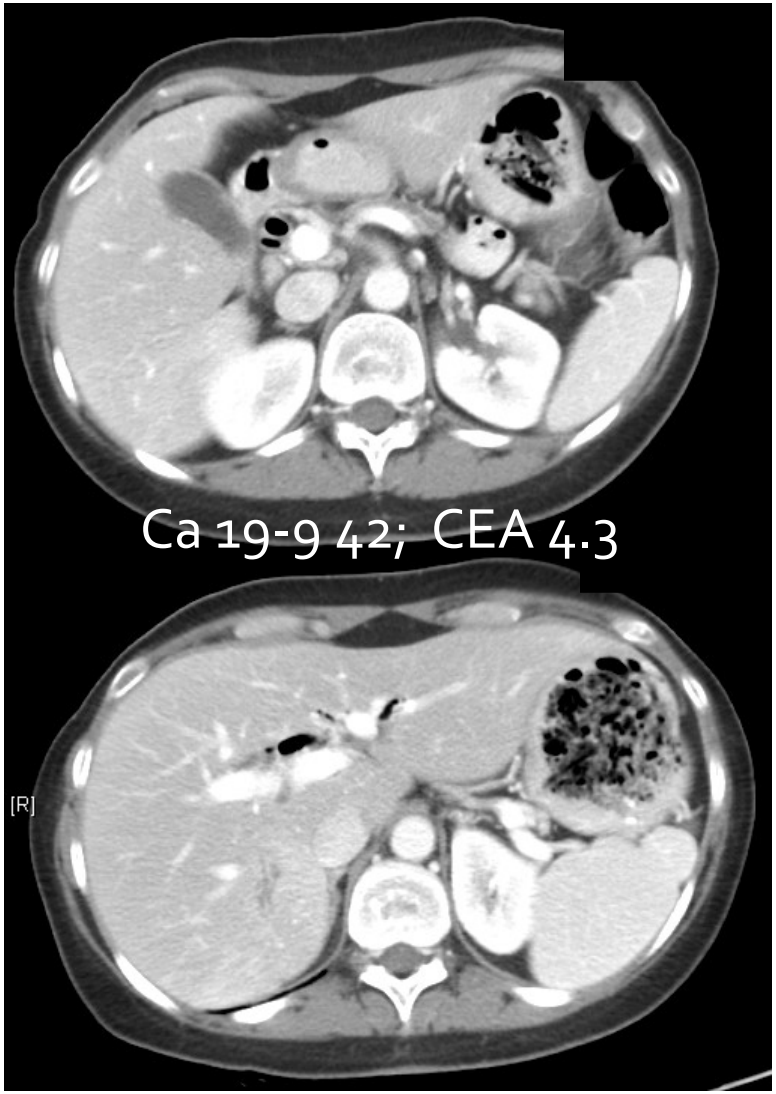


OVERALL SURVIVAL BRCA(+) VS BRCA(-) CISPLATIN/GEMCITABINE + PARPi

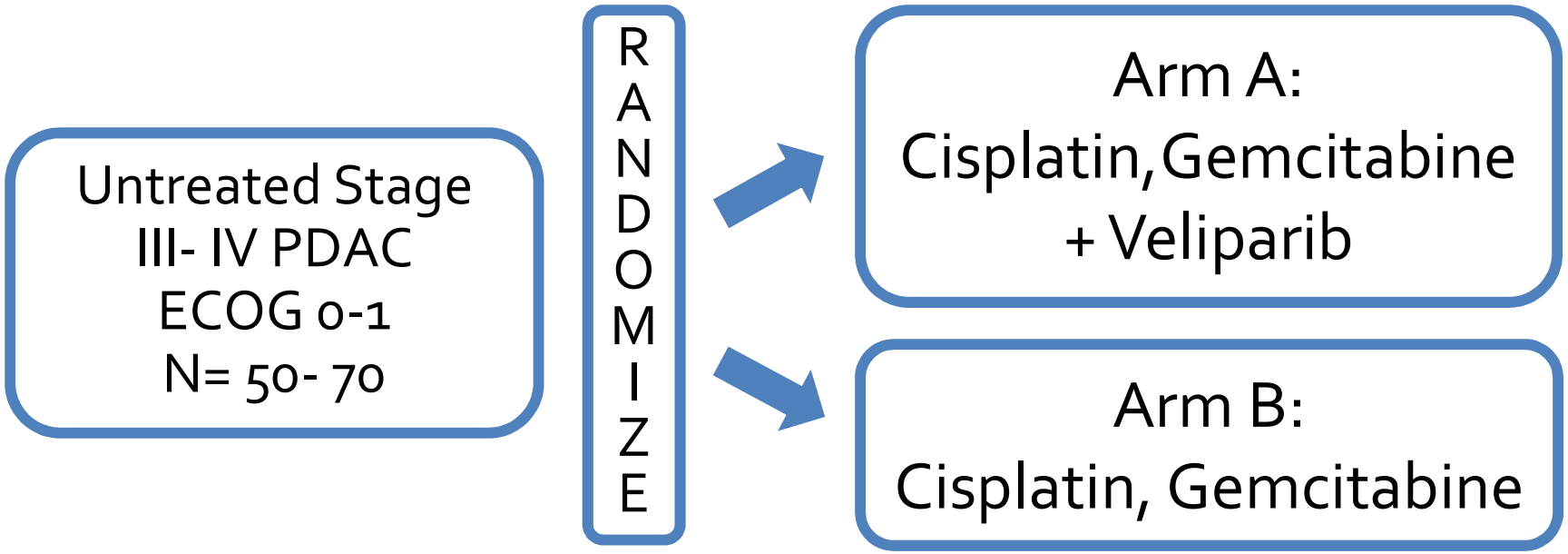
- Germline BRCA(-): OS 11 months (95% CI: 1.5-12.1)
- Germline BRCA(+): OS 23.3 months (95% CI: 3.8-30.2)
- Predictive vs Prognostic effect

PATIENT BRCA1 MUTATION





RANDOMIZED PHASE II TRIAL OF CISPLATIN, GEMCITABINE +/- VELIPARIB IN GERMLINE BRCA/PALB2

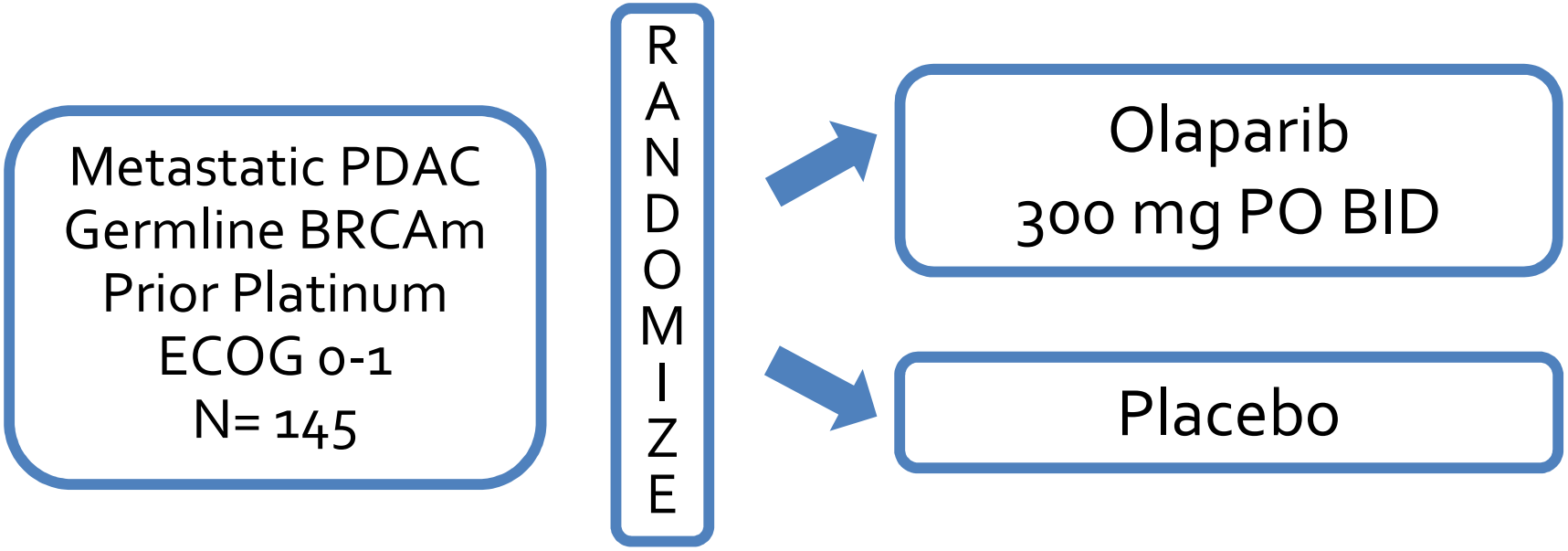


Randomization 1: 1

Primary Endpoint: Response Rate

NCT01585805 O'Reilly, EM, Kelsen, D

PHASE III TRIAL MAINTENANCE (POLO)
PLATINUM THERAPY → OLAPARIB/PLACEBO



Randomization 3: 2

Primary Endpoint: PFS (central review mRECIST 1.1)

NCT02184195 (Astra Zenica, Myriad) Golan, T., Kindler, H

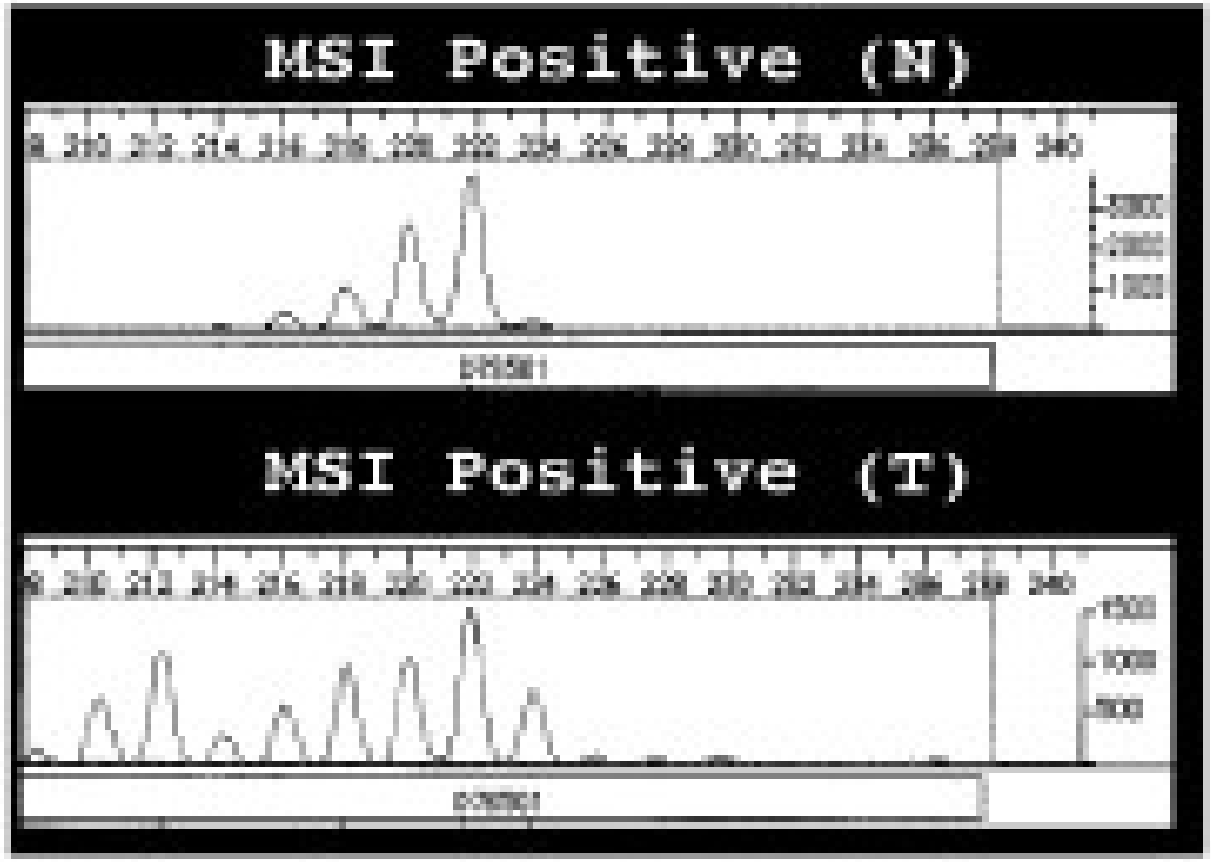
IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY

2536 Vol. 8, 2536–2540, August 2002 Clinical Cancer Research

Prognostic Value of Microsatellite Instability in Resectable Pancreatic Cancer

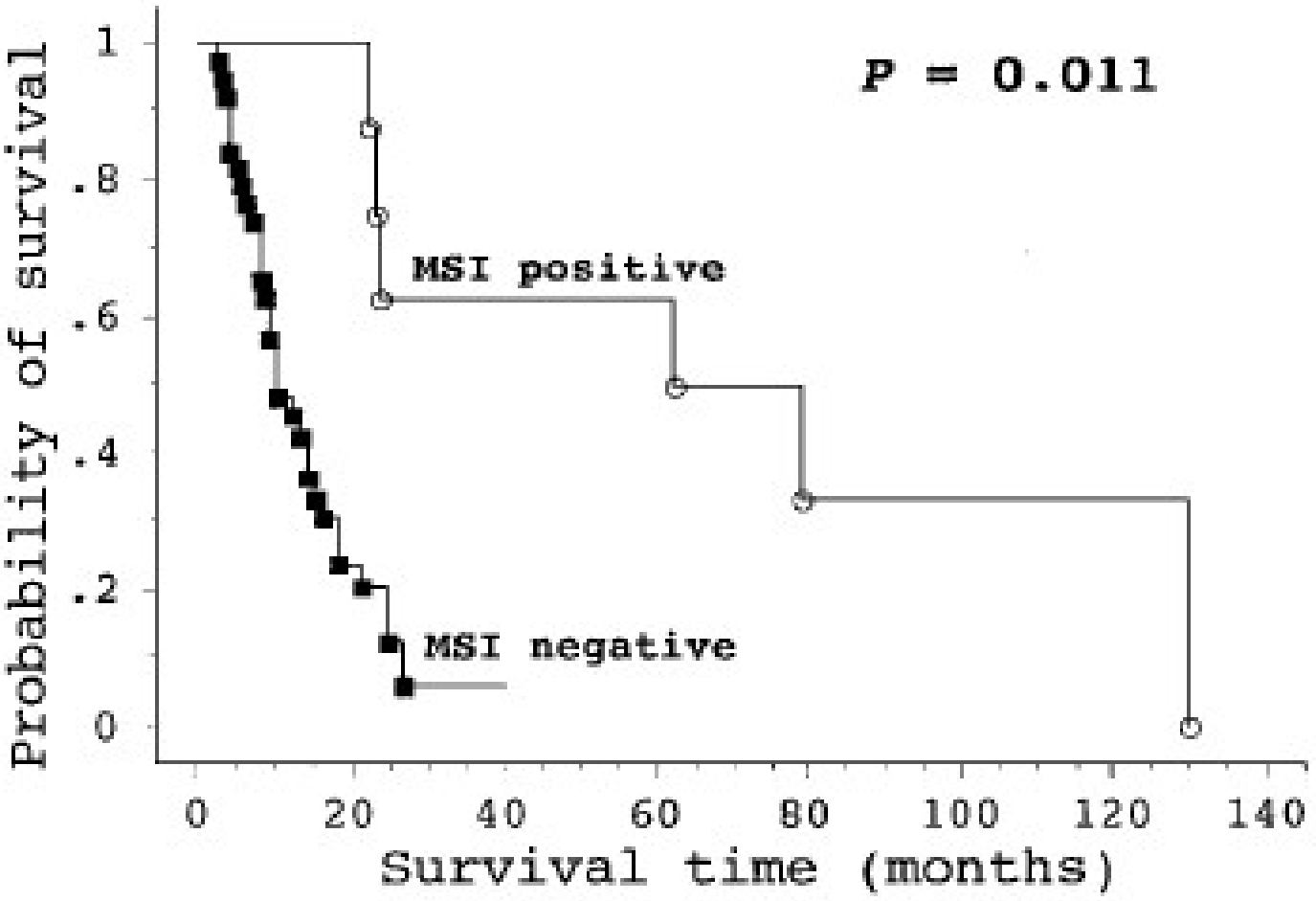
NAKATA ET AL, CANCER RESEARCH 2002

IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY



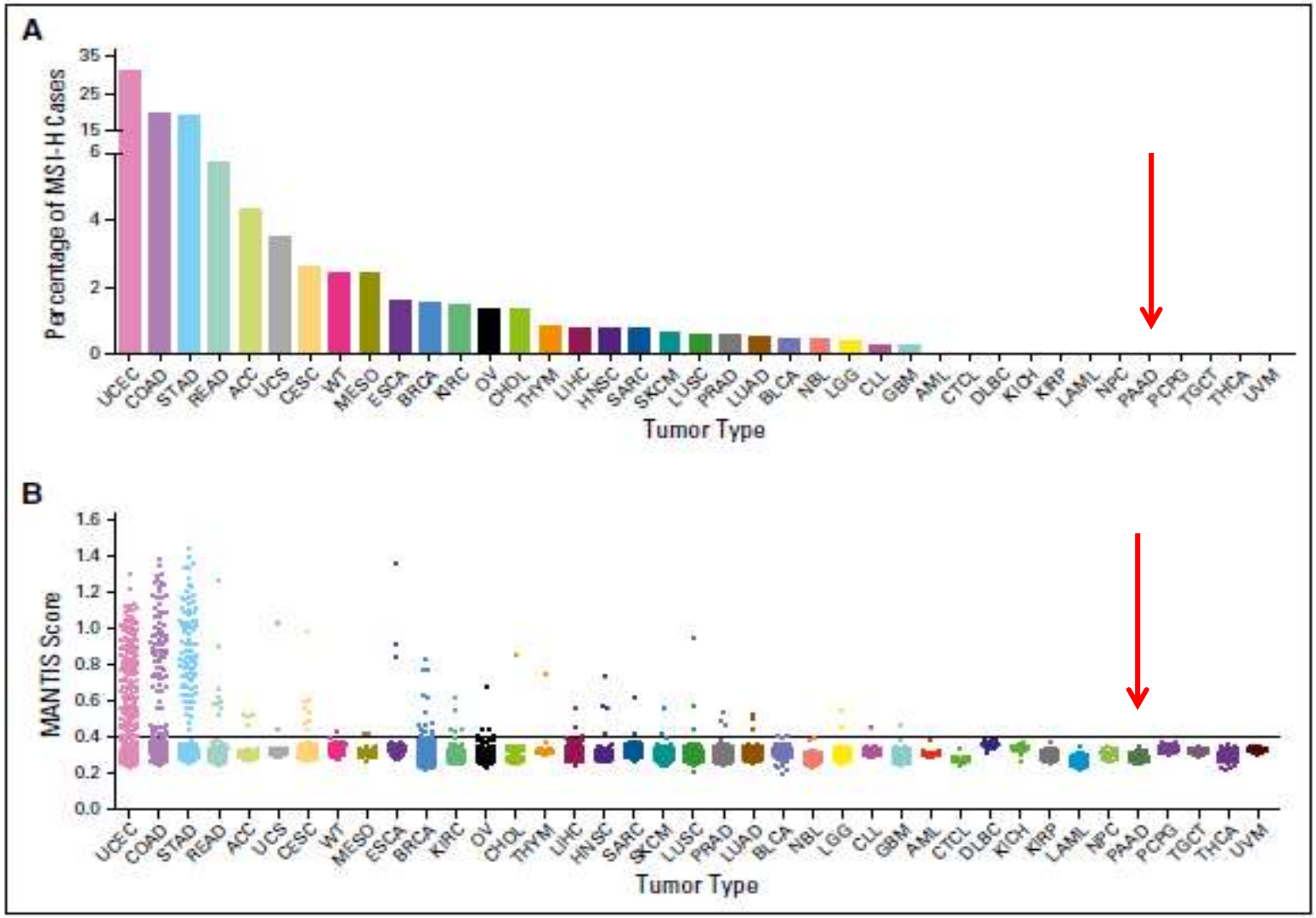
NAKATA ET AL, CANCER RESEARCH 2002

IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY



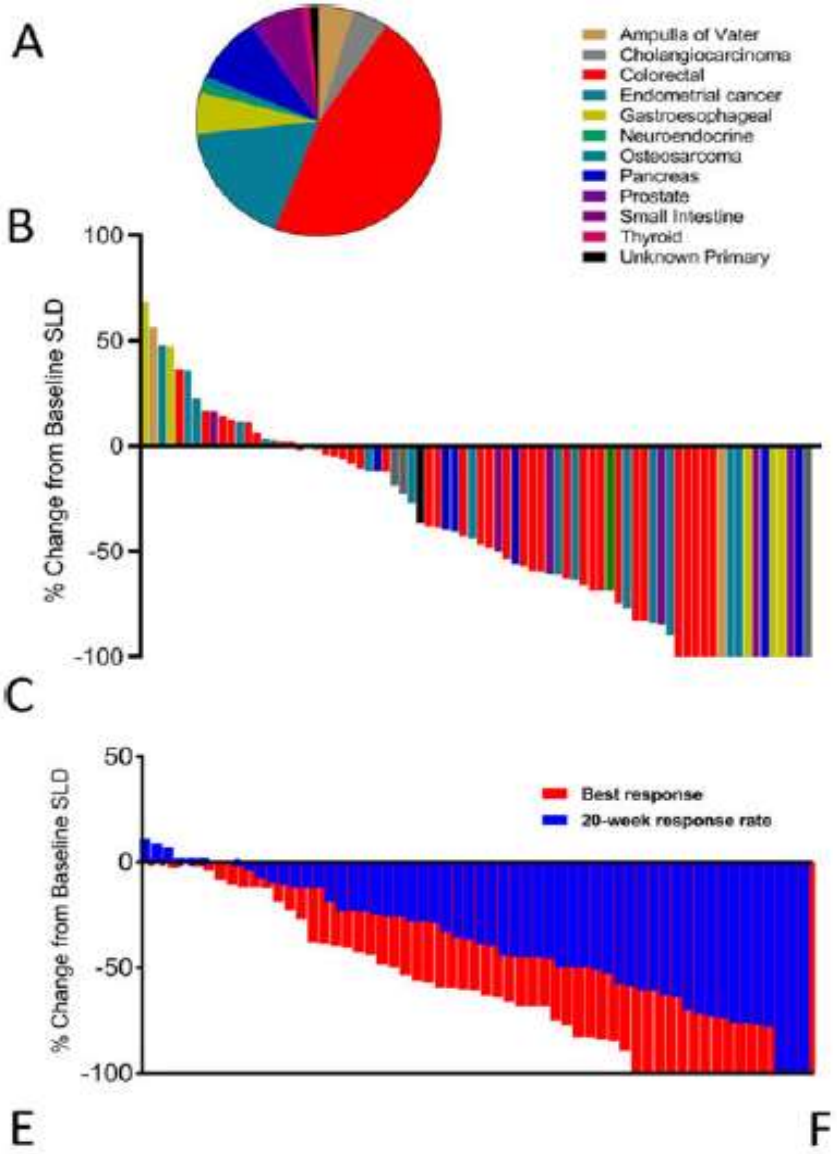
NAKATA ET AL, CANCER RESEARCH 2002

IMMUNOTHERAPY IN PANCREATIC CANCER
MICROSATELLITE INSTABILITY



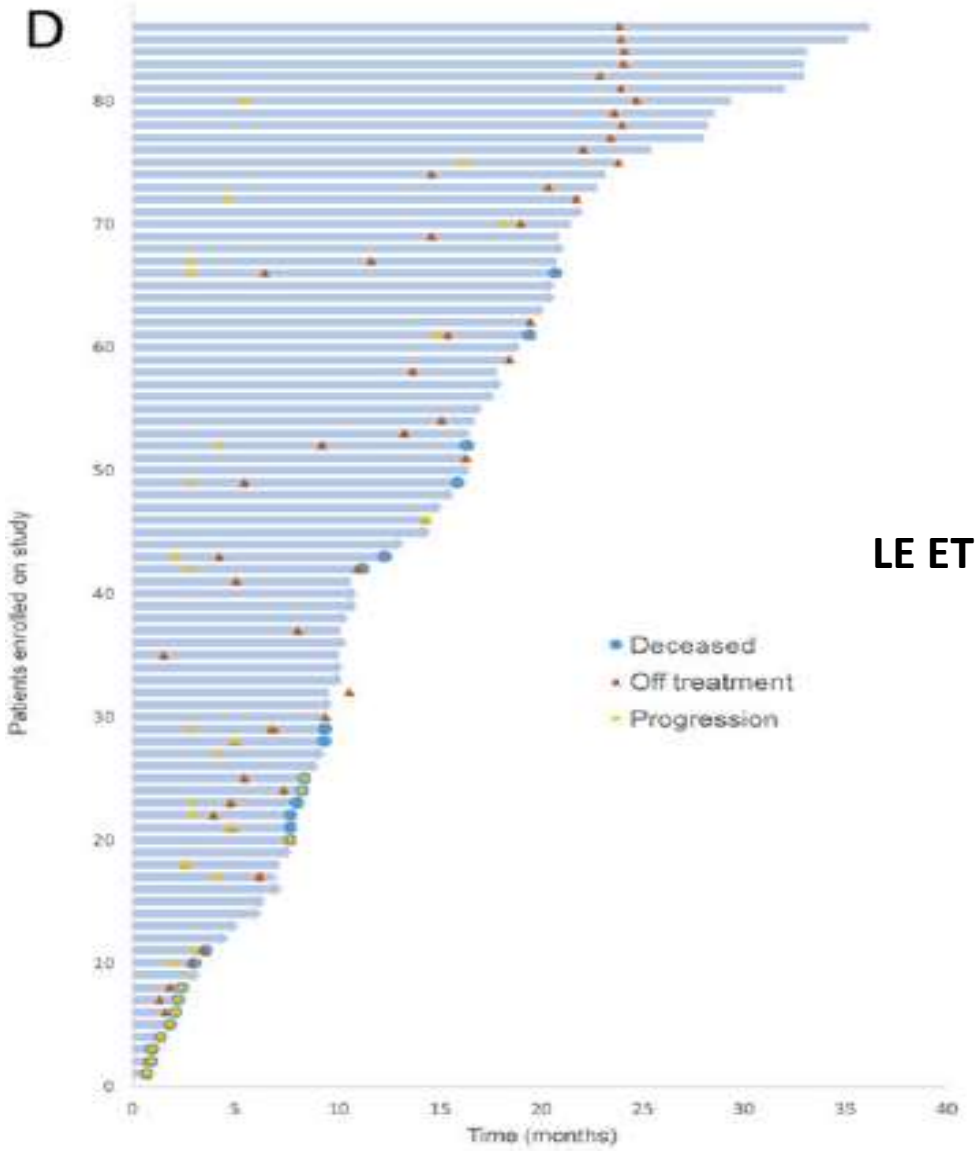
BONNEVILLE ET AL, JCO PRECISION ONCOLOGY 2017

IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY



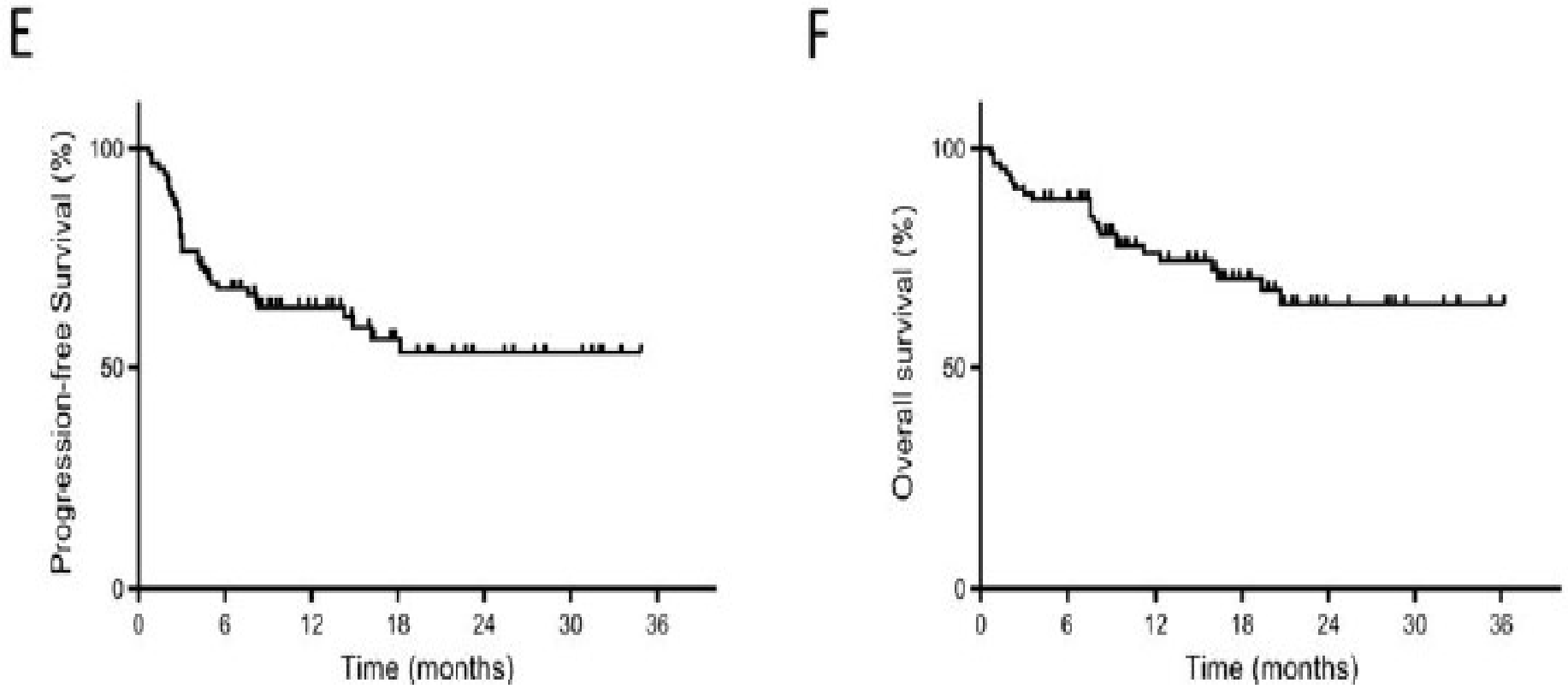
LE ET AL, SCIENCE 2017

IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY



LE ET AL, SCIENCE 2017

IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY



LE ET AL, SCIENCE 2017

IMMUNOTHERAPY IN PANCREATIC CANCER MICROSATELLITE INSTABILITY

PEMBROLIZUMAB APPROVED IN ADULT AND PEDIATRIC PATIENTS WITH:

- **UNRESECTABLE OR METASTATIC, MICROSATELLITE INSTABILITY HIGH (MSI-H) OR MISMATCH REPAIR DEFICIENT (DMMR) SOLID TUMORS THAT HAVE PROGRESSED FOLLOWING PRIOR TREATMENT AND WHO HAVE NO SATISFACTORY ALTERNATIVE TREATMENT OPTIONS**

- **WITH MSI-H OR DMMR COLORECTAL CANCER THAT HAS PROGRESSED FOLLOWING TREATMENT WITH A FLUOROPYRIMIDINE, OXALIPLATIN, AND IRINOTECAN**

sitc
Society for Immunotherapy of Cancer

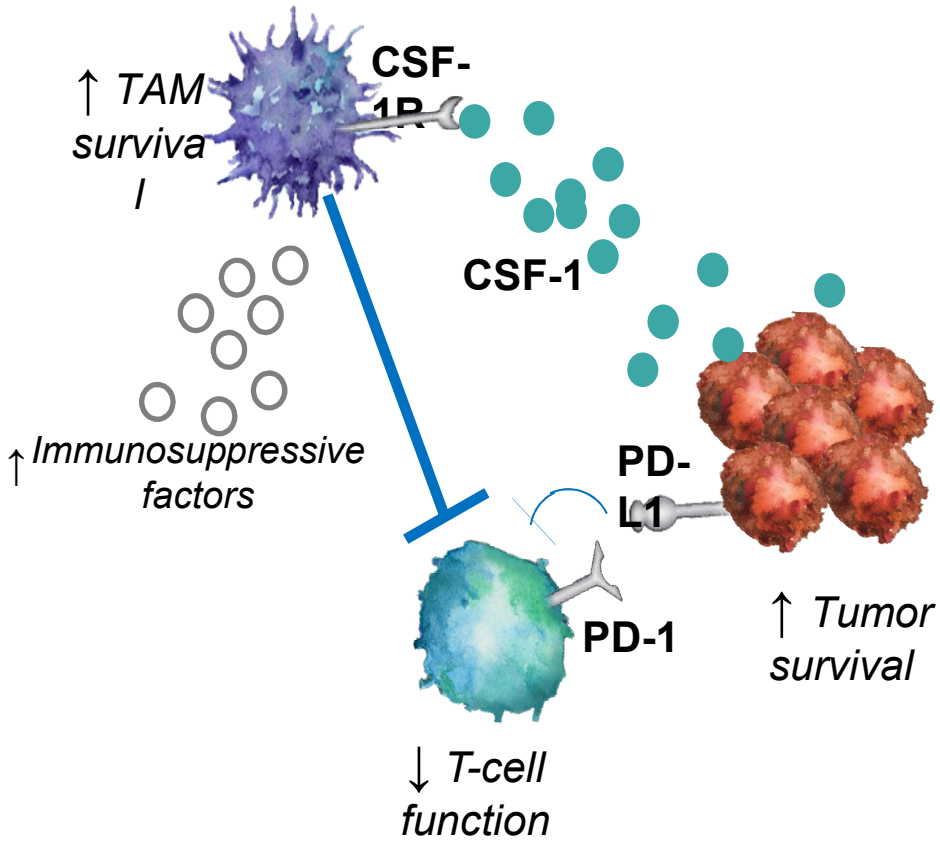
First-in-Human Phase 1 Dose Escalation and Expansion of a Novel Combination, Anti–CSF-1 Receptor (cabiralizumab) Plus Anti–PD-1 (nivolumab), in Patients With Advanced Solid Tumors

Zev A. Wainberg,[1] Sarina A. Piha-Paul,[2] Jason Luke,[3] Edward J. Kim,[4] John A. Thompson,[5] Carolyn D. Britten,[6] Jennifer M. Johnson,[7] Nicklas Pfanzelter,[8] Michael Gordon,[9] Drew W. Rasco,[10] F. Stephen Hodi,[11] Amy Weise,[12] Sandeep Inamdar,[13] Serena Perna,[14] Christy Ma,[13] Janine Powers,[13] Yeonju Lee,[13] Majid Ghoddusi,[13] Michael Carleton,[14] Hong Xiang,[13] Lei Zhou,[13] Helen Collins,[13] James J. Lee[15]

[1]UCLA Medical Center, Los Angeles, CA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]University of Chicago Medical Center, Chicago, IL; [4]UC Davis Cancer Center, Sacramento, CA; [5]University of Washington, Seattle Cancer Center, Seattle, WA; [6]Medical University of South Carolina, Charleston, SC; [7]Sidney Kimmel Cancer Center, Jefferson University, Philadelphia, PA; [8]Rush University Medical Center, Chicago, IL; [9]Honor Health Research Institute, Scottsdale, AZ; [10]South Texas Accelerated Research Therapeutics, San Antonio, TX; [11]Dana-Farber Cancer Institute, Boston, MA; [12]Barbara Ann Karmanos Cancer Institute, Detroit, MI; [13]FivePrime Therapeutics, South San Francisco, CA; [14]Bristol-Myers Squibb, Princeton, NJ; [15]University of Pittsburgh Cancer Institute, Pittsburgh, PA

FPA008-003

Rationale for Cabiralizumab in Combination With Nivolumab



- TAMs inhibit antitumor T-cell activity in the tumor microenvironment[1,2]
  - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis[3-5]
  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs[1,2]

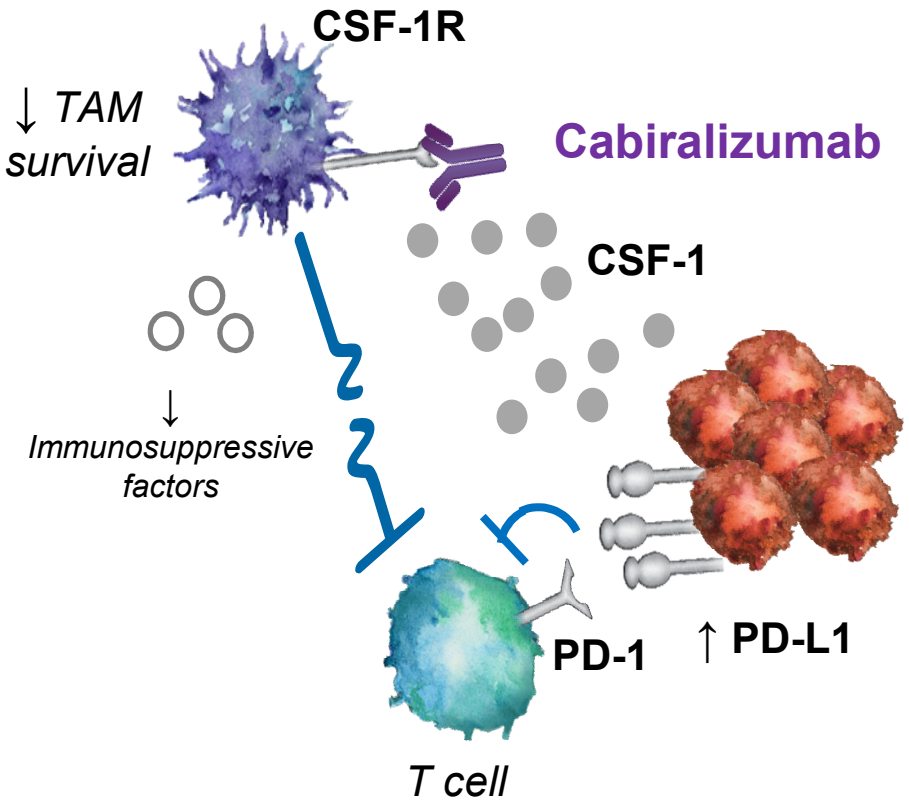
sitc
Society for Immunotherapy of Cancer

CSF-1 = colony stimulating factor 1; TAM = tumor-associated macrophage; PD-1 = programmed death-1

1. Ries CH, et al. *Cancer Cell* 2014;25:846–859. 2. Cannarile M, et al. *J ImmunoTher Cancer* 2017;5:53. 3. Hu H, et al. *Tumour Biol* 2016;37:8657–8664.
4. Kurahara H, et al. *J Surg Res* 2011;167:e211–e219. 5. Goswami KK, et al. *Cell Immunol* 2017;316:1–10.

FPA008-003

Rationale for Cabiralizumab in Combination With Nivolumab



- TAMs inhibit antitumor T-cell activity in the tumor microenvironment[1,2]
  - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis[3-5]
  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs[1,2]
- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R and depletes TAMs

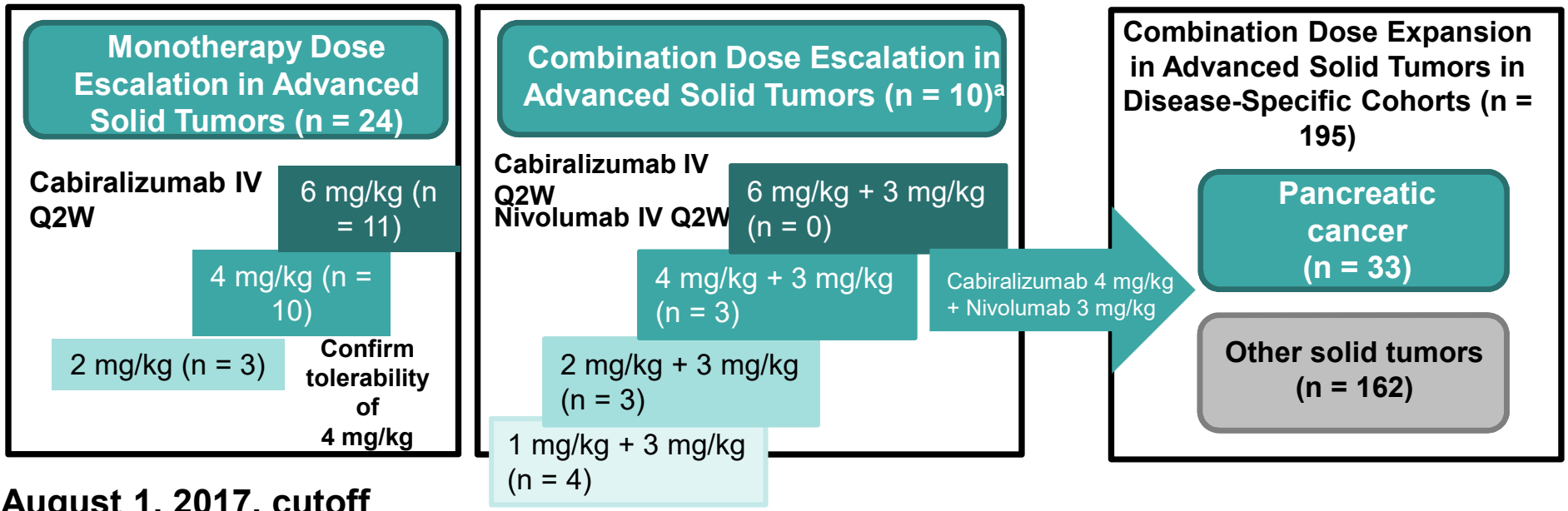
sitc
Society for Immunotherapy of Cancer

CSF-1 = colony stimulating factor 1; TAM = tumor-associated macrophage; IgG = immunoglobulin G, mAb = monoclonal antibody; PD-1 = programmed death-1

1. Ries CH, et al. *Cancer Cell* 2014;25:846–859. 2. Cannarile M, et al. *J ImmunoTher Cancer* 2017;5:53. 3. Hu H, et al. *Tumour Biol* 2016;37:8657–8664. 4. Kurahara H, et al. *J Surg Res* 2011;167:e211–e219. 5. Goswami KK, et al. *Cell Immunol* 2017;316:1–10. 6. Bellovin D, et al. *Cancer Res* 2017;77 (13 suppl) [abstract 1599]).

FPA008-003

Escalation Study of Cabiralizumab ± Nivolumab in Advanced Solid Tumors



August 1, 2017, cutoff

Primary objectives: safety/tolerability, dose-limiting toxicities

Secondary objectives: immunogenicity, PK, pharmacodynamics, preliminary antitumor activity[b]

[a]Initiated after corresponding monotherapy doses were deemed tolerable. [b]Primary objective for expansion phase

IV = intravenous; PK = pharmacokinetics; Q2W = every 2 weeks

sitc
Society for Immunotherapy of Cancer

Rationale for Targeting CSF-1R in Pancreatic Cancer

- Pancreatic cancer is associated with high TAM infiltration and poor prognosis[1,2]
- It typically presents as metastatic disease with a 1-year survival rate of 17%-23%[3] and a 5-year survival rate of 1%-3%[4,5]
- Approximately 95%-99% of patients have microsatellite stable (MSS) pancreatic cancer,[6-8] lack response to anti–PD-1/L1 therapy,[5,9] and are in need of new treatment options
- **Combination of cabiralizumab and nivolumab may benefit patients with pancreatic cancer by simultaneous reduction of TAMs and inhibition of PD-1 signaling**

1. Hu H, et al. *Tumour Biol* 2016;37:8657–8664. 2. Kurahara, et al. *J Surg Res* 2011;167:e211–e219. 3. Von Hoff DD, et al. *N Engl J Med* 2013;369:1691-1703. 4. American Cancer Society. Pancreatic cancer. https://www.cancer.org/cancer/pancreatic-cancer.html. Accessed October 20, 2017. 5. Foley K, et al. *Cancer Lett* 2016;381;244–251. 6. Goggins M, et al. *Am J Pathol* 1998;1501–1507. 7. Luttges J, et al. *Mod Pathol* 2003;16:537–542. 8. Laghi L, et al. *PLOS One* 2012;7:e46002. 9. Brahmer JR, et al. *N Engl J Med* 2012;366;2455–2465.

sitc
Society for Immunotherapy of Cancer

FPA008-003

Pancreatic Cancer Cohort Baseline Demographics and Safety

- Patient demographics and the safety profile in the pancreatic cohort was similar to those in all patients treated with cabiralizumab + nivolumab

Baseline demographics and prior therapy	Cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Pancreatic cancer (n = 33)[a]
Median age (range), years	64 (37–85)
< 65 years, n (%)	17 (52)
Male, n (%)	17 (52)
ECOG performance status, n (%)	
0	13 (39)
1	19 (58)
2	1 (3)
No. of prior regimens, n (%)	
0	1 (3)[b]
1	3 (9)
2	14 (42)
≥ 3	15 (45)
No. of prior regimens for metastatic disease, n (%)	
0	7 (21)
1	4 (12)
2	12 (36)
≥ 3	10 (30)

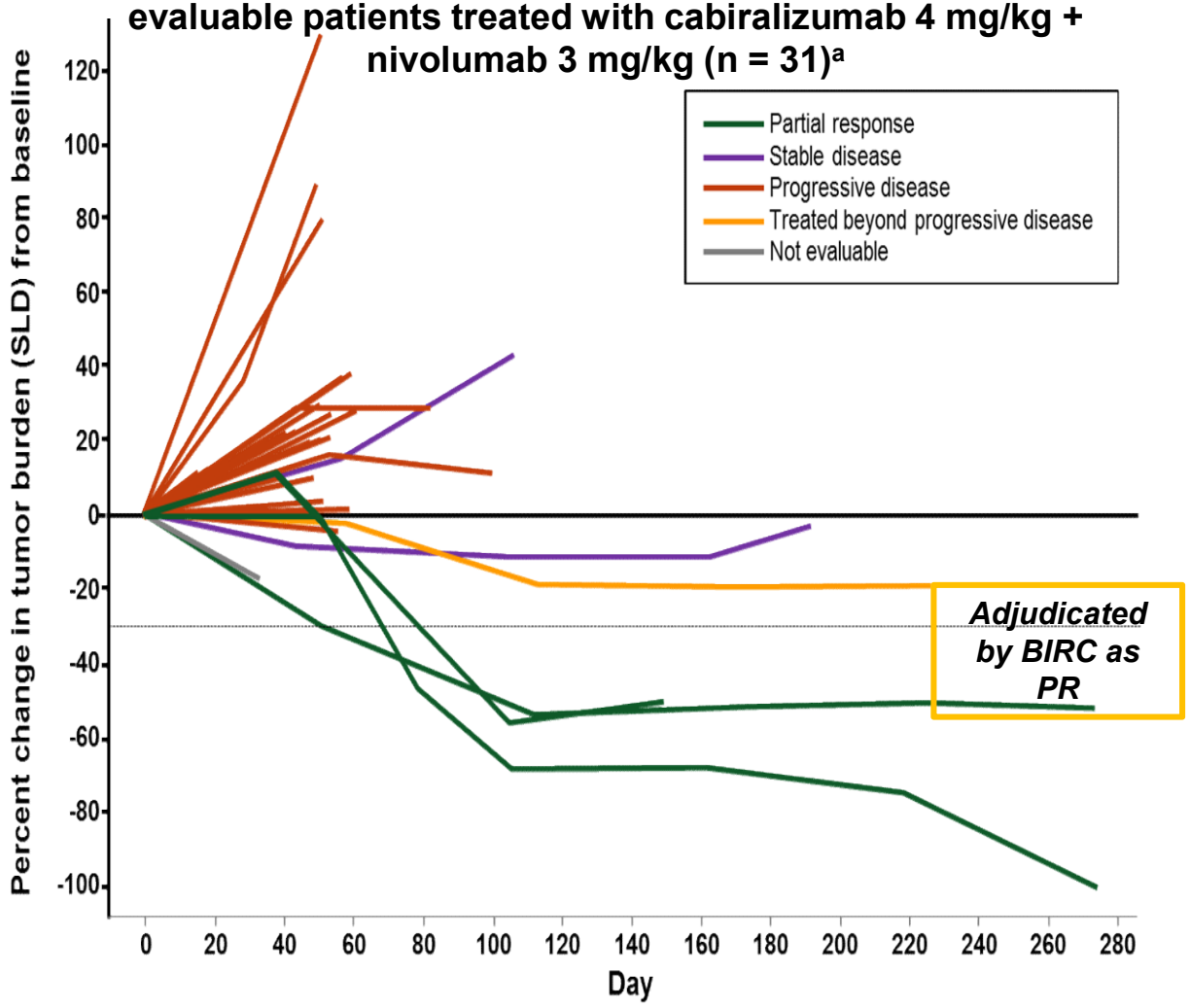
Safety summary	Cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Pancreatic cancer (n = 33)[a]	
	Any grade n (%)	Grade 3/4 n (%)
Any TRAE	31 (94)	20 (61)
AEs leading to discontinuation	3 (9)	3 (9)
Clinical TRAEs in ≥ 15% of patients		
Fatigue	14 (42)	1 (3)
Periorbital edema	10 (30)	0
Rash	7 (21)	0
Vomiting	7 (21)	0
Hyponatremia	6 (18)	3 (9)
Diarrhea	5 (15)	1 (3)
Rash maculopapular	5 (15)	3 (9)
Treatment-related laboratory abnormalities of interest		
Serum enzyme elevations[c]	17 (52)	11 (33)
Pancreatic enzyme elevations[d]	2 (6)	1 (3)
Treatment-related deaths	0	

[a]Of 33 patients, 31 were response evaluable. [b]Patient was ineligible or refused standard therapy. [c]Includes AE terms indicative of elevated CPK, AST, ALT, and LDH. [d]Includes AE terms indicative of elevated amylase and lipase

FPA008-003

Deep and Durable Responses Observed in Patients With Pancreatic Cancer

Best change in tumor burden over time in efficacy-evaluable patients treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg (n = 31)[a]



- In this heavily pretreated population, durable clinical benefit was observed in **5 patients (16%)**

  Confirmed ORR = 10% ***(Updated confirmed ORR = 13%)***

  Duration of treatment for responders = 275+, 168+, 258, and 247+ days

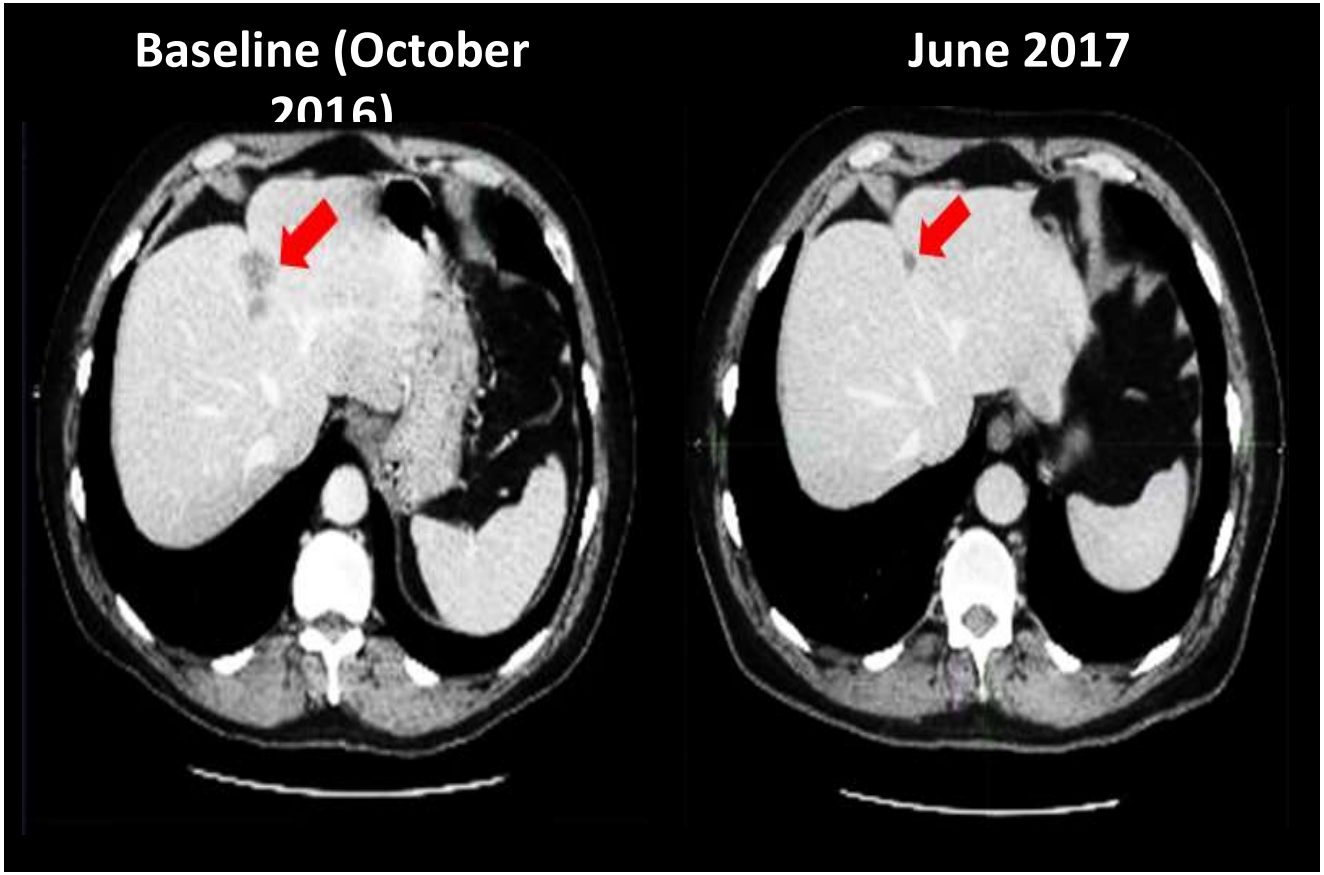
- All 4 confirmed responses were observed in patients with MSS disease, who historically have not shown benefit with anti–PD-1/L1 therapy[1,2]

- Responses were accompanied by steep declines in levels of the pancreatic tumor marker CA19-9 over baseline

[a]Plot shows 31 efficacy-evaluable patients; 2 patients discontinued treatment early due to AEs before disease evaluation. BIRC = blinded independent review committee; ORR = objective response rate; PR = partial response; SLD = sum of longest diameters 1. Overman M et al. *Ann Oncol*. 2016;27:149-206 [abstract 479P]. 2. Le DT, et al. *N Engl J Med* 2015;372;2509–2520.

FPA008-003

Durable Response in the Liver of a Heavily Pretreated Patient With MSS Pancreatic Cancer



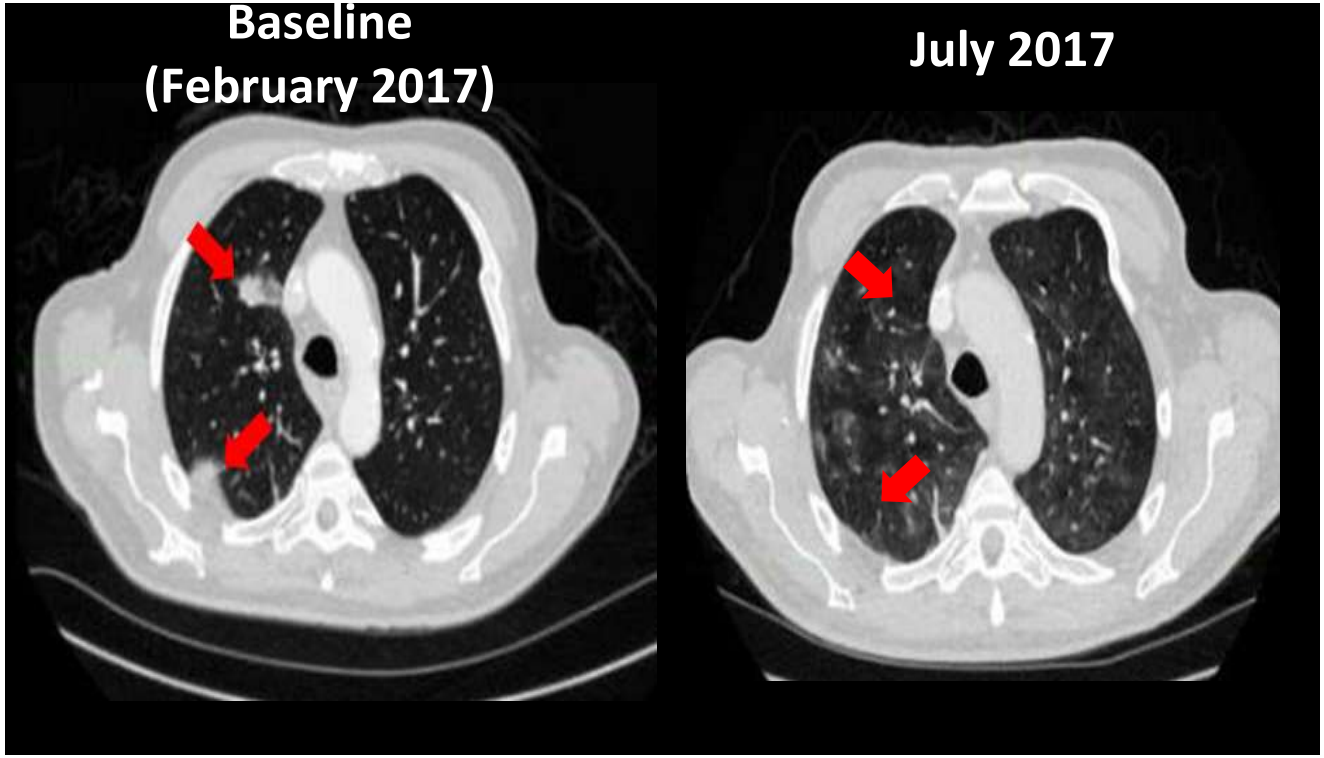
Images provided by James Lee from the University of Pittsburgh Cancer Institute.

- 58-year-old male patient who received 3 prior chemotherapy regimens
  - Neoadjuvant FOLFIRINOX
  - Gemcitabine + *nab*-paclitaxel
  - 5-FU + leucovorin + liposomal irinotecan
- Patient achieved a partial response with a best change in tumor burden of −52%
  - CA19-9 levels declined by 99% from baseline
  - Response is ongoing

5-FU = 5-fluorouracil; FOLFIRINOX = leucovorin + fluorouracil + irinotecan + oxaliplatin

FPA008-003

Durable Response in the Lung of a Heavily Pretreated Patient With MSS Pancreatic Cancer



Images provided by Jennifer Johnson from Thomas Jefferson University Hospital.

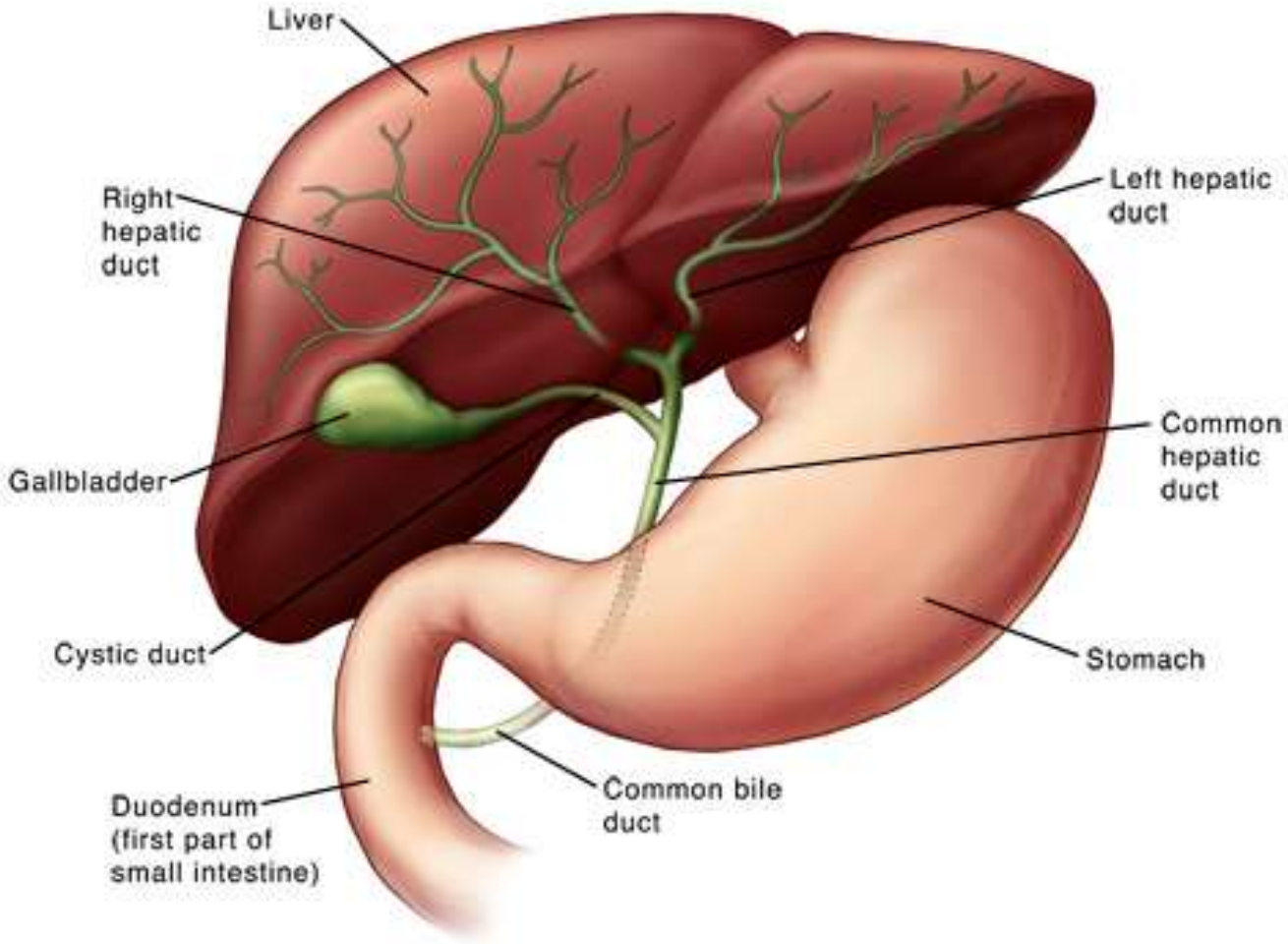
- 63-year-old male patient who received 4 prior chemotherapy regimens
  - Adjuvant FOLFIRINOX
  - FOLFIRINOX
  - Capecitabine
  - Gemcitabine + *nab*-paclitaxel
- Patient achieved a partial response with a best change in tumor burden of −50%
  - CA19-9 levels declined by 96% from baseline
  - Response is ongoing

Conclusions

- Cabiralizumab is a new immunotherapeutic agent that targets TAMs in the immunosuppressive microenvironment
- Cabiralizumab with or without nivolumab demonstrated:
  - Tolerable safety profile that is comparable to either monotherapy
  - Dose-dependent reduction of circulating $CD14^{+}CD16^{++}$ nonclassical monocytes, reaching maximum at 4 mg/kg Q2W when clearance approaches linear dose range
- Preliminary evidence of durable clinical benefit with cabiralizumab plus nivolumab was observed in heavily pretreated patients with advanced MSS pancreatic cancer
  - Further cohort expansion is ongoing as well as additional biomarker analyses
- These data support further study of cabiralizumab plus nivolumab ± chemotherapy in pancreatic cancer (NCT03336216)

sitc
Society for Immunotherapy of Cancer

HEPATOBILIARY CANCERS



HEPATOCELLULAR CANCER

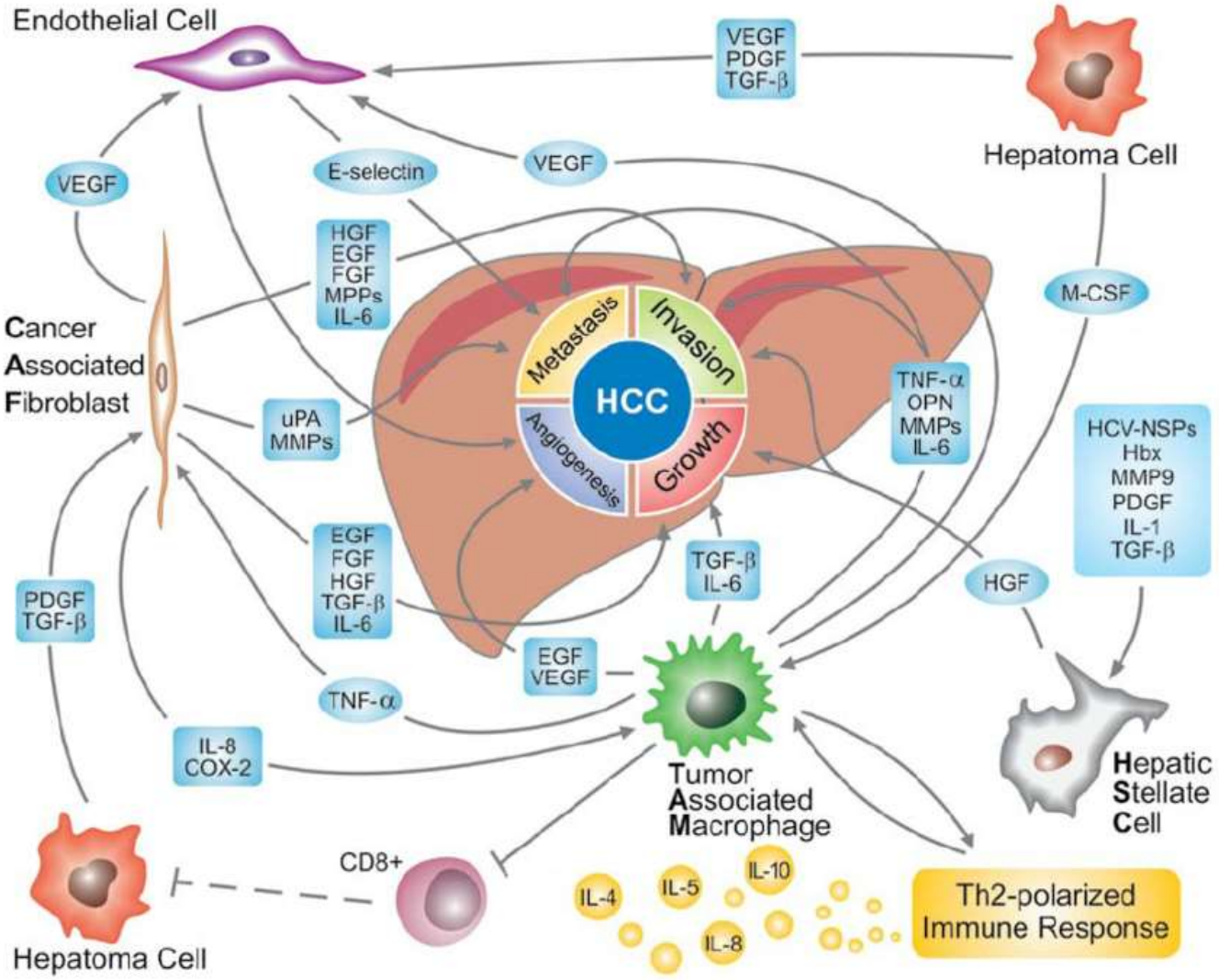
1. Most common primary cancer of the liver

2. Common etiologies include hepatitis B/C, NASH/metabolic syndrome, alcohol and others (e.g. Wilson's disease)

3. Estimated 39,230 cases (27,170 deaths) of HCC in 2016 (SEER) in the US

4. Global incidence ~782,000 cases (~554,000 deaths : GLOBOCAN)

TUMOR MICROENVIRONMENT IN HEPATOCELLULAR CANCER



LEONARDI ET AL, INT J ONC 2012

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C☆

Bruno Sangro[1,2,*], Carlos Gomez-Martin[3], Manuel de la Mata[4,2,5], Mercedes Iñarrairaegui[1,2], Elena Garralda[3], Pilar Barrera[4,2], Jose Ignacio Riezu-Boj[6], Esther Larrea[6], Carlos Alfaro[7], Pablo Sarobe[6], Juan José Lasarte[6], Jose L. Pérez-Gracia[7], Ignacio Melero[6,7,†], Jesús Prieto[1,2,6,†]

[1]*Liver Unit and HPB Oncology, Clinica Universidad de Navarra, Pamplona, Spain;* [2]*Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas (CIBERehd), Spain;* [3]*Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain;* [4]*Hepatology, Hospital Universitario Reina Sofía, Córdoba, Spain;* [5]*Instituto Maimónides de Investigación Biomédica de Córdoba, Córdoba, Spain;* [6]*Center for Applied Medical Research (CIMA), Pamplona, Spain;* [7]*Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain*

METHODS

- Tremelimimumab 15 mg/kg IV on day 1 of a 90-day cycle (up to 4 cycles)

- Inclusion/Exclusion Criteria:

1. Age ≥ 18 years
2. Advanced hepatitis C+ hepatocellular cancer
3. ECOG Performance Status 0-1
4. Measurable disease
5. AST/ALT < 5 x ULN; albumin > 3 g/dl; bilirubin < 3 mg/dl
6. Hemoglobin > 9 g/dl; neutrophils > 1.5 x 10^9/L; platelets > 75 x 10^9/L
7. Measurable disease
8. No systemic immunosuppresants

Sangro et al, J Hepatology 2013

Table 1. Patient characteristics.

Number of patients	21
Male sex, n (%)	15 (71.4)
Age in yr, mean (range)	65.2 (48-79)
HCV genotype 1b	100%
Hemoglobin (g/dl)	13.6 (12.6-14.3)
Platelet count (x10⁹/L)	113 [87.6-200]
Total bilirubin (mg/dl)	1.3 [0.88-2]
AST (IU/ml)	97 [53-121.5]
ALT (IU/ml)	58 [38-125]
Ascites, n (%)	4 (19)
Child-Pugh score	6.5 [5-7]
Child-Pugh stage	
A	12 (57.1)
B	9 (42.9)
Alpha-fetoprotein ≥400 ng/ml	6 (28.6)
ECOG performance status, n (%)	
0	15 (71.4)
1	6 (28.6)
Portal vein thrombosis	6 (28.6)
Extrahepatic disease	2 (9.5)
BCLC stage	
A	3 (14.3)
B	6 (28.6)
C	12 (57.1)
Prior antitumor therapy	
Any	12 (57.4)
Resection	1 (4.8)
RFA	4 (19)
TA(C)E	7 (33.3)
Radioembolization	6 (28.6)
Sorafenib	5 (23.8)
Prior antiviral therapy	7 (33.3)

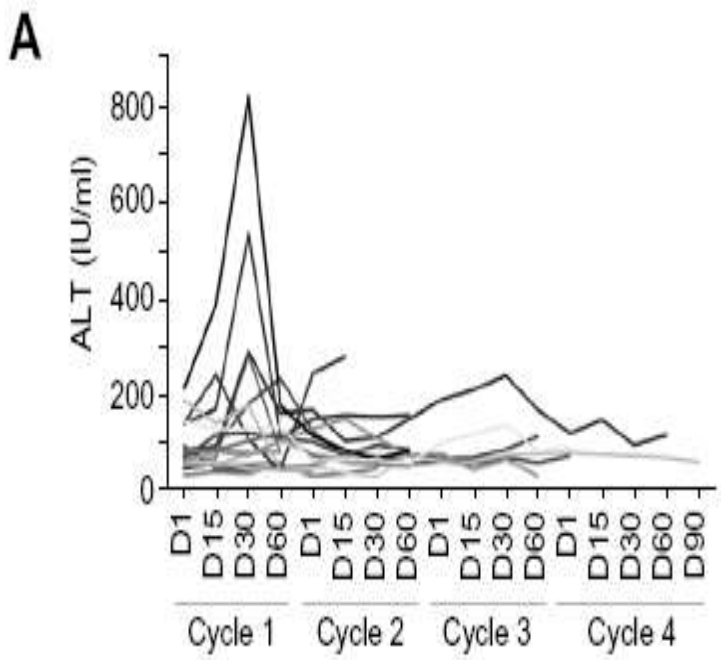
All values are expressed as median (IQR) unless otherwise specified.
HCV, hepatitis C virus. TA(C)E: transarterial (chemo)embolization.

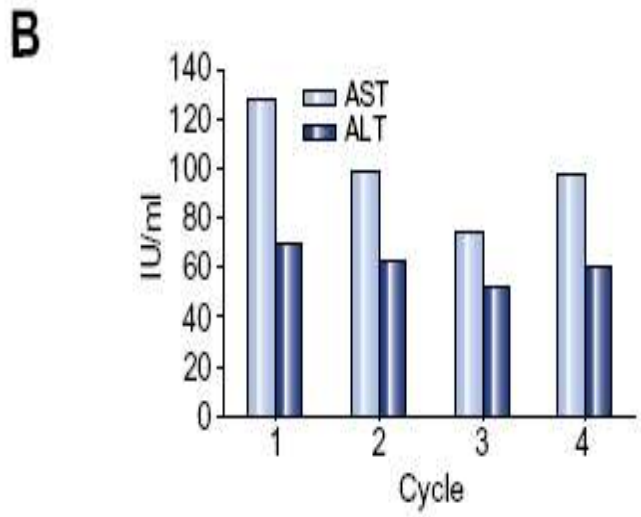
Sangro et al, J Hepatology 2013

Table 2. Clinical and laboratory adverse events according to CTCAE v 3.0.

	Grade		Most likely cause
	All N (%)	>3 N (%)	
Clinical			
Skin rash	13 (65)	1 (5)	Treatment
Fatigue	11 (55)	0	Treatment
Anorexia	10 (50)	0	Cirrhosis
Edema	7 (35)	0	Cirrhosis
Ascites	7 (35)	0	Cirrhosis
Diarrhea	6 (30)	1 (5)	Treatment
Respiratory infection	6 (30)	0	Others
Encephalopathy	5 (25)	3 (15)	Cirrhosis
Acute renal failure	3 (15)	2 (10)	Cirrhosis
Syncope	3 (15)	2 (10)	Treatment
Insomnia	3 (15)	0	Treatment
Abdominal pain	2 (10)	0	Treatment
Urinary tract infection	2 (10)	0	Others
Diverticulitis	1 (5)	1 (5)	Treatment
Depression	1 (5)	1 (5)	Treatment
Alopecia	1 (5)	0	Treatment
Hypothyroidism	1 (5)	0	Treatment
Arthritis	1 (5)	0	Treatment
Pleural effusion	1 (5)	0	Treatment
Gastrointestinal hemorrhage	1 (5)	1 (5)	Cirrhosis
Cholangitis	1 (5)	1 (5)	Others
Pneumonia	1 (5)	1 (5)	Others
Ophthalmic zoster	1 (5)	0	Others
Oral candidiasis	1 (5)	0	Others
Laboratory*			
Hypoalbuminemia	15 (75)	1 (5)	Cirrhosis
AST	14 (70)	9 (45)	Treatment
Hyponatremia	13 (65)	6 (30)	Cirrhosis
ALT	11 (55)	5 (25)	Treatment
Anemia	9 (45)	0	Cirrhosis
Total bilirubin	7 (35)	2 (10)	Cirrhosis
Thrombocytopenia	6 (30)	1 (5)	Cirrhosis
Neutropenia	4 (20)	1 (5)	Treatment
Hyperglycemia	4 (20)	0	Cirrhosis

*Only changes in CTCAE grade from baseline are considered an AE.





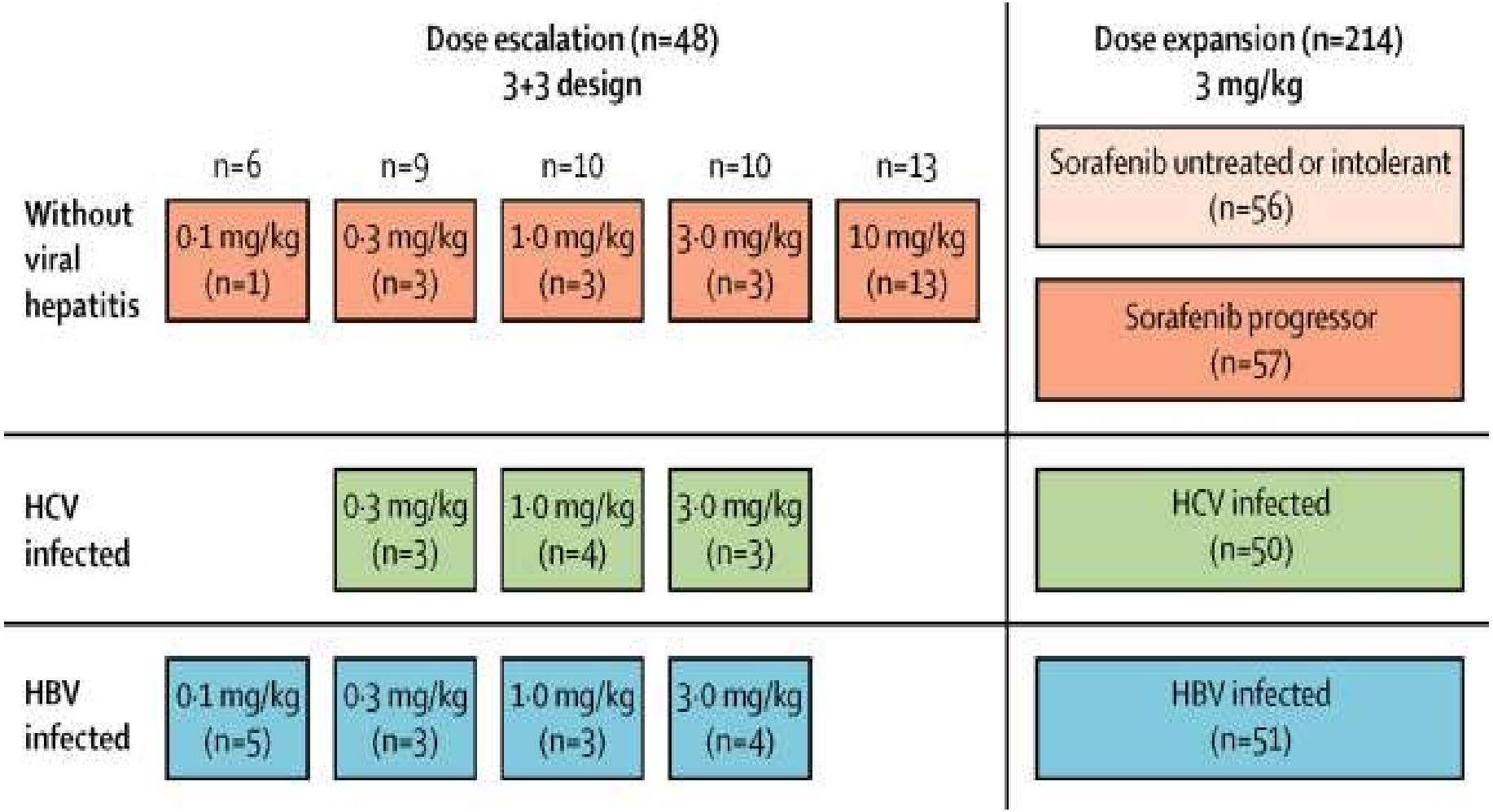
Sangro et al, J Hepatology 2013

EFFICACY

- Total evaluable patients (n=17)
- Complete response (n=0; 0%)
- Partial response (n=3; 17.6%) [Duration of response 3.6, 6.9 and 15.2 mths]
- Stable disease (n=10; 58.8%)
- Alpha-fetoprotein evaluable patient (n=11)
- Alpha-fetoprotein response (>50% decrease): n=4 (36%)
- Median time to tumor progression (TTP): 6.48 mth (95% CI: 3.95-9.14 mth)
- Median overall survival (OS): 8.2 mth (95% CI: 4.64-21.34 mth)

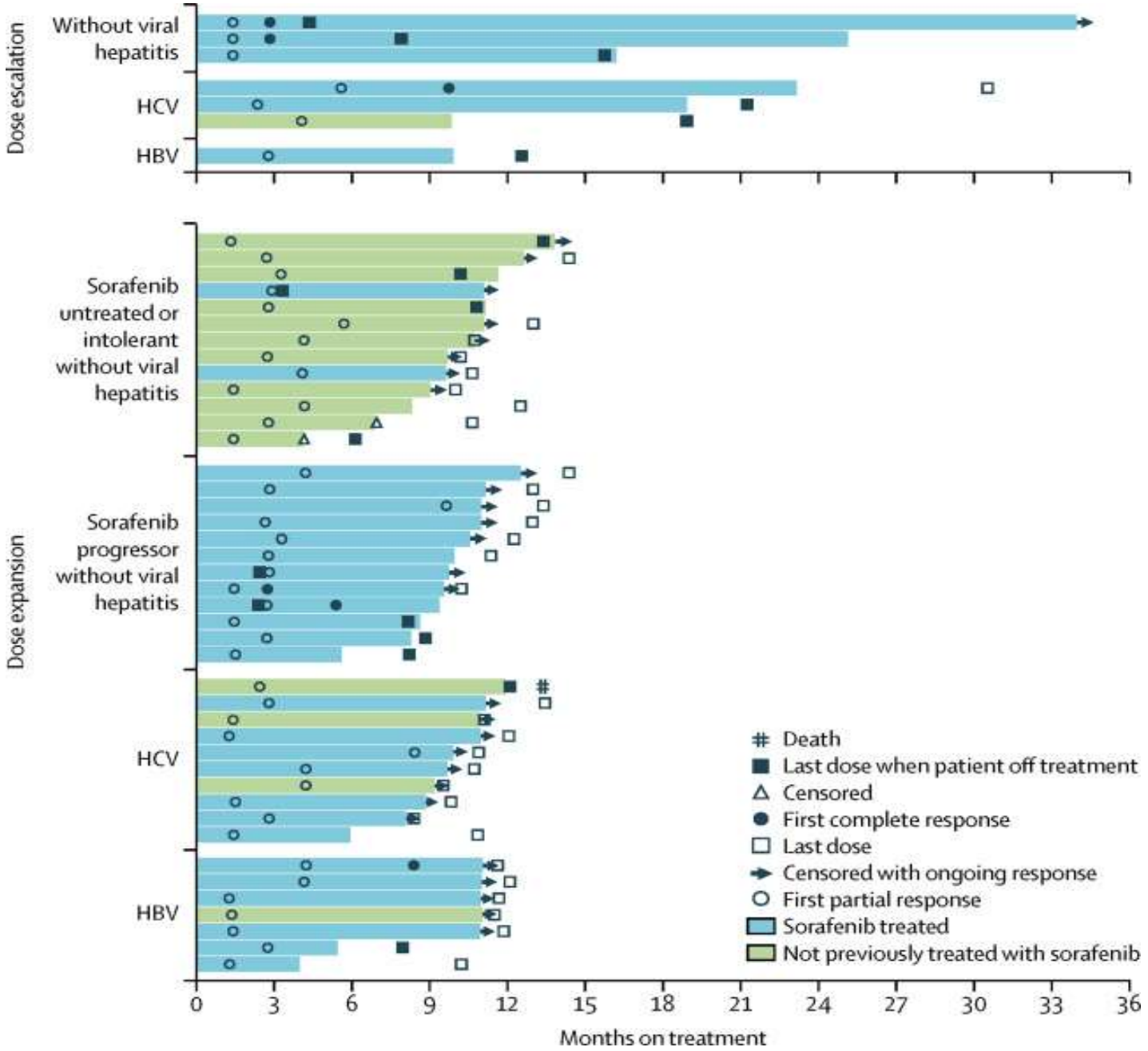
Sangro et al, J Hepatology 2013

NIVOLUMAB IN HEPATOCELLULAR CANCER

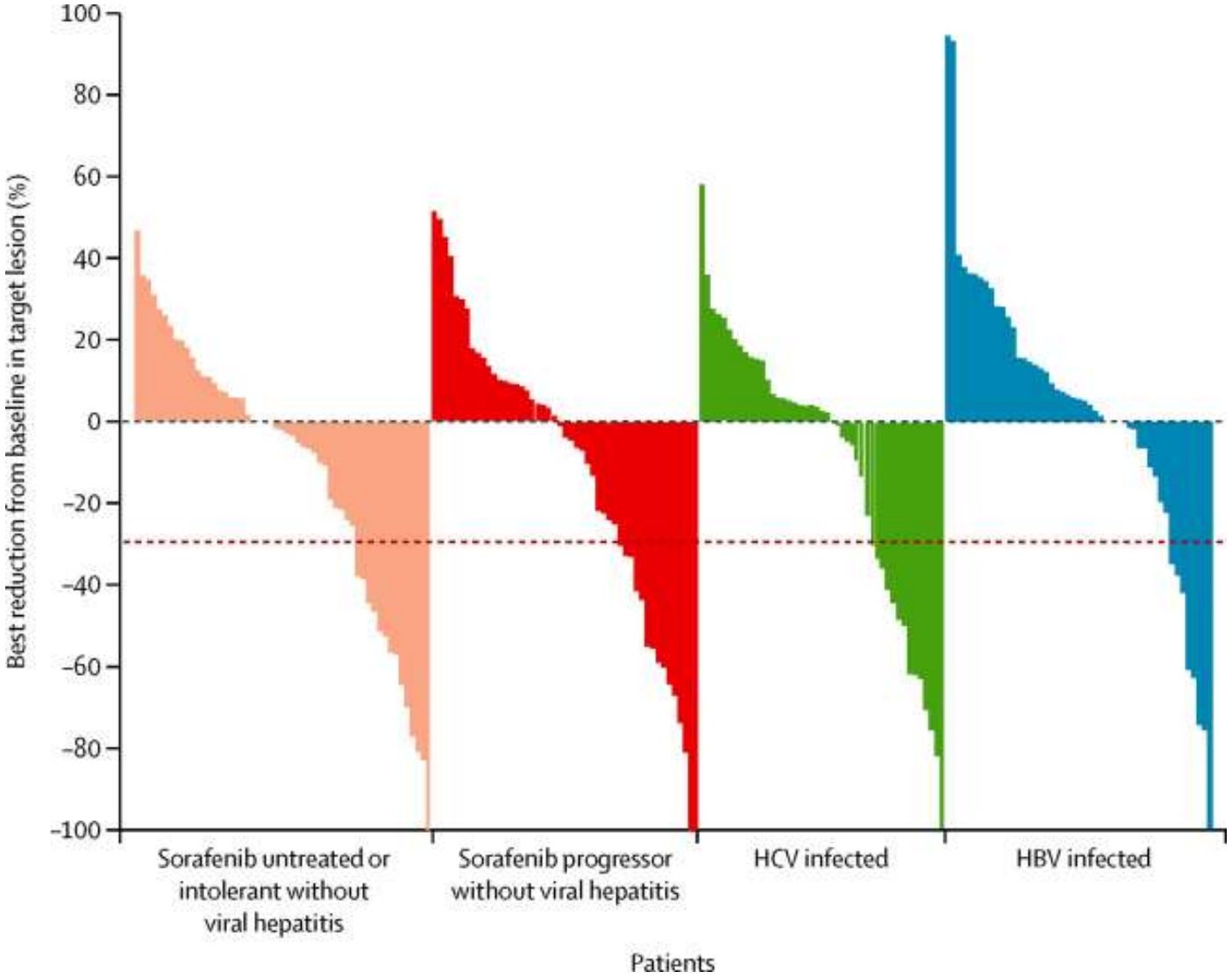


El-Khoueiry et al, Lancet 2017

NIVOLUMAB IN HEPATOCELLULAR CANCER



NIVOLUMAB IN HEPATOCELLULAR CANCER



El-Khoueiry et al, Lancet 2017

NIVOLUMAB IN HEPATOCELLULAR CANCER

	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

El-Khoueiry et al, Lancet 2017

NIVOLUMAB IN HEPATOCELLULAR CANCER

	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 patients (n=48)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related serious AEs	1 (17%)*	1 (17%)*	1 (11%)†	1 (11%)†	0	0	0	0	1 (8%)‡	0	3 (6%)	2 (4%)
AEs leading to discontinuation	0	0	1 (11%)§	1 (11%)§	0	0	1 (10%)¶	1 (10%)¶	1 (8%)‖	1 (8%)‖	3 (6%)	3 (6%)
Treatment-related deaths	0	0	0	0	0	0	0	0	0	0	0	0
Patients with a treatment-related AE	4 (67%)	2 (33%)	8 (89%)	3 (33%)	8 (80%)	5 (50%)	9 (90%)	2 (20%)	11 (85%)	0	40 (83%)	12 (25%)
Treatment-related AEs**												
Rash	1 (17%)	0	2 (22%)	0	2 (20%)	0	2 (20%)	0	4 (31%)	0	11 (23%)	0
Pruritus	2 (33%)	0	3 (33%)	0	0	0	1 (10%)	0	3 (23%)	0	9 (19%)	0
Diarrhoea	0	0	3 (33%)	0	0	0	1 (10%)	0	1 (8%)	0	5 (10%)	0
Decreased appetite	1 (17%)	0	2 (22%)	0	1 (10%)	0	0	0	1 (8%)	0	5 (10%)	0
Fatigue	1 (17%)	1 (17%)	2 (22%)	0	1 (10%)	0	0	0	0	0	4 (8%)	1 (2%)
Asthenia	0	0	1 (11%)	0	0	0	1 (10%)	0	1 (8%)	0	3 (6%)	0
Weight decreased	0	0	1 (11%)	0	0	0	0	0	2 (15%)	0	3 (6%)	0
Nausea	0	0	1 (11%)	0	0	0	1 (10%)	0	1 (8%)	0	3 (6%)	0
Dry mouth	0	0	1 (11%)	0	1 (10%)	0	0	0	1 (8%)	0	3 (6%)	0
Laboratory treatment-related AEs**												
AST increase	0	0	2 (22%)	2 (22%)	3 (30%)	2 (20%)	1 (10%)	1 (10%)	4 (31%)	0	10 (21%)	5 (10%)
ALT increase	0	0	2 (22%)	2 (22%)	1 (10%)	0	2 (20%)	1 (10%)	2 (15%)	0	7 (15%)	3 (6%)
Lipase increase	1 (17%)	1 (17%)	1 (11%)	0	4 (40%)	4 (40%)	2 (20%)	1 (10%)	2 (15%)	0	10 (21%)	6 (13%)
Amylase increase	1 (17%)	0	0	0	4 (40%)	1 (10%)	2 (20%)	1 (10%)	2 (15%)	0	9 (19%)	2 (4%)
Anaemia	0	0	1 (11%)	0	1 (10%)	1 (10%)	0	0	2 (15%)	0	4 (8%)	1 (2%)
Hypoalbuminaemia	0	0	1 (11%)	0	1 (10%)	0	0	0	1 (8%)	0	3 (6%)	0
Hyponatraemia	0	0	0	0	2 (20%)	0	0	0	1 (8%)	0	3 (6%)	0

Data are n (%). AE=adverse event. AST=aspartate aminotransferase. ALT=alanine aminotransferase. *Pemphigoid (n=1). †Adrenal insufficiency (n=1). ‡Liver disorder (n=1). §Malignant neoplasm progression (n=1). ¶Grade 3 ALT increase (n=1), grade 2 AST increase. ‖Grade 3 blood bilirubin increase (n=1). **Treatment-related AEs reported in ≥5% of all patients, any grade.

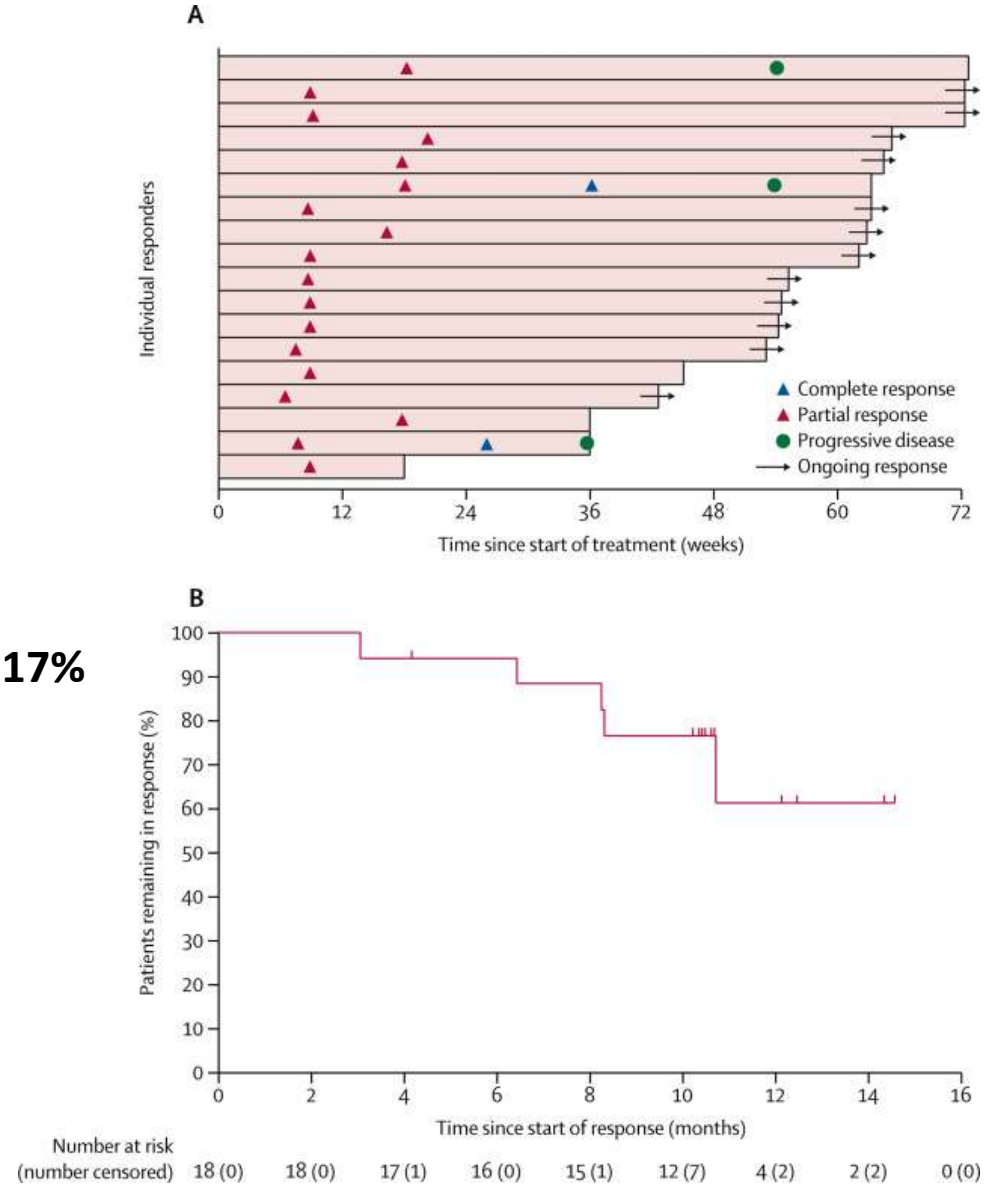
Table 3: Safety and tolerability of nivolumab in the dose-escalation phase

PEMBROLIZUMAB IN HCC

N =104

RESPONSE RATE = 17%

200 MG IV Q3W

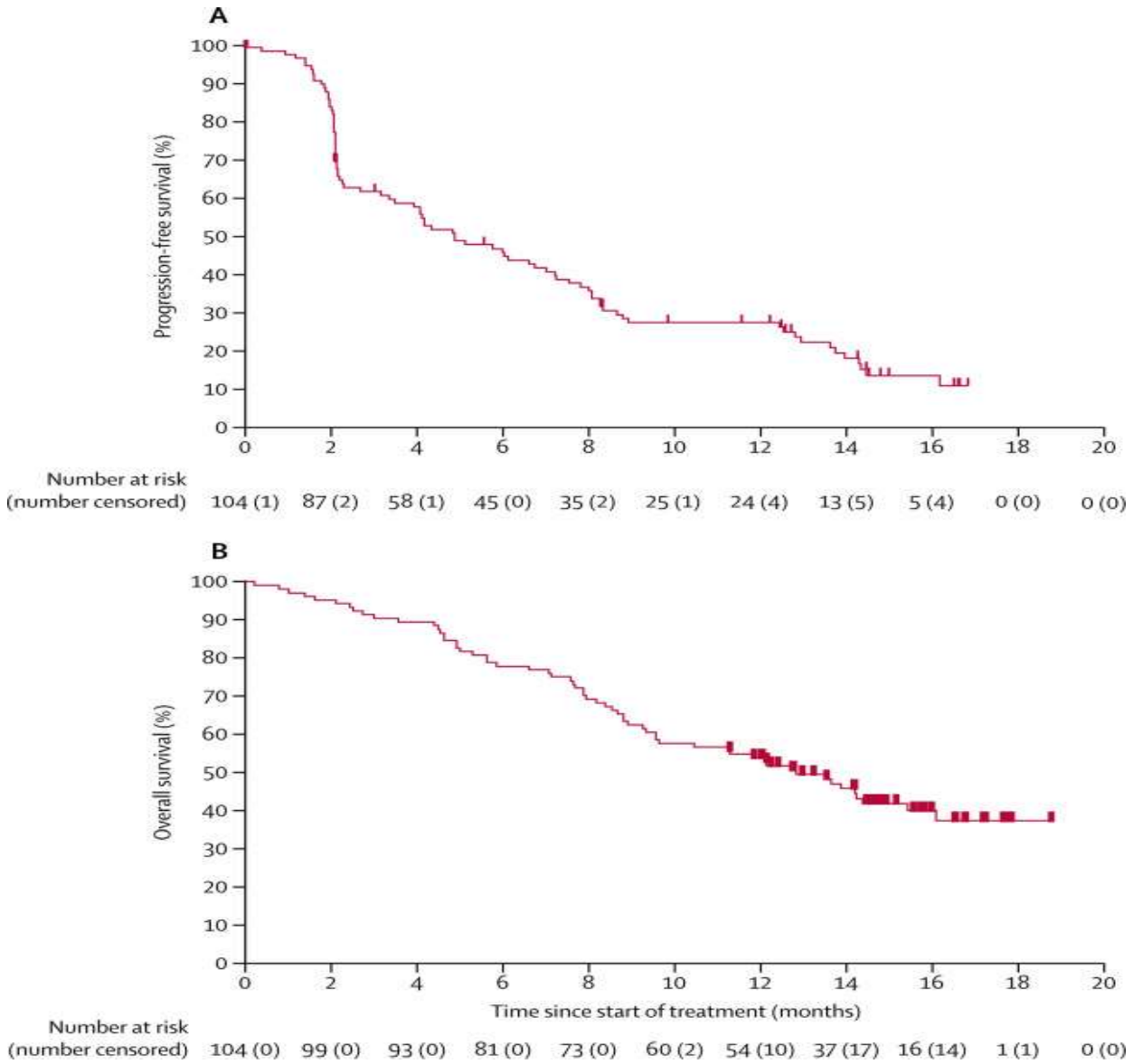


Zhu et al, Lancet Onc 2018

PEMBROLIZUMAB IN HCC

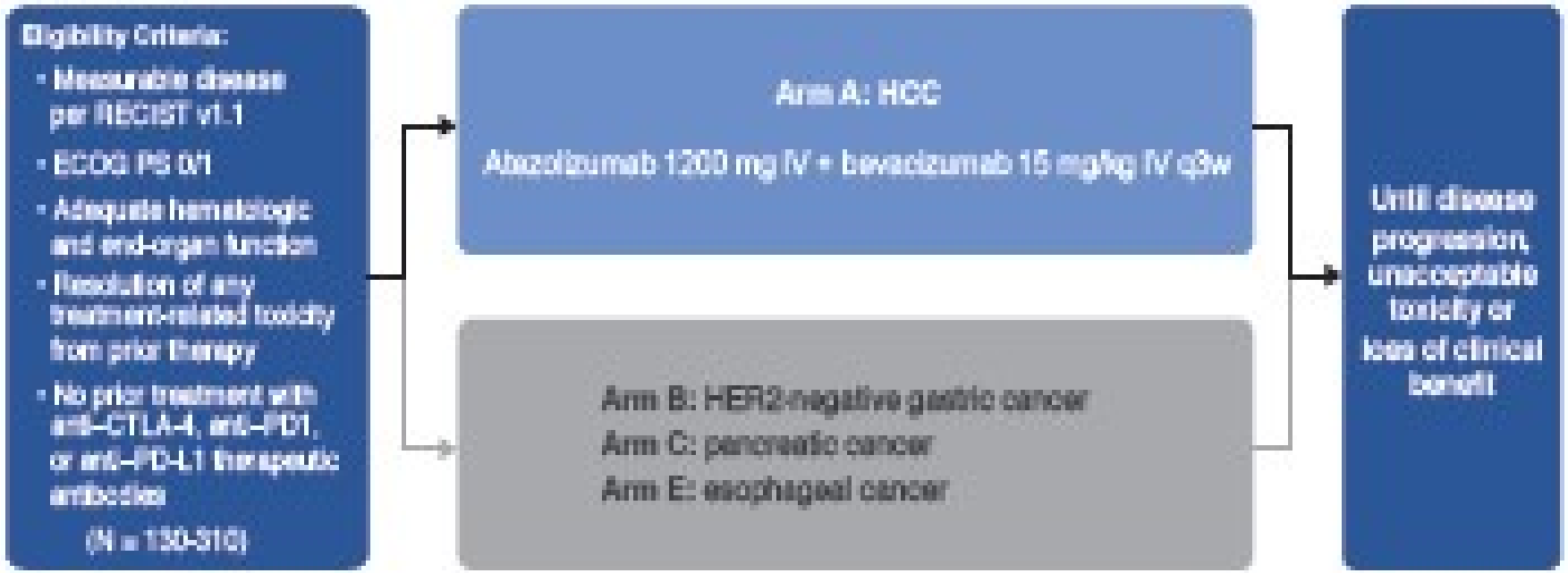
PFS =4.9 MTHS

OS = 12.9 MTHS



Zhu et al, Lancet Onc 2018

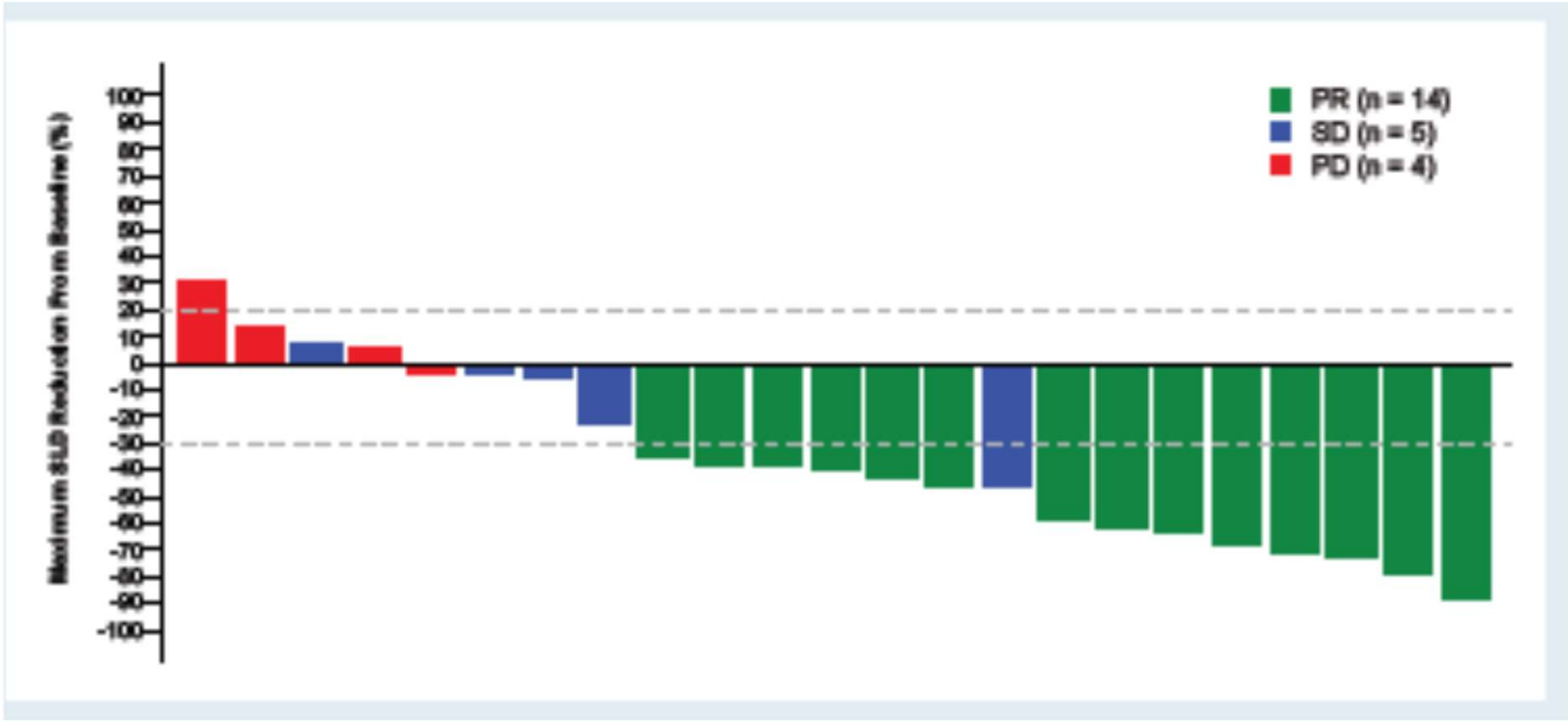
ATEZOLIZUMAB + BEVACIZUMAB IN HCC



Stein et al, ASCO 2018

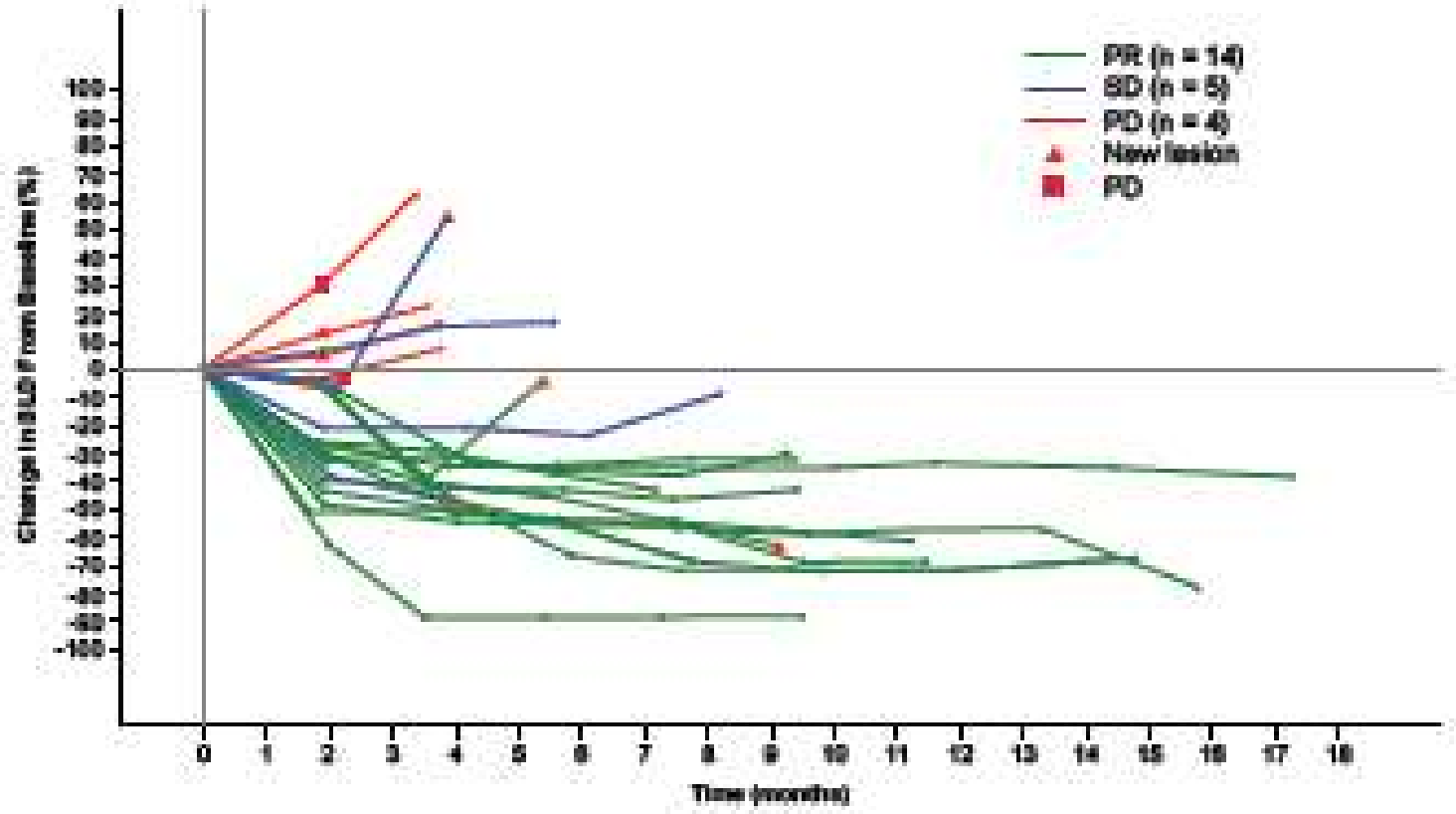
ATEZOLIZUMAB + BEVACIZUMAB IN HCC

UPDATED RESPONSE RATE 32%, PFS = 14.9 MONTHS



Stein et al, ASCO 2018

ATEZOLIZUMAB + BEVACIZUMAB IN HCC



Stein et al, ASCO 2018

ATEZOLIZUMAB + BEVACIZUMAB IN HCC

Table 3. Common Adverse Events	
All-Cause AEs, Any Grade (≥ 20% of patients), n (%)	**Safety-Evaluable Population (N = 43)**
Decreased appetite	14 (33%)
Fatigue	13 (30%)
Rash	12 (28%)
Proteinuria	11 (26%)
Abdominal pain	11 (26%)
Diarrhea	10 (23%)
Hypertension	9 (21%)
Treatment-Related AEs, Grade 3-4 (≥ 5% of patients), n	
Hypertension	7 (16%)

Stein et al, ASCO 2018

OTHER CHECKPOINT + ANTI-ANGIOGENIC COMBOS

LENVATINIB + PEMBROLIZUMAB
(CLINICALTRIALS.GOV: NCT03006926)

CABOZANTINIB + ATEZOLIZUMAB
(CLINICALTRIALS.GOV: NCT03755791)

SORAFENIB + NIVOLUMAB
(CLINICALTRIALS.GOV: NCT03439891)

BEVACIZUMAB + NIVOLUMAB
(CLINICALTRIALS.GOV: NCT03382886)

REGORAFENIB + PEMBROLIZUMAB
(CLINICALTRIALS.GOV: NCT03347292)

CONCLUSIONS

1. ANTI-PD-1/PD-L1 AND ANTI-CTLA-4 ANTIBODIES HAVE EXHIBITED PROMISING ACTIVITY IN EARLY TRIALS IN ADVANCED HCC PATIENTS

2. COMBINATION VEGF/VEGFR + PD-1/PD-L1 WILL FORM THE BASIS FOR MANY FUTURE INITIATIVES

CANCERS OF THE BILIARY TRACT

- **Cholangiocarcinoma Incidence 1-2/100,000 in the United States**

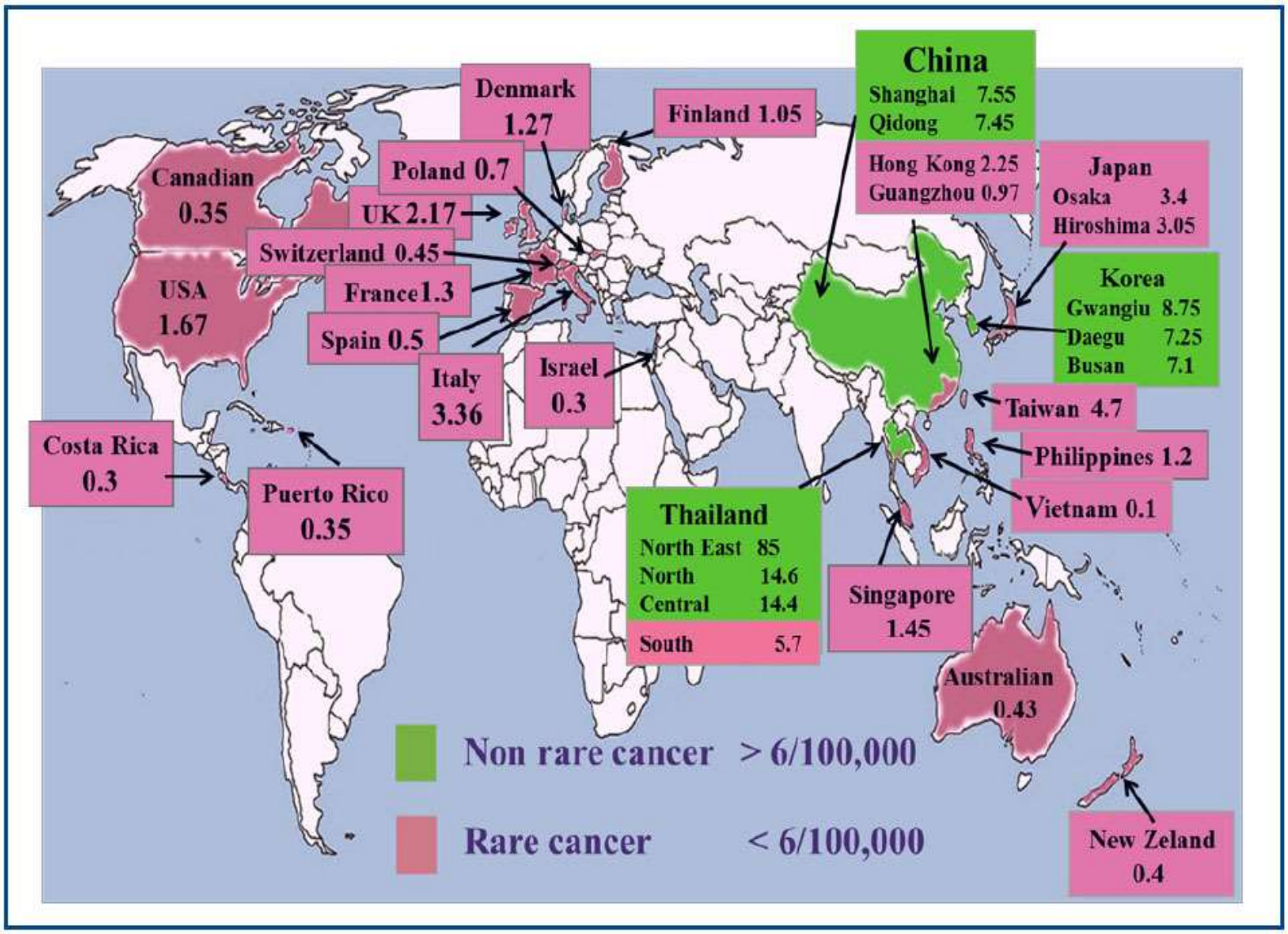
- **Gallbladder Cancer Incidence 1-2/100,000 in the United States**

- **Risk factors :**
  - **PSC/UC**
  - **NASH/NAFLD**
  - **Hepatitis B/C**
  - **Biliary Stones/Gallstones**
  - **Thorotrast Exposure**
  - **Salmonella infections**
  - ***O. viverrini* and *C. sinensis* (Liver Flukes)**

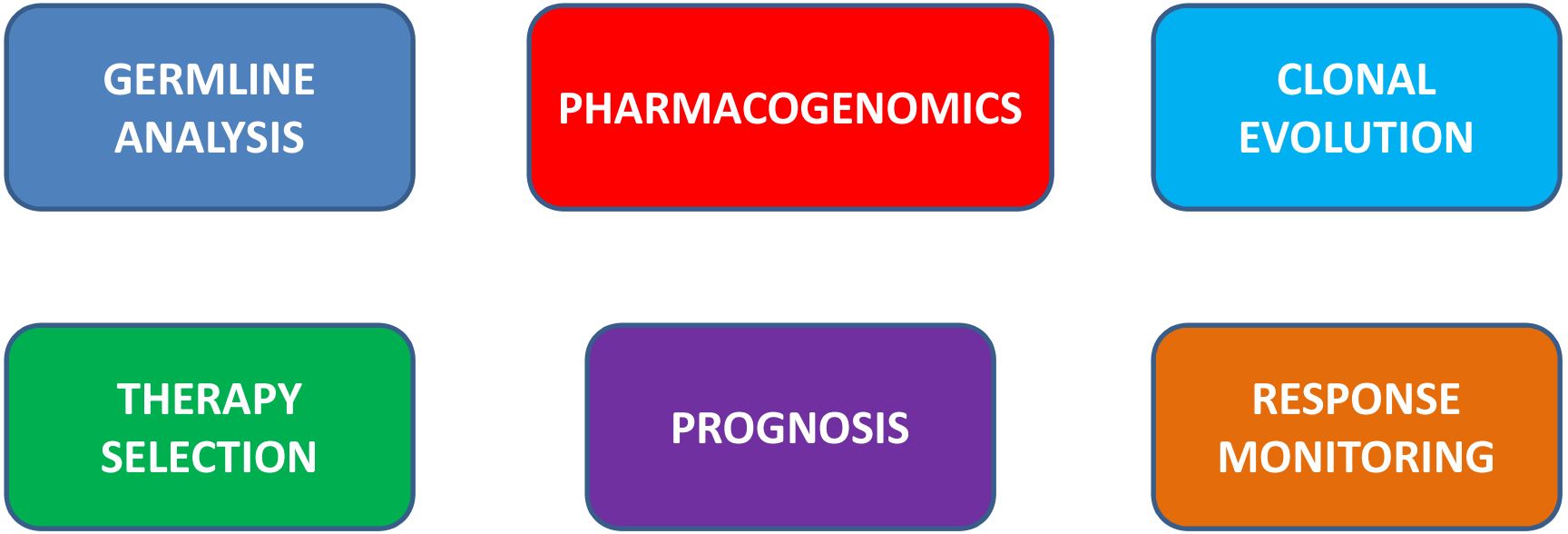
CANCERS OF THE BILIARY TRACT

- **Median Age 60s**
  (Rising Incidence in Younger Patients ?)
- **Incidence similar in men and women**
- **Higher incidence in Native Americans and Eskimos**
- **High mortality**

GLOBAL DISTRIBUTION OF CHOLANGIOCARCINOMA



PRECISION MEDICINE
APPLICATIONS OF GENOMIC PROFILING

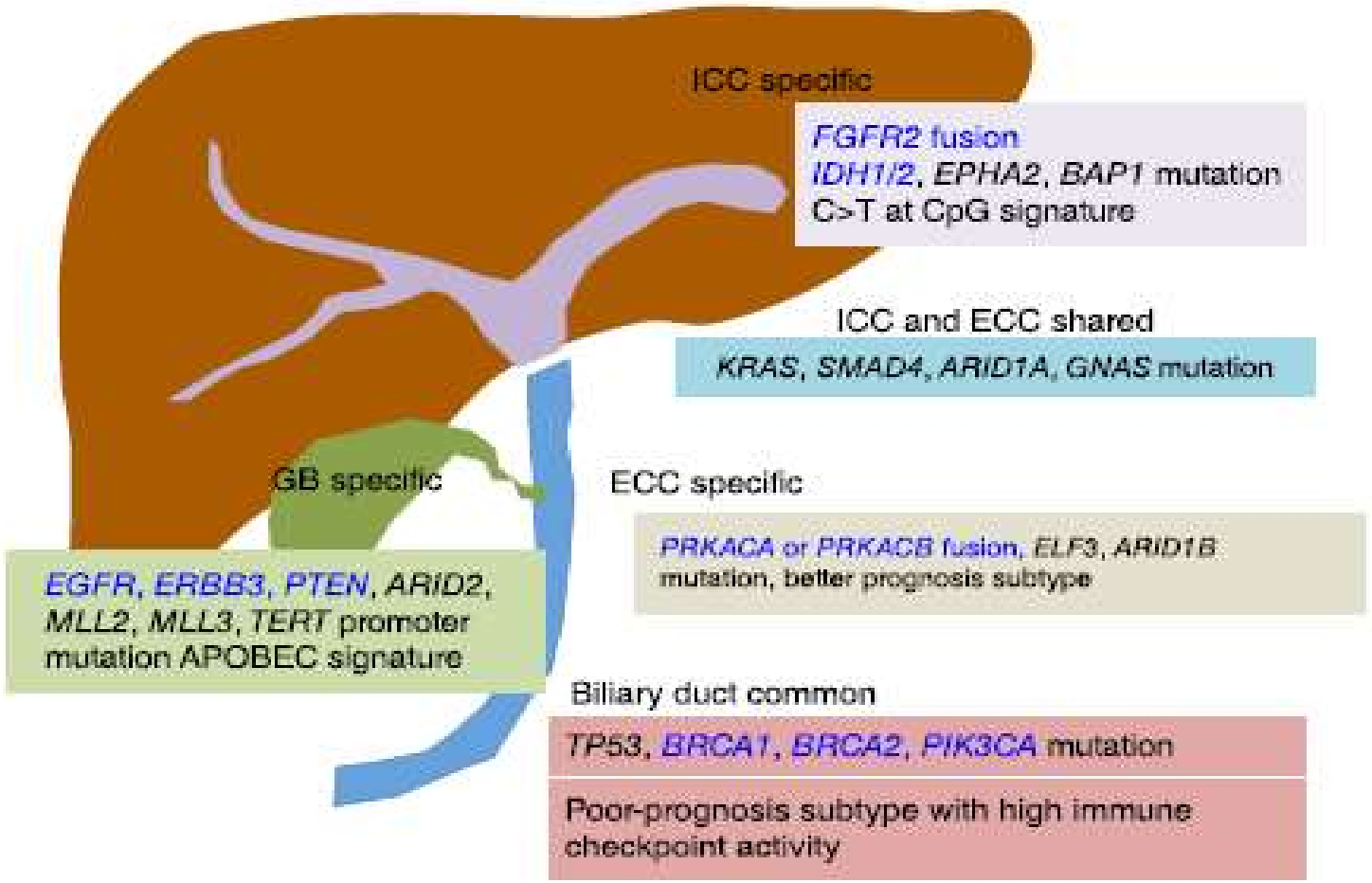


nature genetics

Genomic spectra of biliary tract cancer

Hiromi Nakamura[1,9], Yasuhito Arai[1,9], Yasushi Totoki[1,9], Tomoki Shirota[1,2,9], Asmaa Elzawahry[1,9], Mamoru Kato[3], Natsuko Hama[1], Fumie Hosoda[1], Tomoko Urushidate[4], Shoko Ohashi[1], Nobuyoshi Hiraoka[5], Hidenori Ojima[5,6], Kazuaki Shimada[7], Takuji Okusaka[8], Tomoo Kosuge[7], Shinichi Miyagawa[2] & Tatsuhiro Shibata[1,4]

GENOMIC DIVERSITY BY LOCATION IN BILIARY TRACT

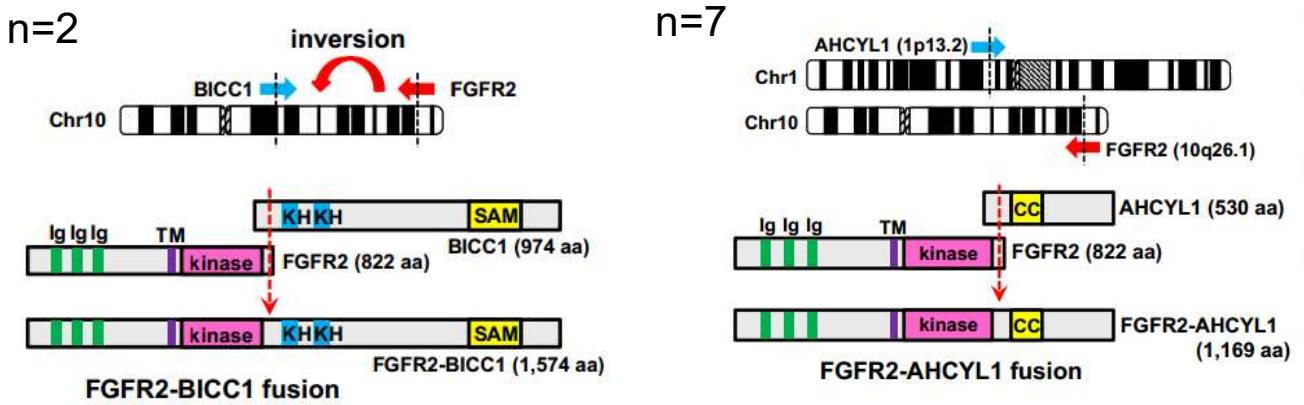


Nakamura et al, Nature Genetics 2015

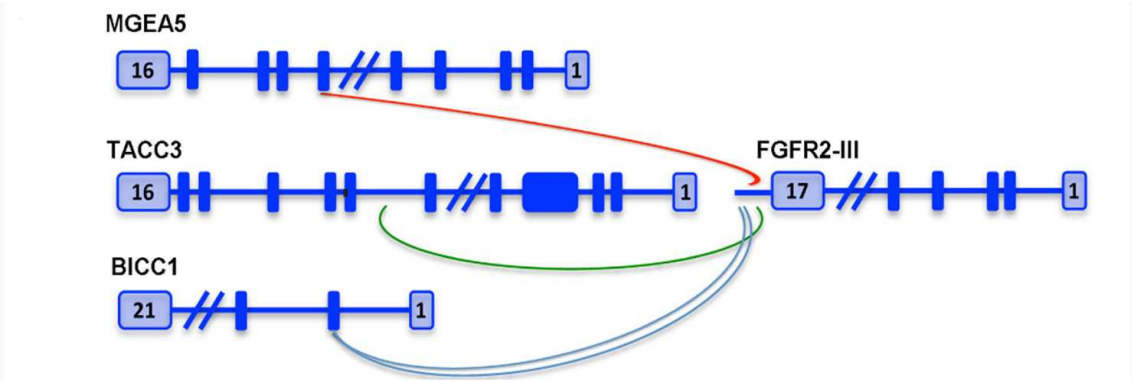
FGFR2 Gene Fusions Cholangiocarcinoma

Wu et al, 2013

Arai et al, 2013



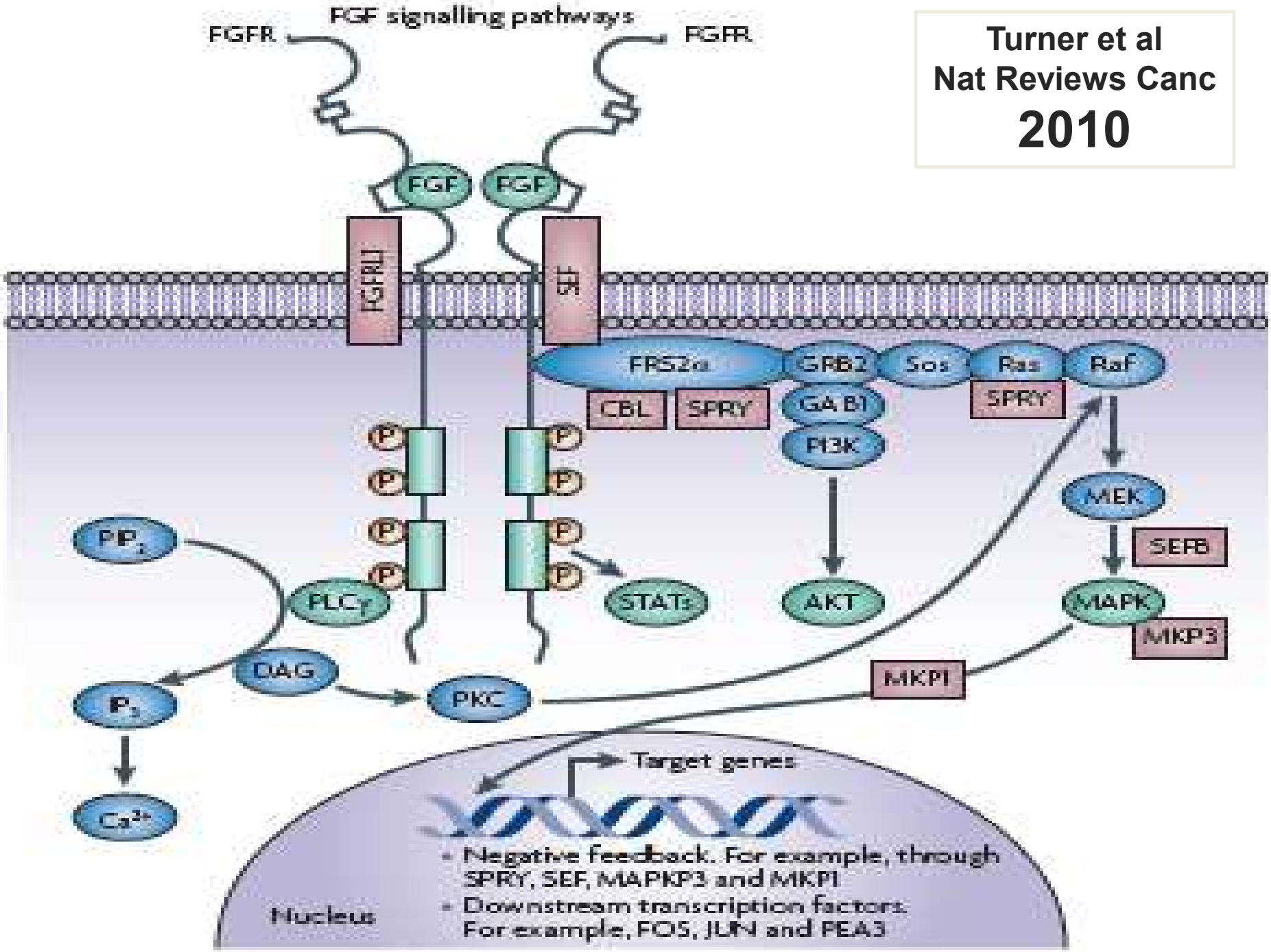
Borad et al, 2014



PREVALENCE OF FGFR2 FUSIONS IN CHOLANGIOCARCINOMA

ARAI ET AL	13.6%	N=66
GRAHAM ET AL	13%	N=96

Turner et al
Nat Reviews Canc
2010



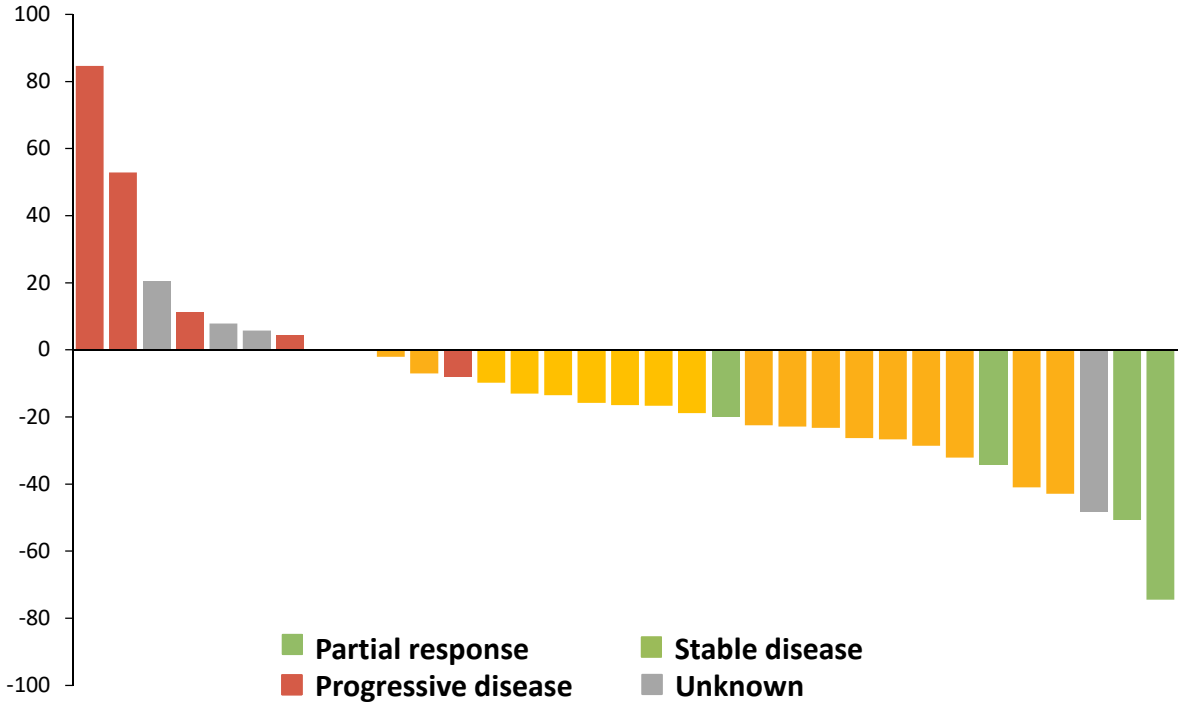
A Phase 2 Study of BGJ398 in Patients With Advanced or Metastatic FGFR-Altered Cholangiocarcinoma Who Failed or are Intolerant to Platinum-Based Chemotherapy

Milind Javle,[1] Rachna T. Shroff,[1] Andrew X. Zhu,[2] Saeed Sadeghi,[3] SuPin Choo,[4] Mitesh J. Borad,[5] Maeve Lowery,[6] Anthony B. El-Khoueiry,[7] Teresa Macarulla,[8] Philip A. Philip,[9] Do-Youn Oh,[10] Eric Van Cutsem,[11] Kun-Huei Yeh,[12] Katie Kelley,[13] Randi Isaacs,[14] Carolyn McGarry,[14] Suman K. Sen,[14] Tanios Bekaii-Saab[15]

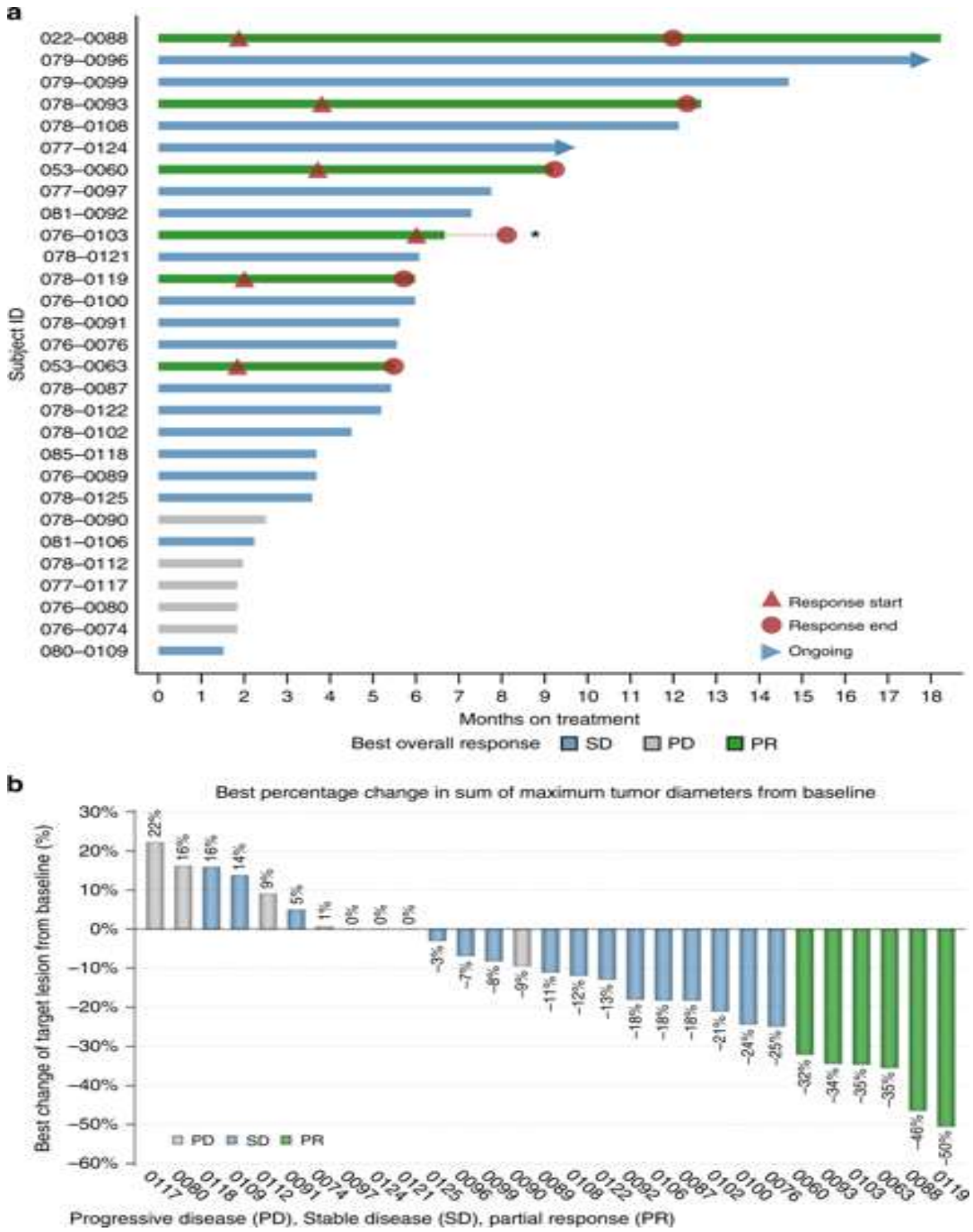
[1] MD Anderson Cancer Center, Houston, TX; [2] Massachusetts General Hospital, Boston, MA; [3] David Geffen School of Medicine at UCLA, Santa Monica, CA; [4] National Cancer Centre Singapore, Singapore; [5] Mayo Clinic, Scottsdale, AZ; [6] Memorial Sloan Kettering Cancer Center, New York, NY; [7] University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [8] Vall d´Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO); [9] Karmanos Cancer Center, Wayne State University, Detroit, MI; [10] Seoul National University Hospital, Seoul, South Korea; [11] University Hospitals Leuven and KULeuven, Leuven, Belgium; [12] National Taiwan University Hospital, Taipei, Taiwan; [13] UCSF Comprehensive Cancer Center, San Francisco, CA; [14] Novartis Pharmaceuticals Corporation, East Hanover, NJ; [15] The Ohio State University James Cancer Hospital, Columbus, OH

PROSPECTIVE TRIAL OF FGFR INHIBITOR IN FGFR2 FUSION+ CCA

Figure 2. Best Percentage Change From Baseline in the Size of Target Lesions With BGJ398 Treatment (n = 33)[a]



RESPONSE RATE: 18.8% **PFS: 5.8 MTH** **DCR: 83.3%**



MAZZAFERO ET AL
BR J CANCER 2018

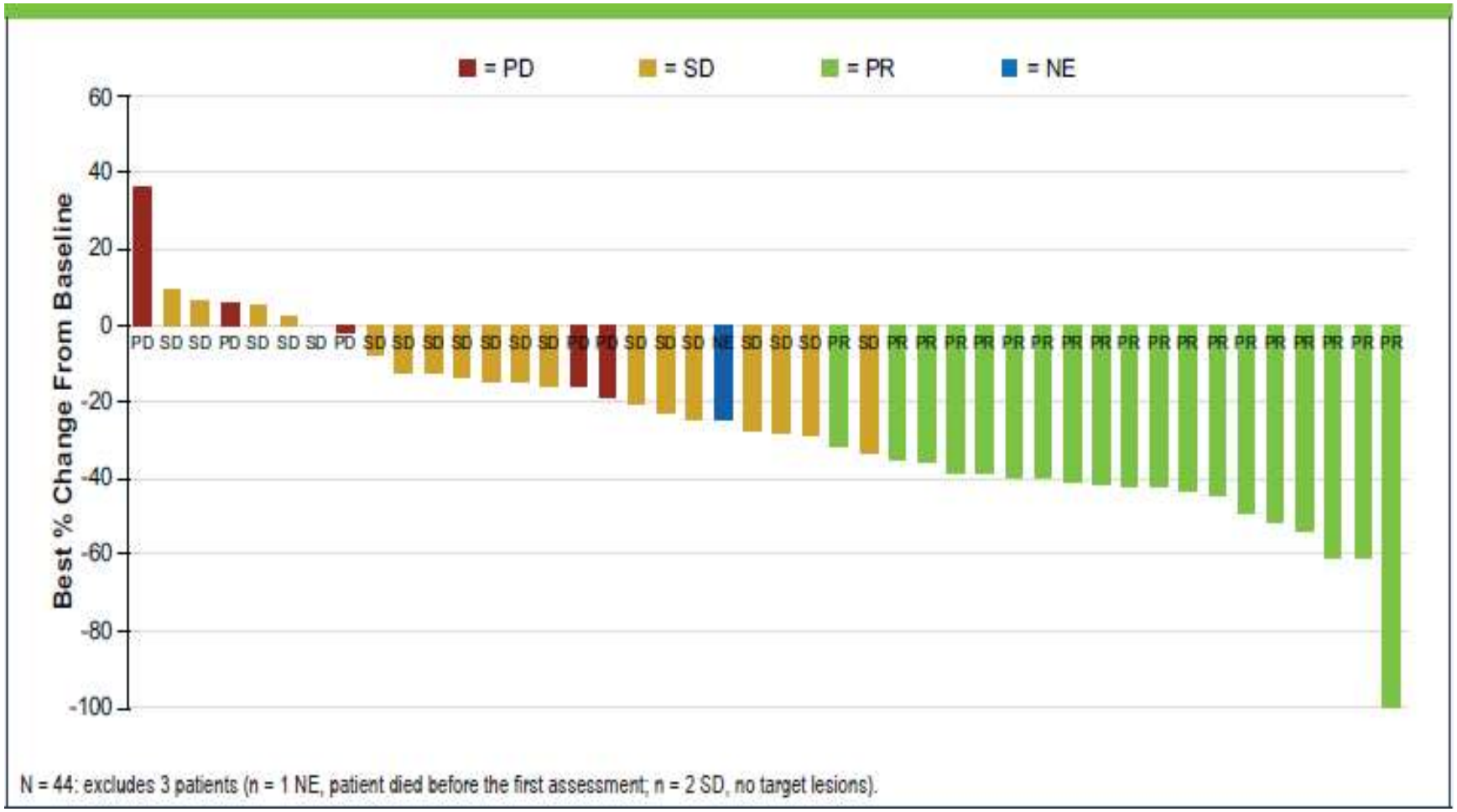
RESPONSE RATE: 20.7%

DCR: 82.8%

PFS: 5.7 MTHS

ARQ-087 (DERAZANTANIB)

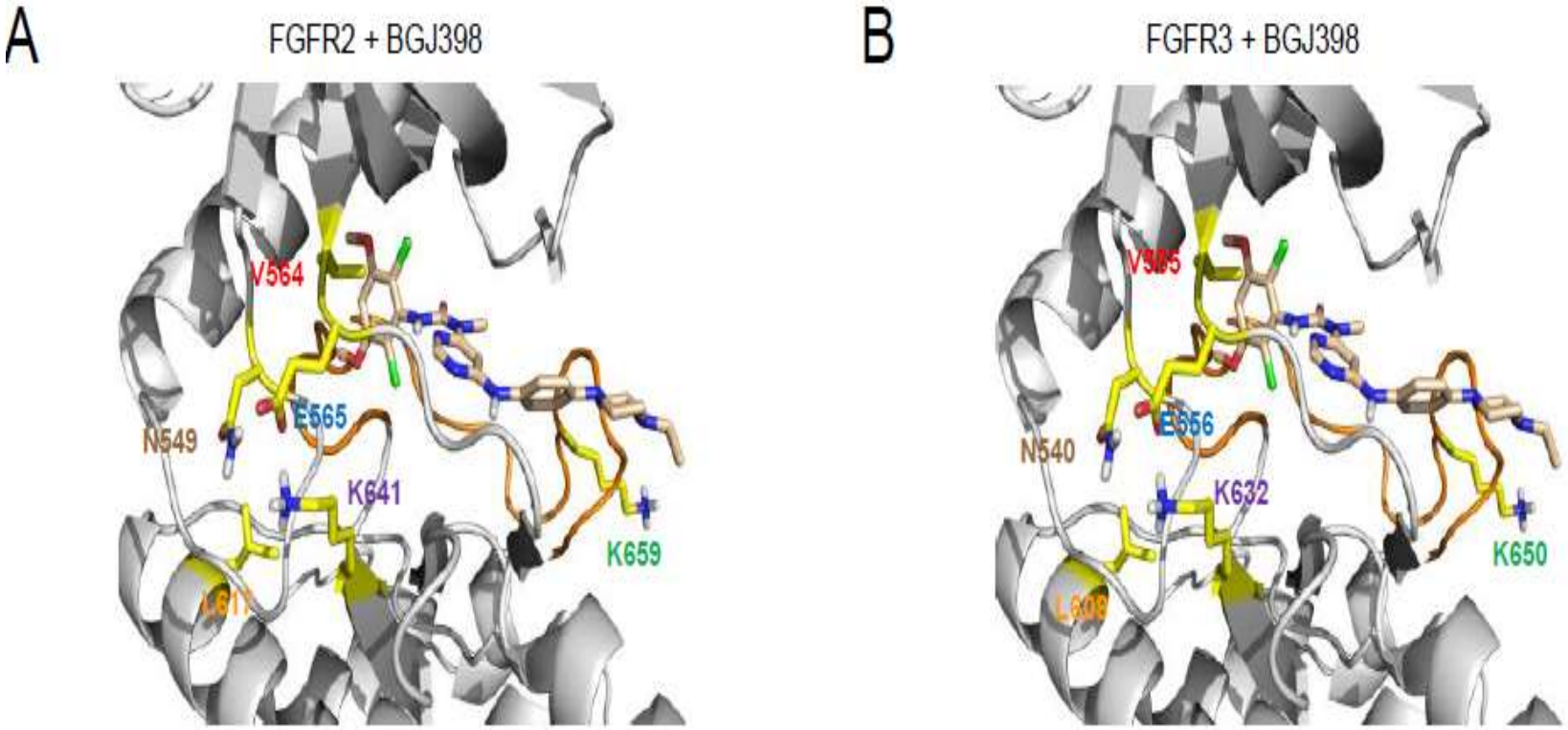
PEMIGATINIB IN FGFR2 FUSION+ CHOLANGIOCARCINOMA



RESPONSE RATE: 40.4% **PFS: 9.2 MTH** **OS: 15.8 MTH**

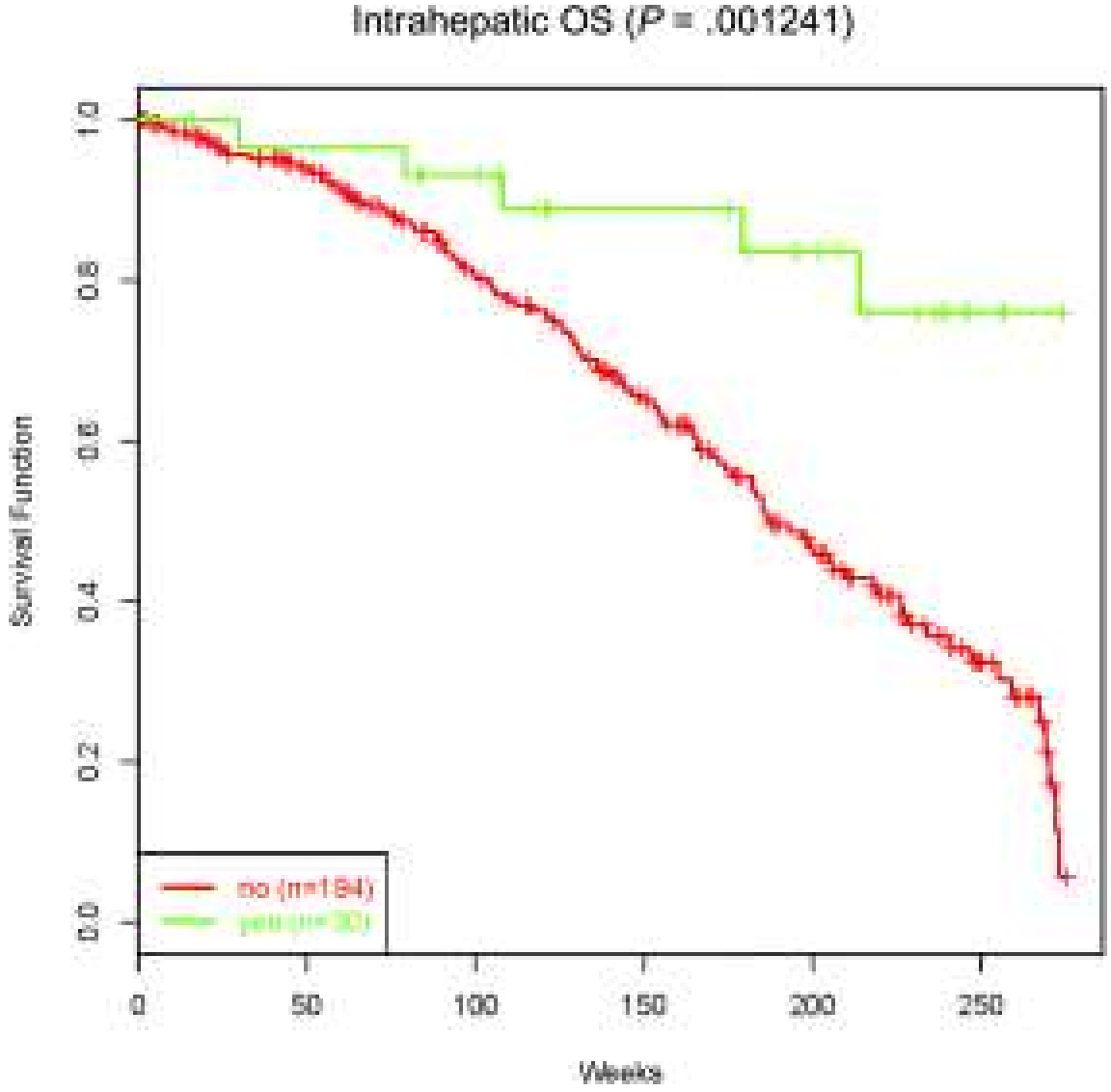
HOLLENBEQUE ET AL, ESMO 2018

MECHANISMS OF RESISTANCE



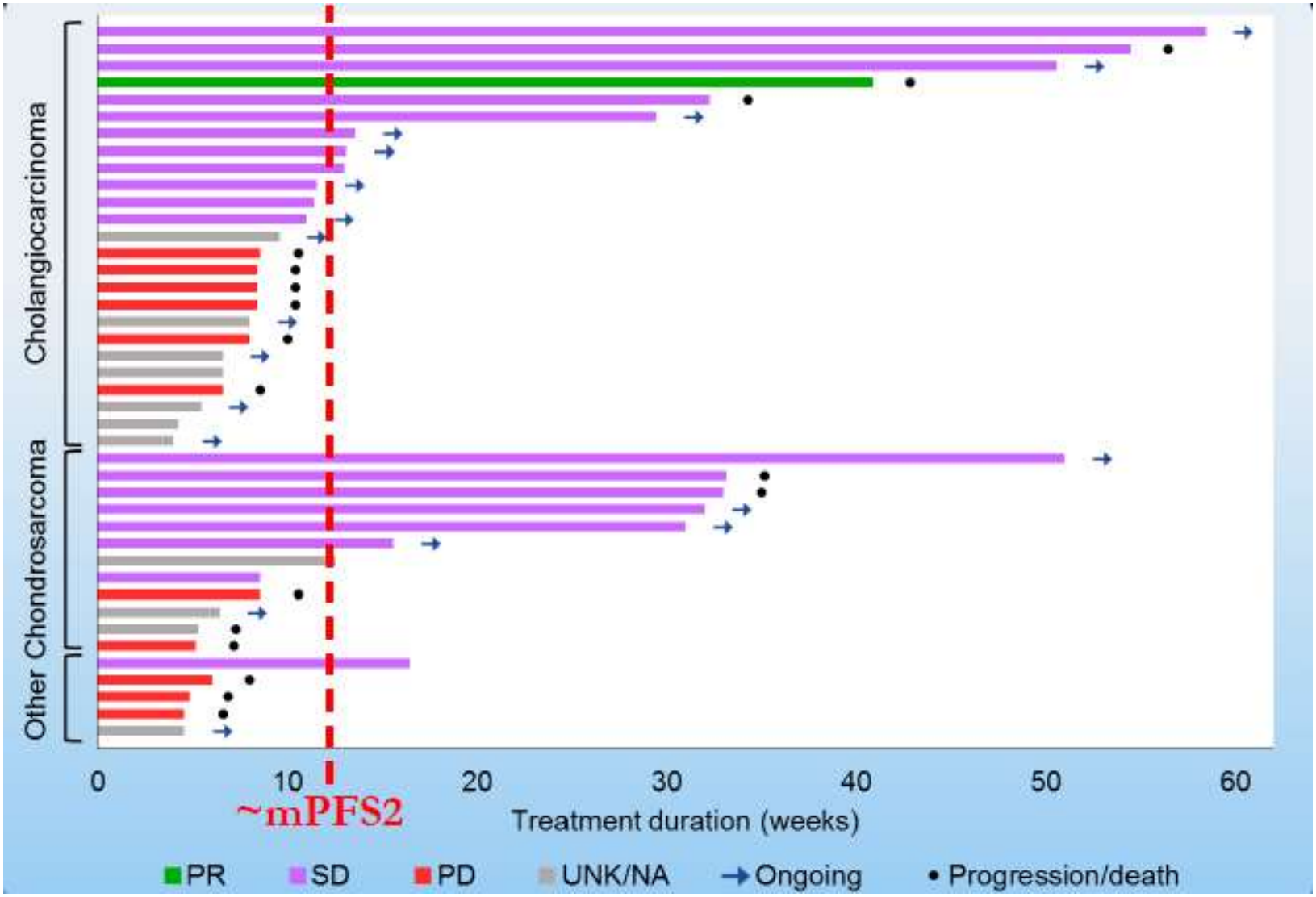
Goyal et al, Cancer Disc 2016

PROGNOSIS OF PATIENTS WITH FGFR2 FUSION+ CHOLANGIOCARCINOMA PATIENTS



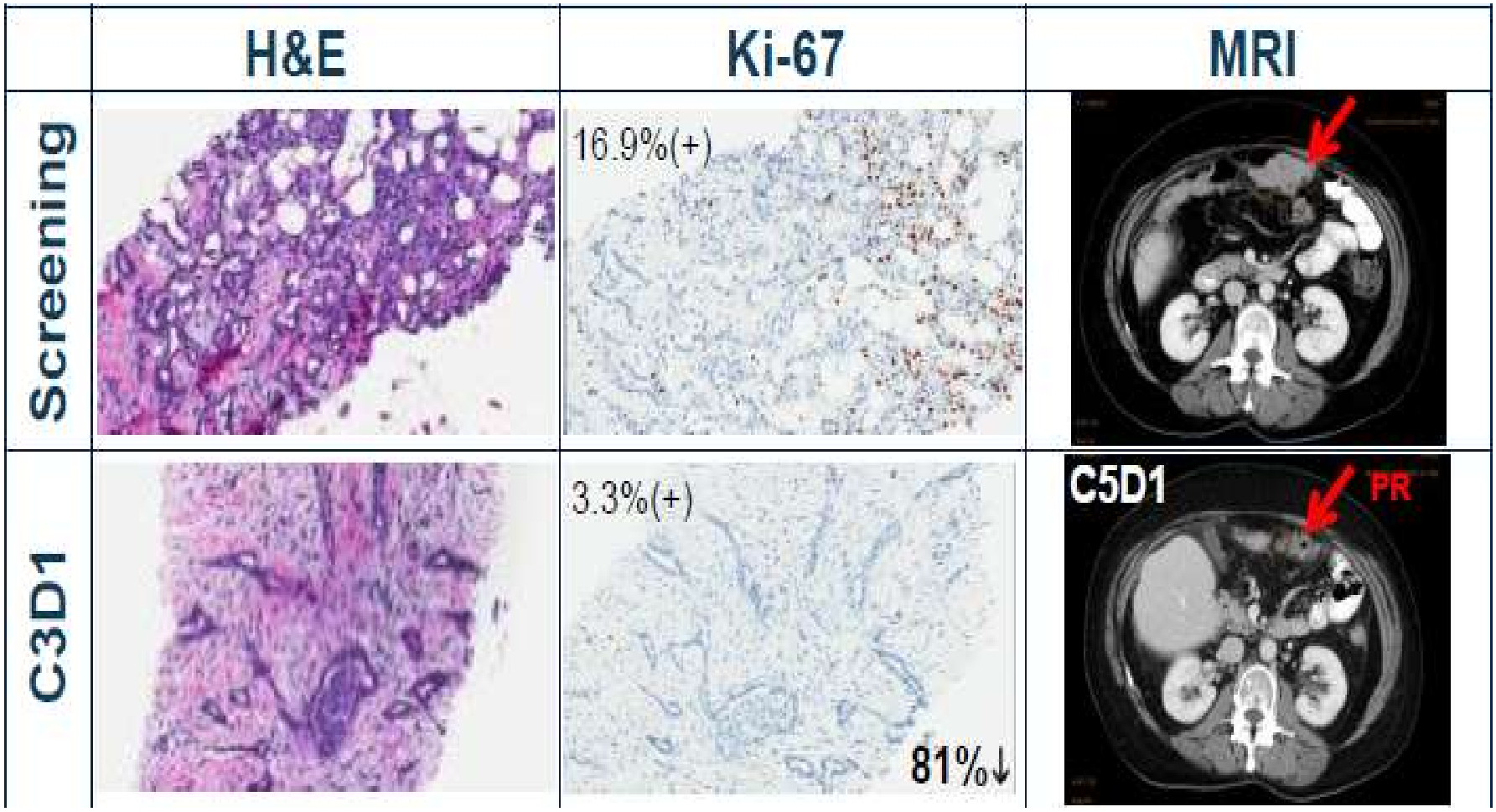
Javle et al, Cancer 2016

IDH1 INHIBITOR AG-120 IN CHOLANGIOCARCINOMA PATIENTS



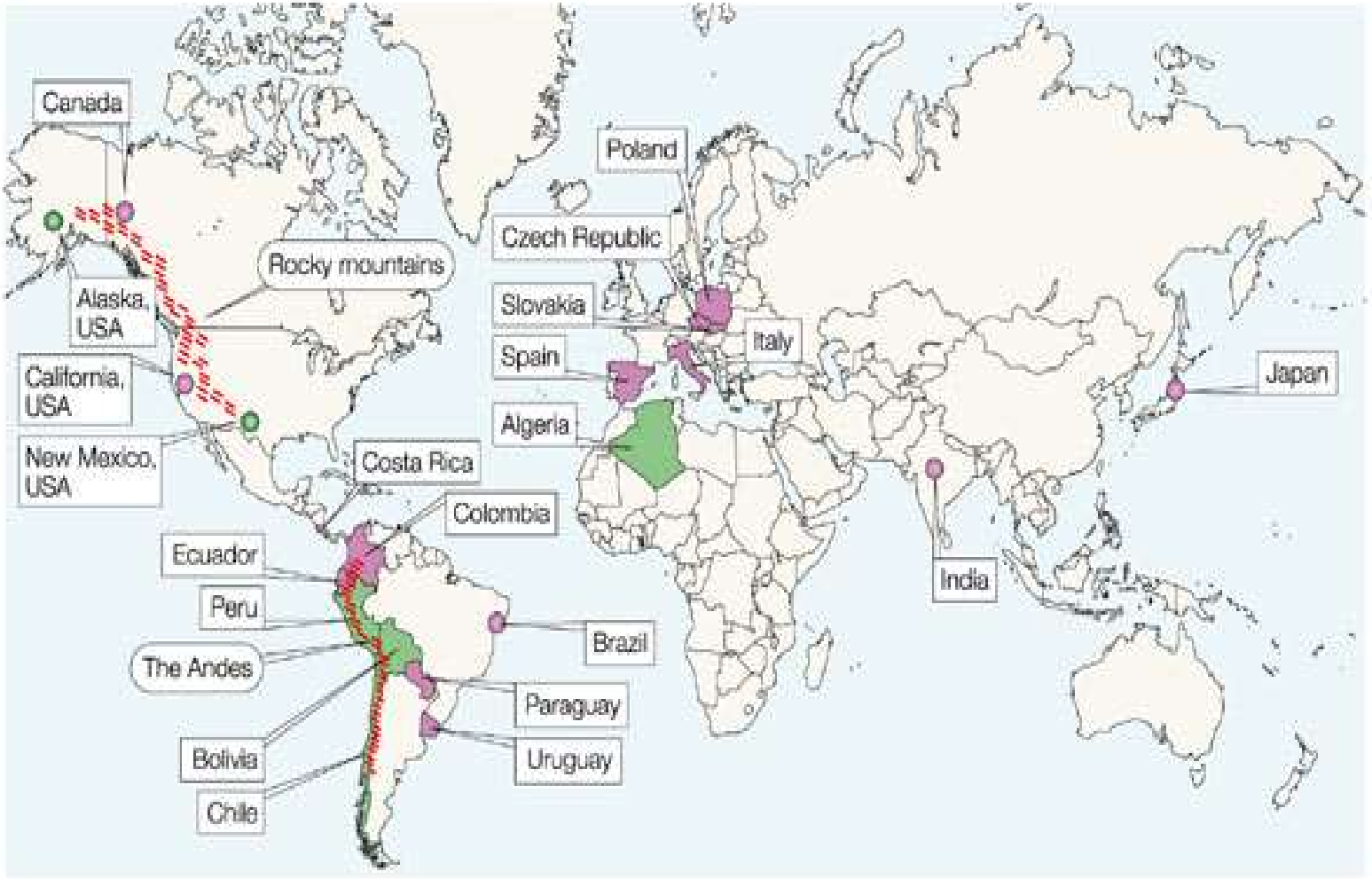
Burris et al, NCI-EORTC-AACR 2015

IDH1 INHIBITOR AG-120 IN CHOLANGIOCARCINOMA PATIENTS



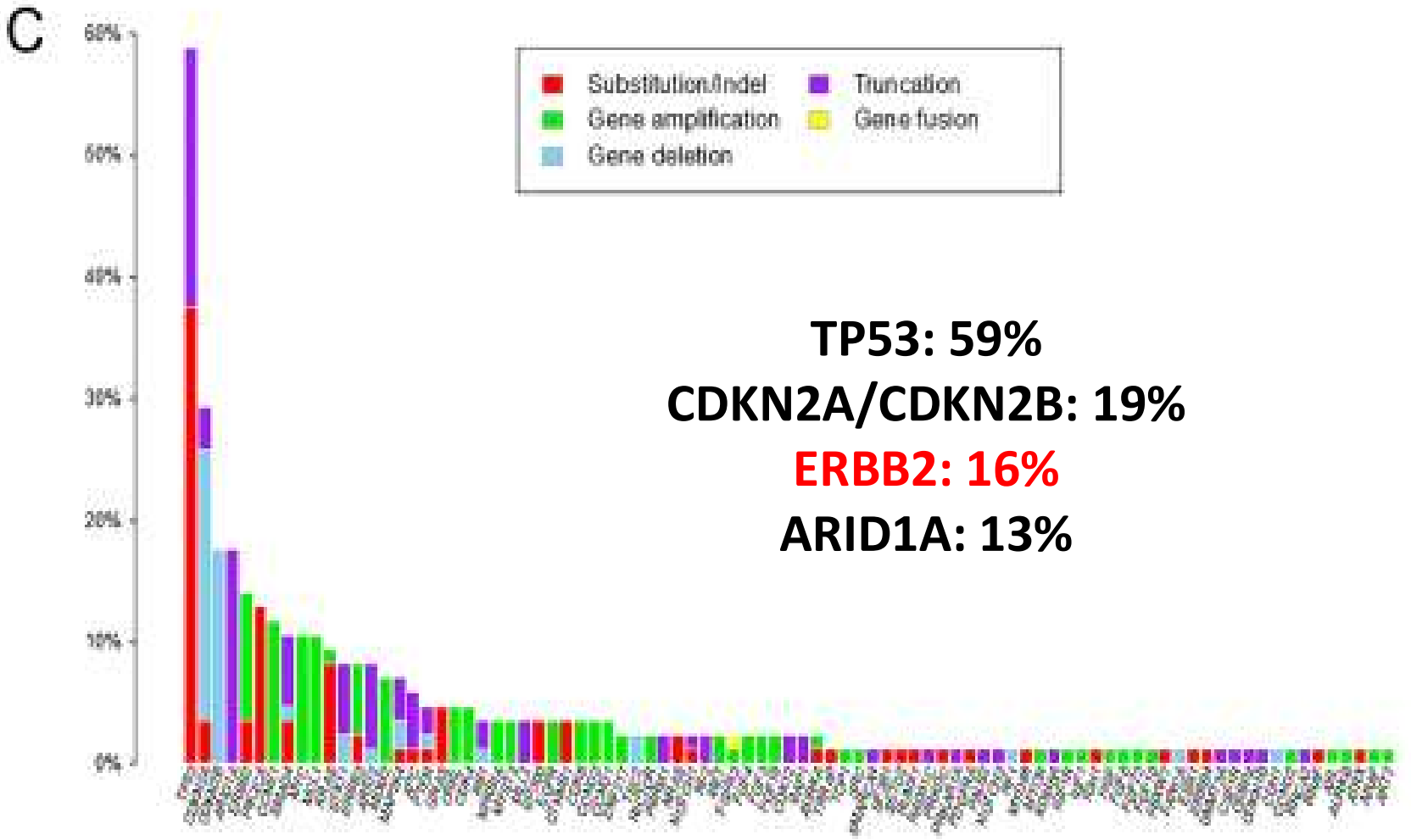
Burris et al, NCI-EORTC-AACR 2015

GLOBAL DISTRIBUTION OF GALLBLADDER CANCER



Nature Reviews | Cancer

DISTRIBUTION OF GENOMIC MARKERS IN GALLBLADDER CANCER



TP53: 59%

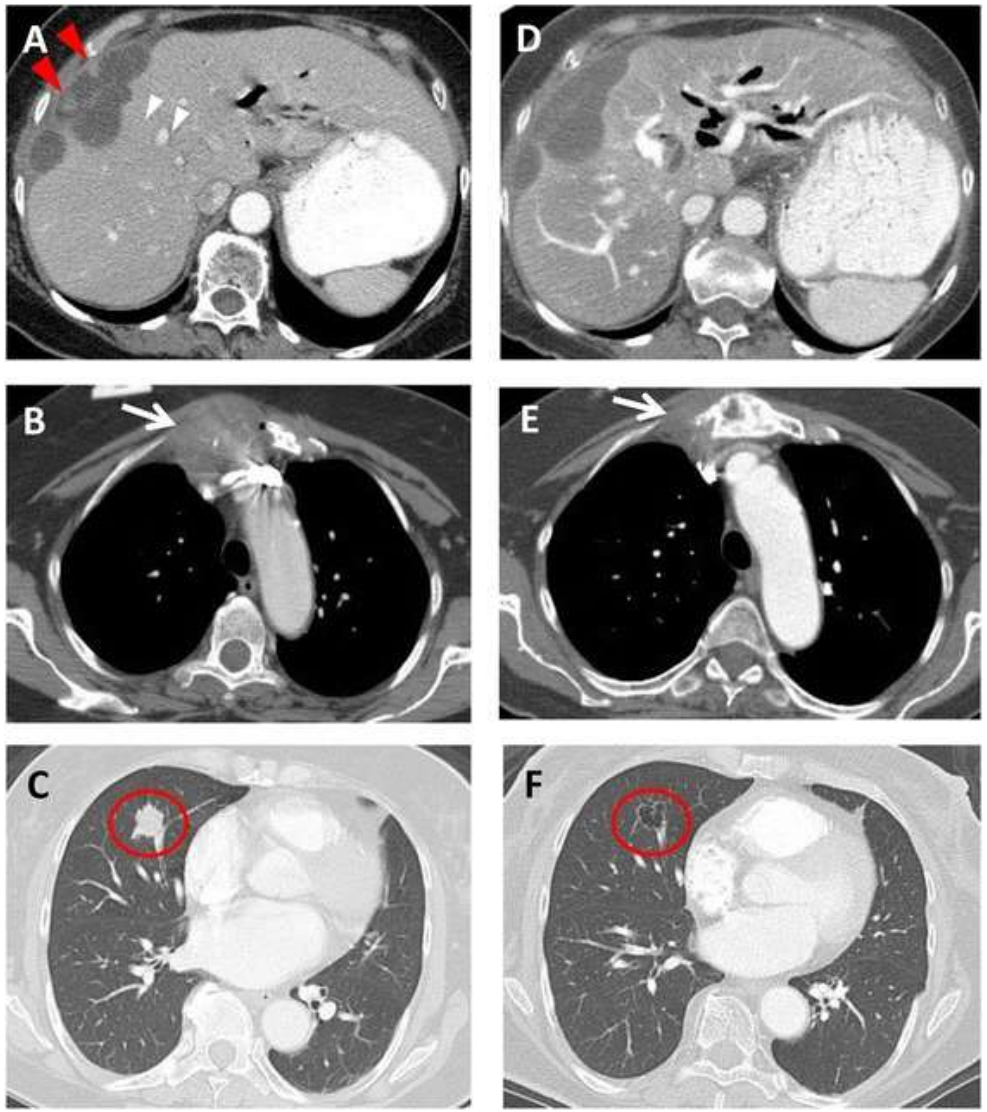
CDKN2A/CDKN2B: 19%

ERBB2: 16%

ARID1A: 13%

Javle et al, Cancer 2016

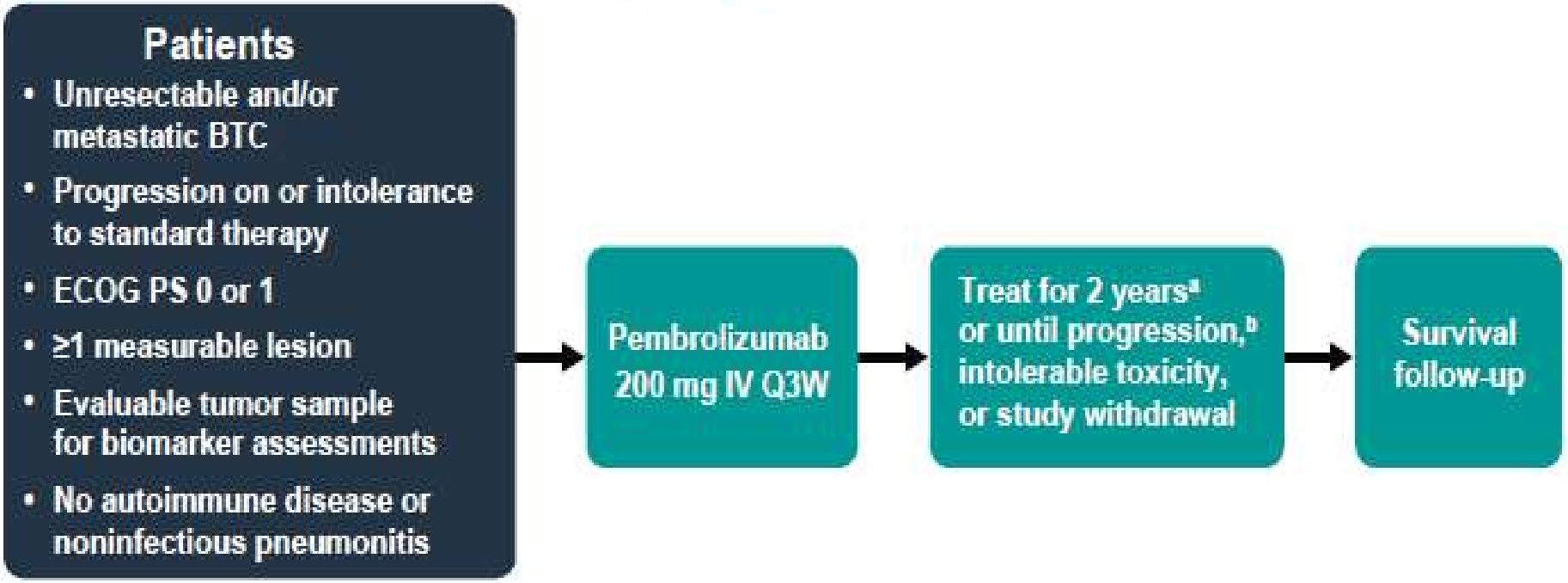
TARGETING HER2 IN GALLBLADDER CANCER
TRASTUZUMAB IN A PATIENT WITH HER2 AMPLIFIED GB CANCER



Javle et al, J Hemat Onc 2015

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

Figure 1. KEYNOTE-158 Study Design



UENO ET AL, ESMO 2018

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	N = 104
Age, years, median (range) <65 years, n (%)	63.0 (34–81) 60 (57.7)
Male, n (%)	51 (49.0)
Race, n (%) Asian White	 37 (35.6) 67 (64.4)
ECOG performance status 1, n (%)	62 (59.6)
Stage M1 disease, n (%)	94 (90.4)
PD-L1–positive tumor,[a] n (%)	61 (58.7)
MSI-H,[b] n (%)	0
Histology, n (%) Adenocarcinoma Adenosquamous Tubular adenocarcinoma	 101 (97.1) 2 (1.9) 1 (1.0)
Baseline tumor size,[c] mm, median (range)	84.0 (10.5–434.7)
Prior (neo)adjuvant therapy, n (%)	22 (21.2)
No. prior therapies for recurrent/metastatic disease, n (%) Adjuvant/neoadjuvant 1 2 3 ≥4	 7 (6.7) 43 (41.3) 36 (34.6) 12 (11.5) 6 (5.8)

UENO ET AL, ESMO 2018

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

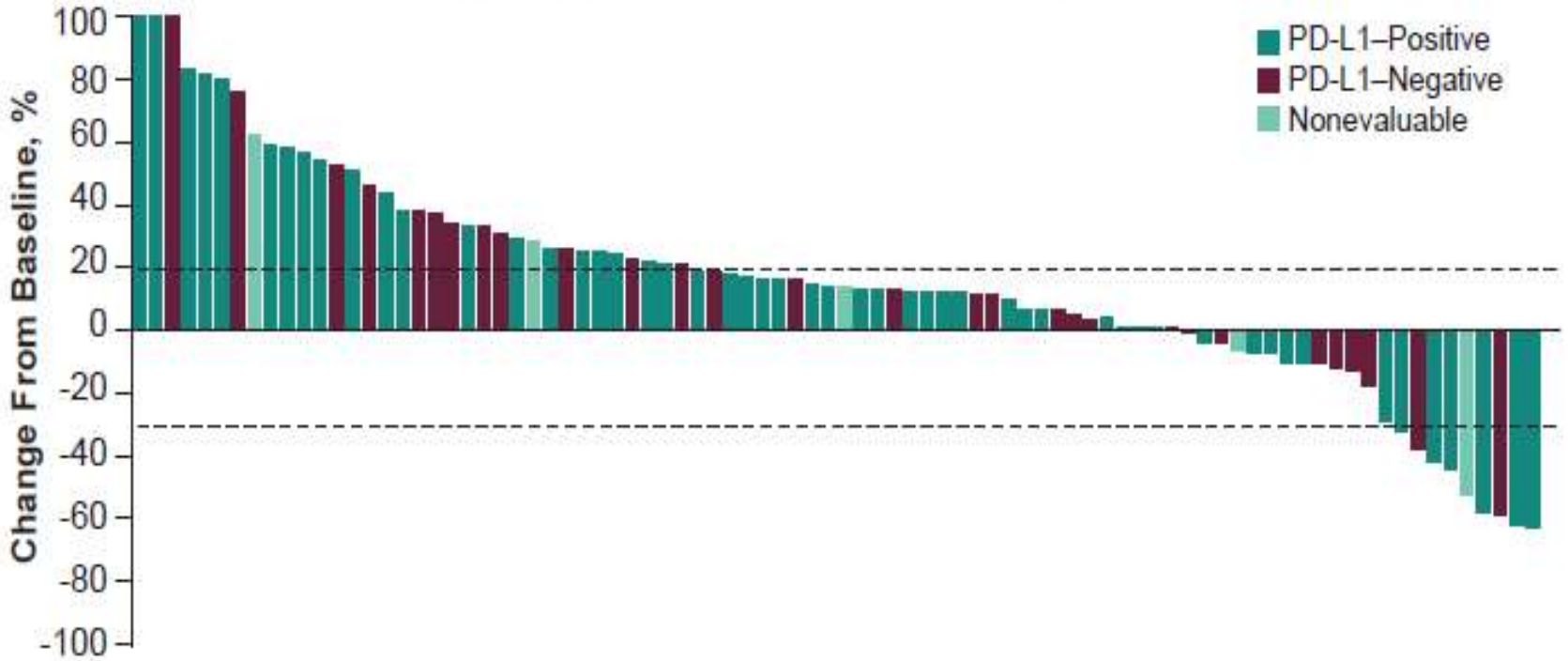
Table 2. Summary of Response (RECIST version 1.1 by Independent Central Review)

	Overall[a]	PD-L1–Positive	PD-L1–Negative
Total population	**N = 104**	**n = 61**	**n = 34**
ORR,[b] % (95% CI)	5.8 (2.1–12.1)	6.6 (1.8–15.9)	2.9 (0.1–15.3)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	6 (5.8)	4 (6.6)	1 (2.9)
Stable disease	17 (16.3)	6 (9.8)	11 (32.4)
Progressive disease	65 (62.5)	44 (72.1)	17 (50.0)
Nonevaluable[c]	2 (1.9)	2 (3.3)	0
No assessment[d]	14 (13.5)	5 (8.2)	5 (14.7)
Patients with response	**n = 6**	**n = 4**	**n = 1**
Time to response, months, median (range)	2.2 (1.9–6.0)	3.3 (2.1–6.0)	1.9 (1.9–1.9)
Kaplan-Meier estimate of response ≥15 months, n (%)[e]	2 (50.0)	2 (75.0)	0 (0.0)
Duration of response, months, median (range)	NR (6.2–15.7+)	NR (10.4–15.7+)	7.4 (7.4–7.4)

UENO ET AL, ESMO 2018

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

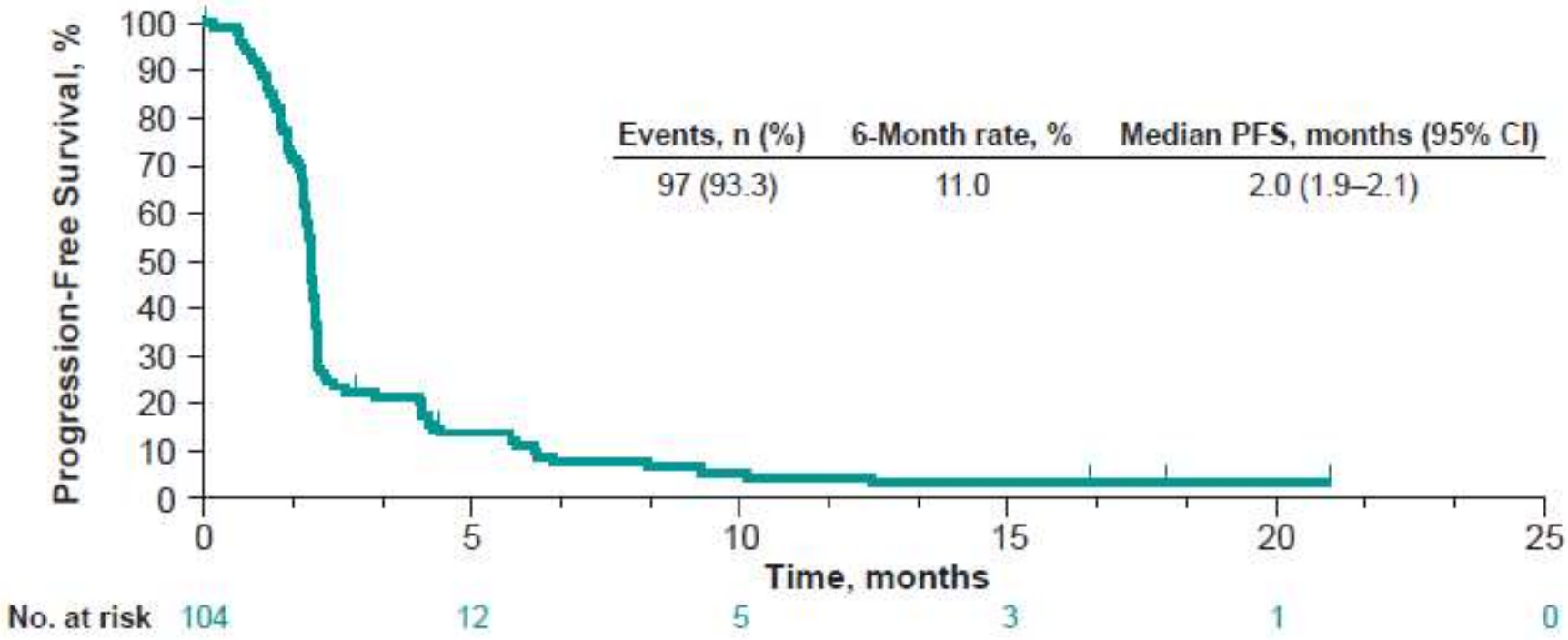
Figure 2. Best Percentage Change From Baseline in Target Lesion Size (RECIST version 1.1 by Independent Central Review)



UENO ET AL, ESMO 2018

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

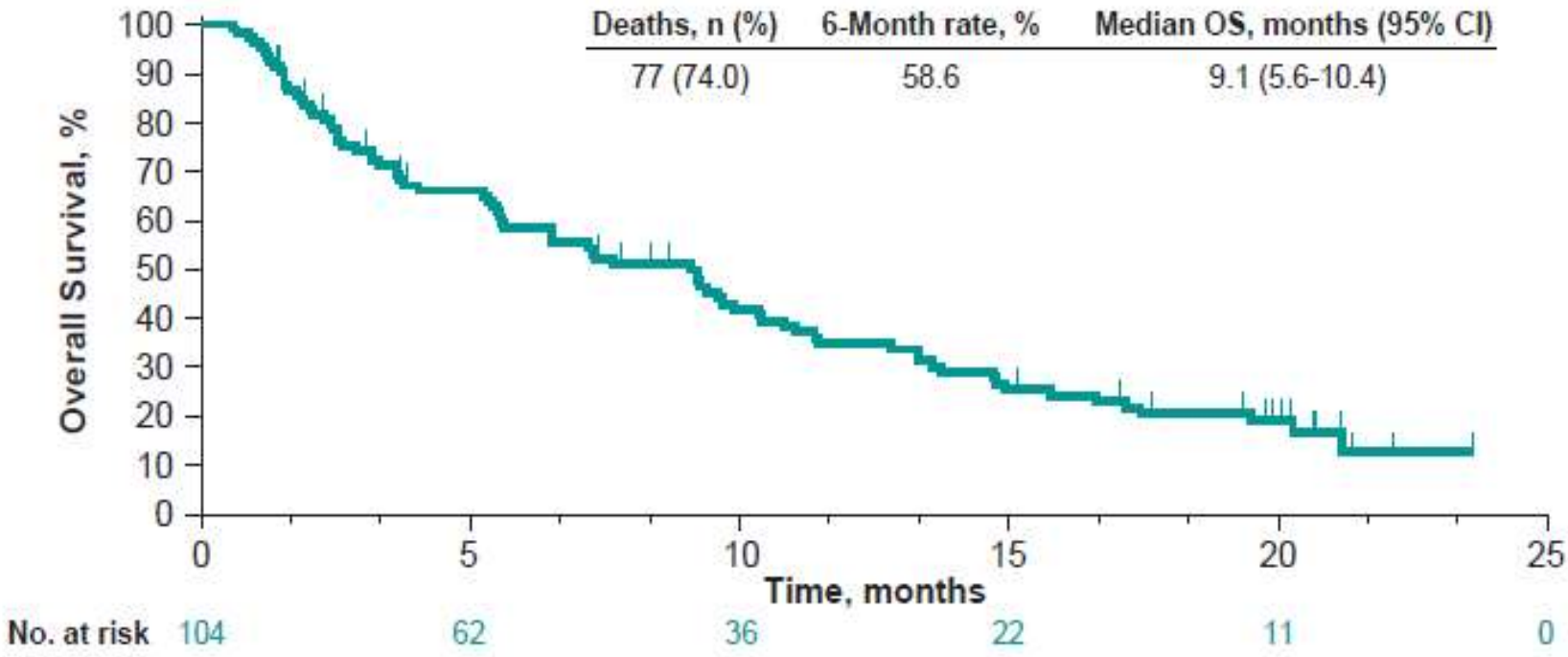
Figure 4. Kaplan-Meier Estimate of PFS (RECIST version 1.1 by Independent Central Review)



UENO ET AL, ESMO 2018

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

Figure 5. Kaplan-Meier Estimate of OS



UENO ET AL, ESMO 2018

PEMBROLIZUMAB IN BILIARY TRACT CANCERS

Table 3. Treatment-Related AEs

AEs, n (%)	N = 104	
Any	57 (54.8)	
Grade 3–4	13 (12.5)	
Grade 5[a]	1 (1.0)	
Leading to discontinuation	6 (5.8)	
	Any Grade	Grade 3–4
AEs of any grade that occurred in ≥5 patients or of grade 3–4 that occurred in ≥2 patients		
Fatigue	15 (14.4)	0
Rash	12 (11.5)	0
Pruritus	9 (8.7)	1 (1.0)
Diarrhea	8 (7.7)	1 (1.0)
Asthenia	7 (6.7)	0
Hypothyroidism	7 (6.7)	0
Increased blood alkaline phosphatase	5 (4.8)	2 (1.9)
Pneumonitis	5 (4.8)	1 (1.0)

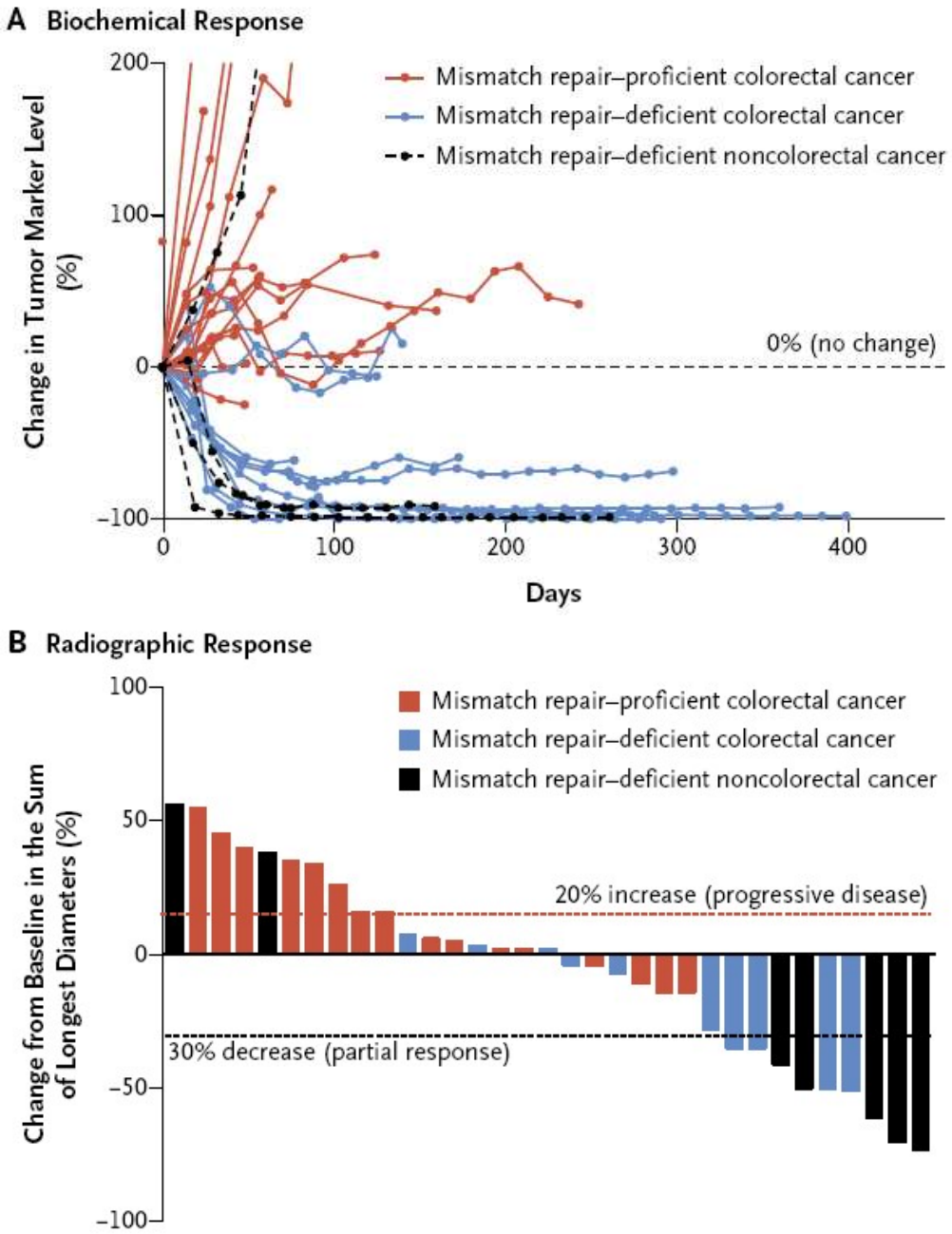
UENO ET AL, ESMO 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

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



Le et al, NEJM 2015

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%

Javle et al, ASCO Clinical Science Symposium 2015

CONCLUSIONS

- Biliary tract cancers are enriched with targetable genomic alterations

- NGS based approaches represent a promising clinical tool for genomic profiling in the clinic

- Differences in genomic spectra of intrahepatic CCA, extrahepatic CCA and gallbladder cancer may highlight differences in etiologic factors and developmental differences

- FGFR2 is both predictive and prognostic in intrahepatic CCA

- IDH mutations are a promising genomic target in CCA

- ERBB2 may represent a novel therapeutic target in gallbladder cancer

QUESTIONS ?

Borad.mitesh@mayo.edu