MAYO CLINIC

ASCO GI 2023 Updates

Tanios Bekaii-Saab, MD
Program Leader, GI Cancer, Mayo Clinic Cancer Center (AZ, FL and MN)
Professor , Mayo Clinic College of Medicine and Science
Consultant, Mayo Clinic AZ
Chair , ACCRU Consortium

Targeting RAS in GI Malignancies

The NEW ENGLAND JOURNAL of MEDICINE

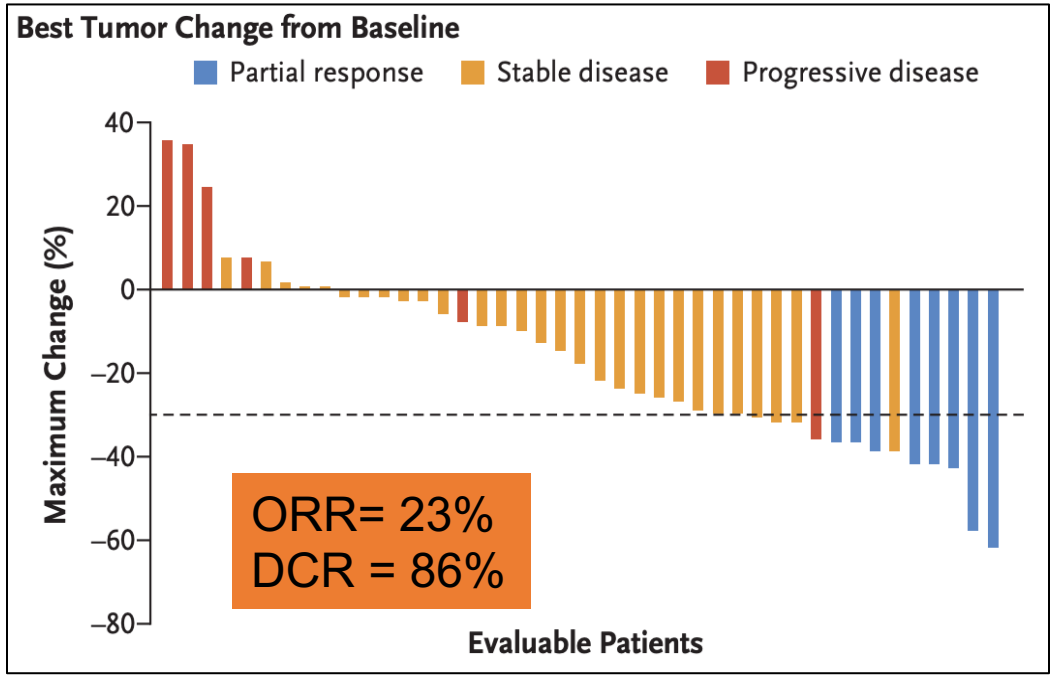
ORIGINAL ARTICLE

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

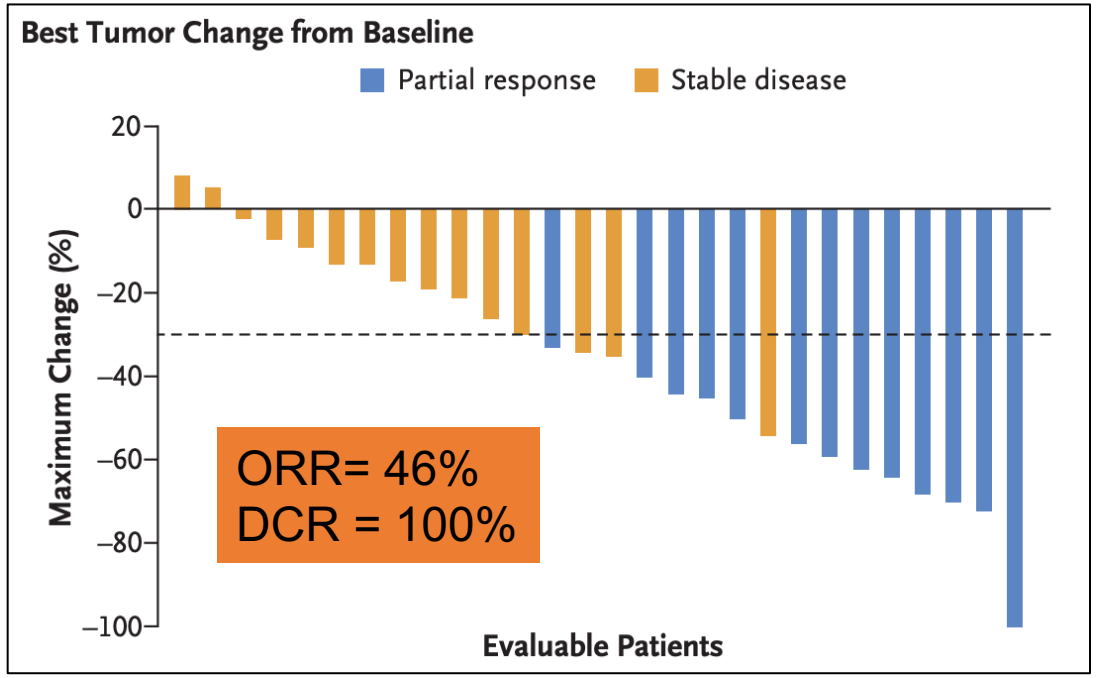
Rona Yaeger, M.D., Jared Weiss, M.D., Meredith S. Pelster, M.D., Alexander I. Spira, M.D., Ph.D., Minal Barve, M.D., Sai-Hong I. Ou, M.D., Ph.D., Ticiana A. Leal, M.D., Tanios S. Bekaii-Saab, M.D., Cloud P. Paweletz, Ph.D., Grace A. Heavey, B.A., James G. Christensen, Ph.D., Karen Velastegui, B.Sc., Thian Kheoh, Ph.D., Hirak Der-Torossian, M.D., and Samuel J. Klempner, M.D.

Best tumor change from baseline

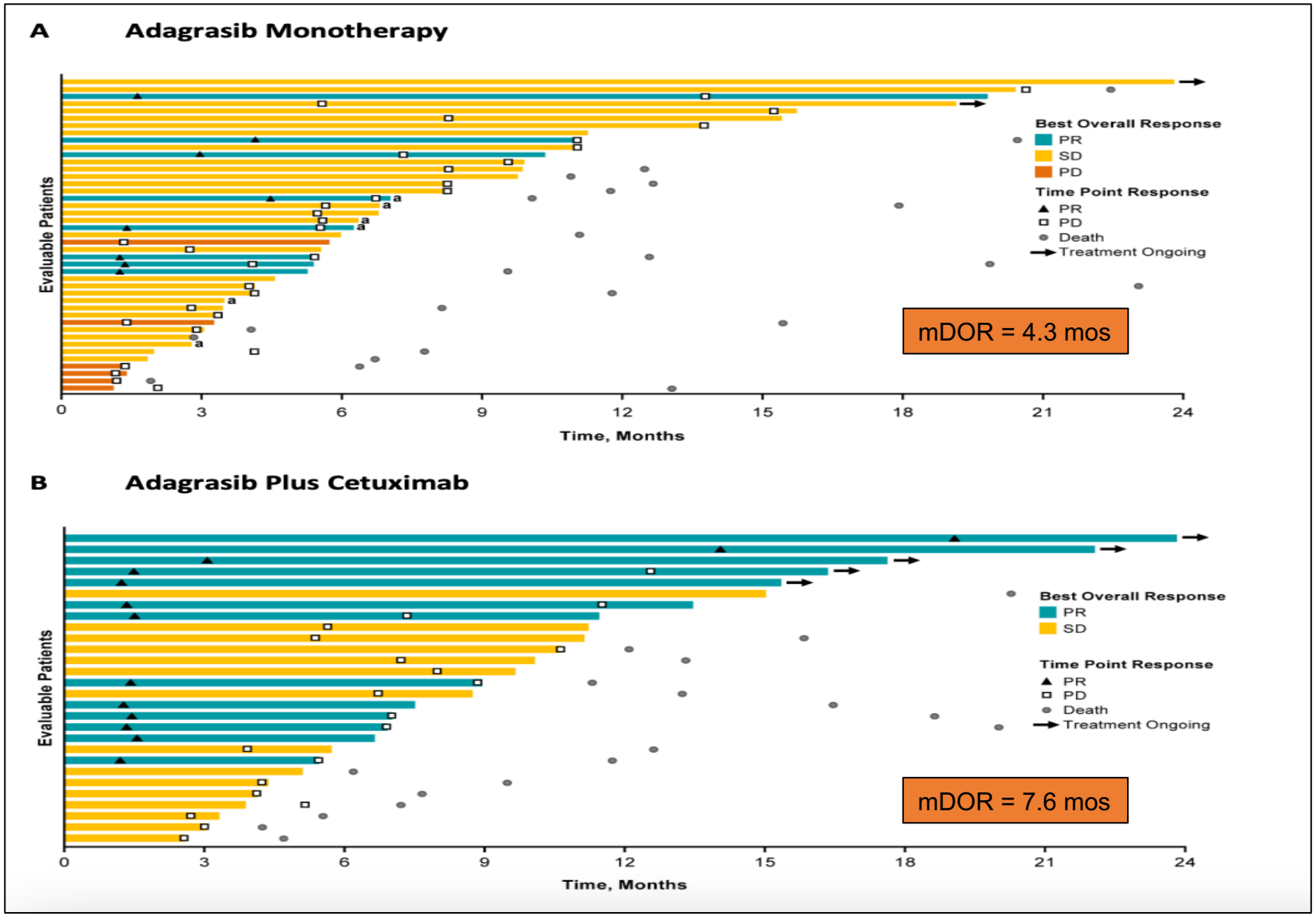
Adagrasib



Adagrasib plus Cetuximab



Time to Response and Duration of Treatment



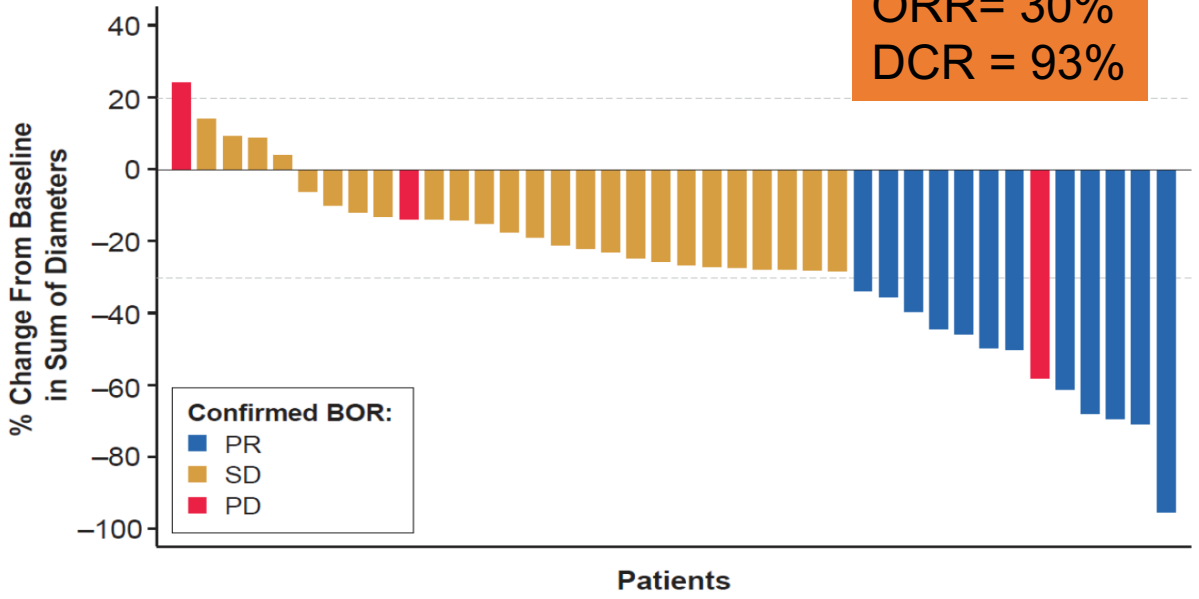
Summary of Treatment-Related Adverse Events

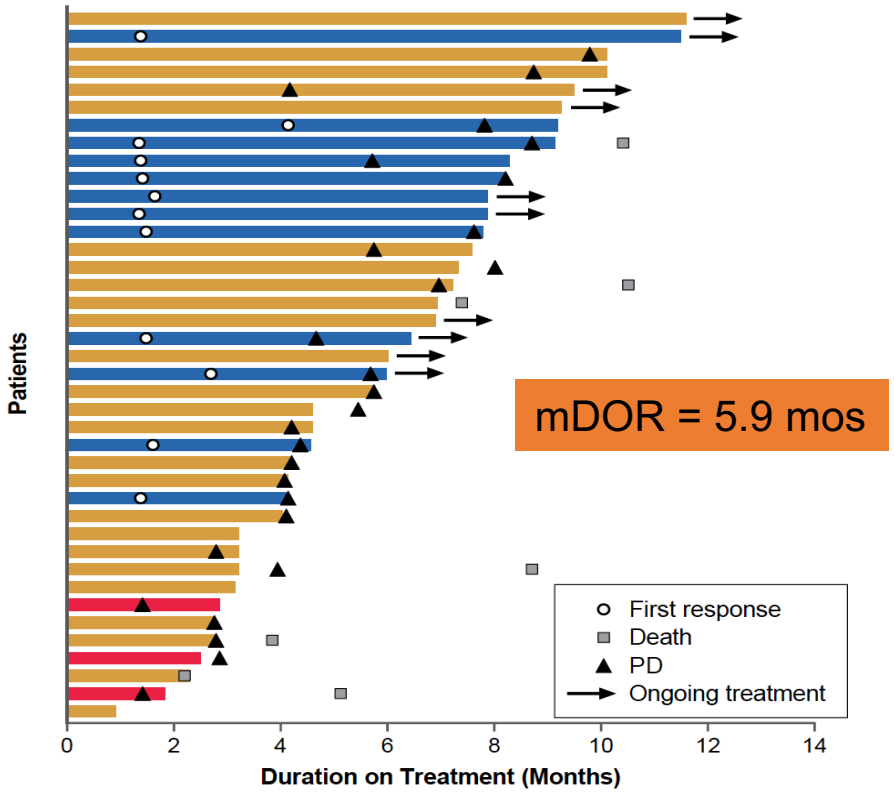
Adverse Event	Adagrasib Monotherapy (N=44)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)				
Any event	41 (93)	10 (23)	16 (36)	13 (30)	2 (5)
Leading to dose discontinuation	0	—	—	—	—
Leading to dose interruption	20 (45)	—	—	—	—
Leading to dose reduction	17 (39)	—	—	—	—
Most frequent events†					
Diarrhea	29 (66)	16 (36)	10 (23)	3 (7)	0
Nausea	25 (57)	15 (34)	10 (23)	0	0
Vomiting	20 (45)	12 (27)	8 (18)	0	0
Fatigue	20 (45)	11 (25)	7 (16)	2 (5)	0
Anemia	7 (16)	2 (5)	1 (2)	4 (9)	0
Prolonged QT interval on ECG	7 (16)	2 (5)	3 (7)	2 (5)	0
Peripheral edema	7 (16)	6 (14)	1 (2)	0	0
Decreased appetite	8 (18)	4 (9)	4 (9)	0	0
Increased ALT	5 (11)	3 (7)	0	2 (5)	0
Increased AST	5 (11)	3 (7)	0	2 (5)	0

	Adagrasib plus Cetuximab (N=32)				
Any event	32 (100)	5 (16)	22 (69)	3 (9)	2 (6)
Leading to dose discontinuation					
Adagrasib	0	—	—	—	—
Cetuximab	5 (16)	—	—	—	—
Leading to dose interruption					
Adagrasib	14 (44)	—	—	—	—
Cetuximab	10 (31)	—	—	—	—
Leading to dose reduction					
Adagrasib	10 (31)	—	—	—	—
Cetuximab	1 (3)	—	—	—	—
Most frequent events†					
Nausea	20 (62)	13 (41)	7 (22)	0	0
Diarrhea	18 (56)	11 (34)	6 (19)	1 (3)	0
Vomiting	17 (53)	13 (41)	4 (12)	0	0
Dermatitis acneiform	15 (47)	11 (34)	3 (9)	1 (3)	0
Fatigue	15 (47)	8 (25)	7 (22)	0	0
Dry skin	13 (41)	11 (34)	2 (6)	0	0
Headache	10 (31)	7 (22)	3 (9)	0	0
Dizziness	8 (25)	4 (12)	4 (12)	0	0
Maculopapular rash	8 (25)	7 (22)	1 (3)	0	0
Stomatitis	7 (22)	5 (16)	1 (3)	1 (3)	0
Dyspepsia	6 (19)	4 (12)	2 (6)	0	0
Hypomagnesemia	6 (19)	3 (9)	3 (9)	0	0
Infusion-related reaction	6 (19)	1 (3)	4 (12)	0	1 (3)

CodeBreak101 : Sotorasib + Panitumumab

Tumour Response





- **Reduction in RECIST target lesions observed in 88% of patients**
- **Median (range) duration of treatment was 5.9 (0.5, 11.3) months, with 25% of patients remaining on treatment**

Kuboki Y et al . ESMO 2022

ASCO® Plenary Series

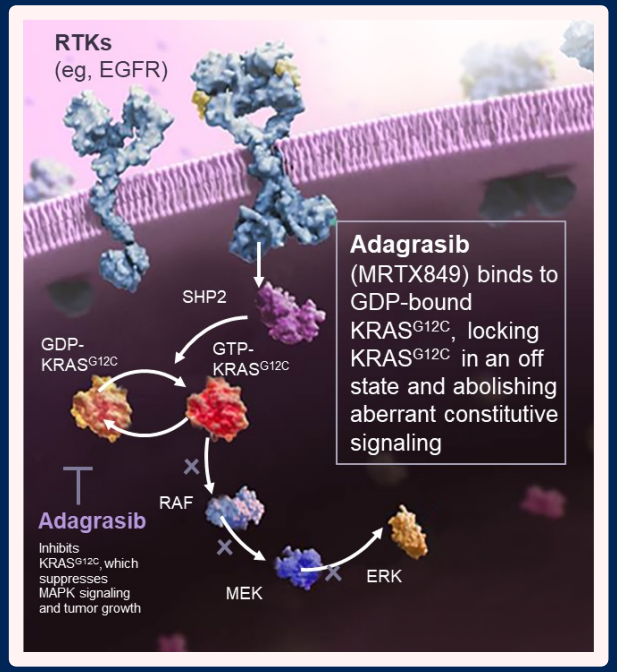
KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients With Advanced Solid Tumors Harboring a $KRAS^{G12C}$ Mutation

Shubham Pant[1], Rona Yaeger[2], Alexander I. Spira[3], Meredith S. Pelster[4], Joshua K. Sabari[5], Navid Hafez[6], Minal Barve[7], Karen Velastegui[8], Xiaohong Yan[8], Hirak Der-Torossian[8], Tanios S. Bekaii-Saab[9]

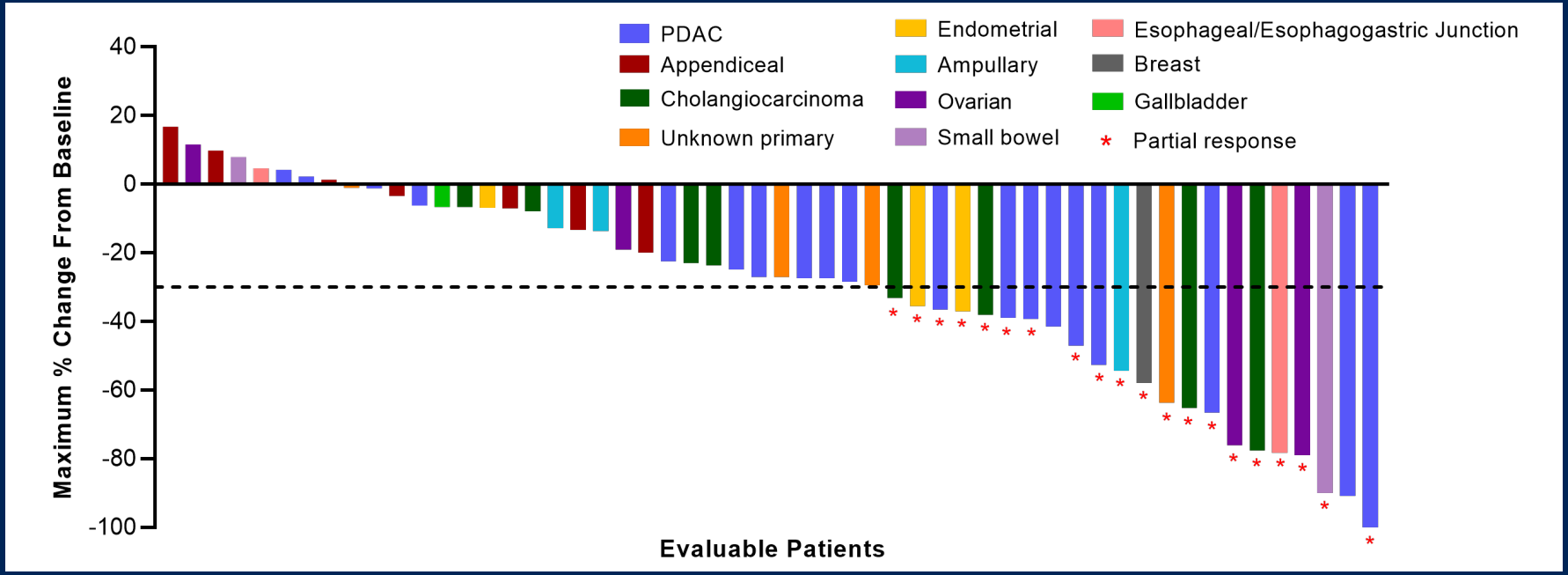
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA; [3]Virginia Cancer Specialists, Fairfax, VA; NEXT Oncology, Fairfax, VA; US Oncology Research, The Woodlands, TX, USA; [4]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [5]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA; [6]Yale Cancer Center, New Haven, CT, USA; [7]Mary Crowley Cancer Research, Dallas, TX, USA; [8]Mirati Therapeutics, Inc., San Diego, CA, USA; [9]Department of Medical Oncology and Hematology, Mayo Clinic, Scottsdale, AZ, USA

Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- KRAS^{G12C} mutations act as oncogenic drivers in a range of solid tumors:
  - NSCLC (~14%)[1]
  - CRC (3–4%)[1–3]
  - Appendiceal (3–4%)[1,2]
  - Ovarian (0.4%)[1]
  - PDAC (1–3%)[4]
  - Small bowel (1–3%)[1,2]
  - Biliary tract (1%)[2]
  - Endometrial (1.5%)[1]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, was selected for favorable properties, including a long half-life (23 hours), dose-dependent PK and CNS penetration[5–7]
- Adagrasib has been granted accelerated approval by the FDA and is under review by the EMA for the treatment of KRAS^{G12C}-mutated NSCLC
- Adagrasib has been granted breakthrough therapy designation, in combination with cetuximab, for the treatment of patients with KRAS^{G12C}-mutated CRC



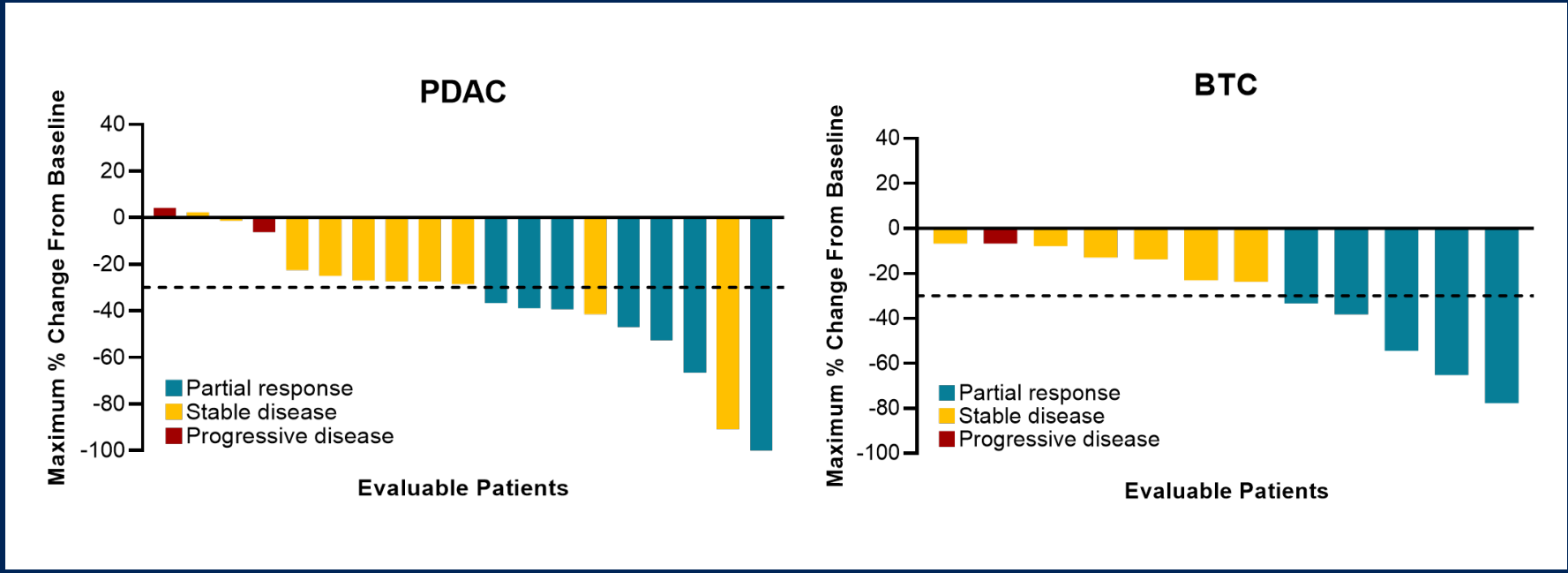
Adagrasib in Patients With Solid Tumors[a]: Best Tumor Change from Baseline



- Confirmed objective responses were observed in 20/57 patients (35.1%)
- Disease control was observed in 49/57 patients (86.0%)

[a]Excluding non-small cell lung cancer and colorectal cancer
All results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With PDAC and BTC: Best Tumor Change From Baseline



- Confirmed ORR of 33.3% (7/21 patients)
- Disease control was observed in 17/21 (81.0%) patients

- Confirmed ORR of 41.7% (5/12 patients)
- Disease control was observed in 11/12 (91.7%) patients

All results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

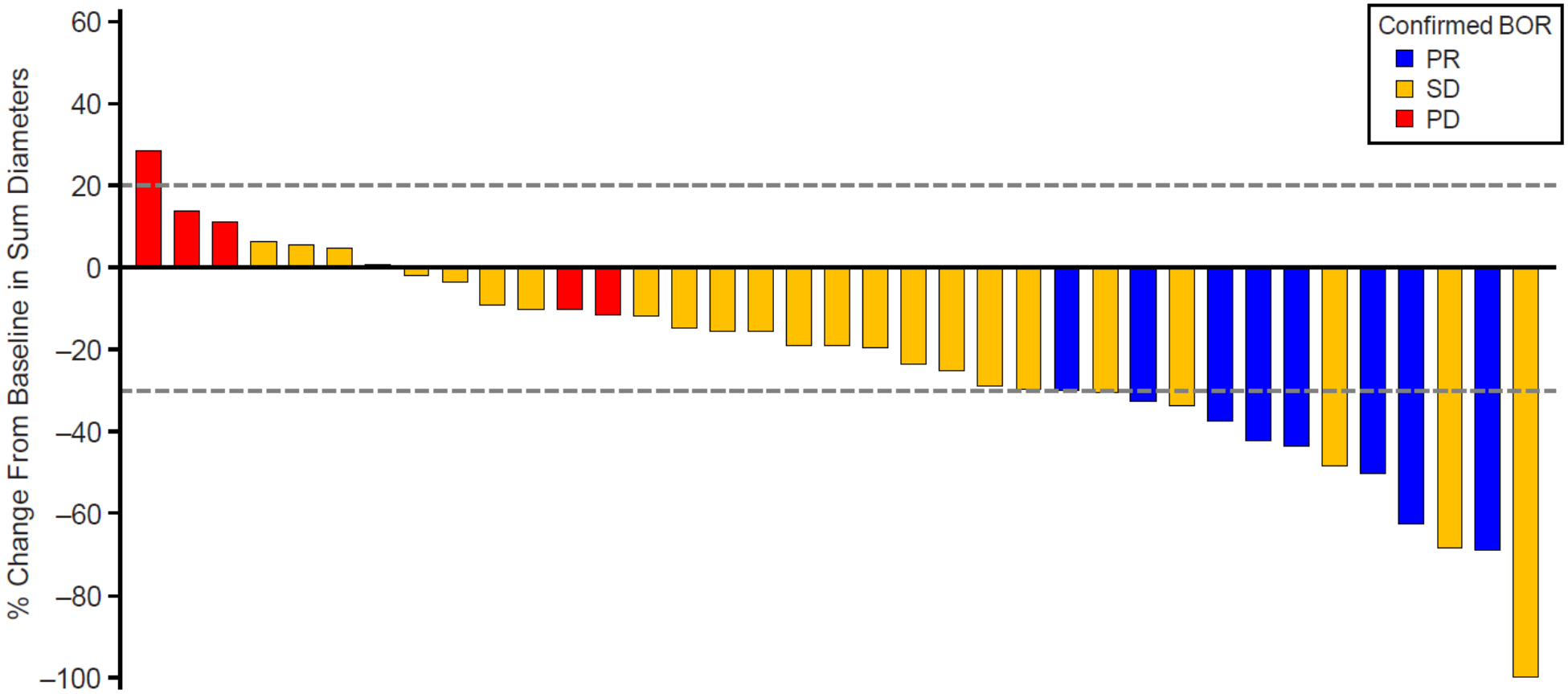
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

J.H. Strickler, H. Satake, T.J. George, R. Yaeger, A. Hollebecque, I. Garrido-Laguna, M. Schuler, T.F. Burns, A.L. Coveler, G.S. Falchook, M. Vincent, Y. Sunakawa, L. Dahan, D. Bajor, S.-Y. Rha, C. Lemech, D. Juric, M. Rehn, G. Ngarmchamnanrith, P. Jafarinasabian, Q. Tran, and D.S. Hong

Best Tumor Shrinkage by Central Review

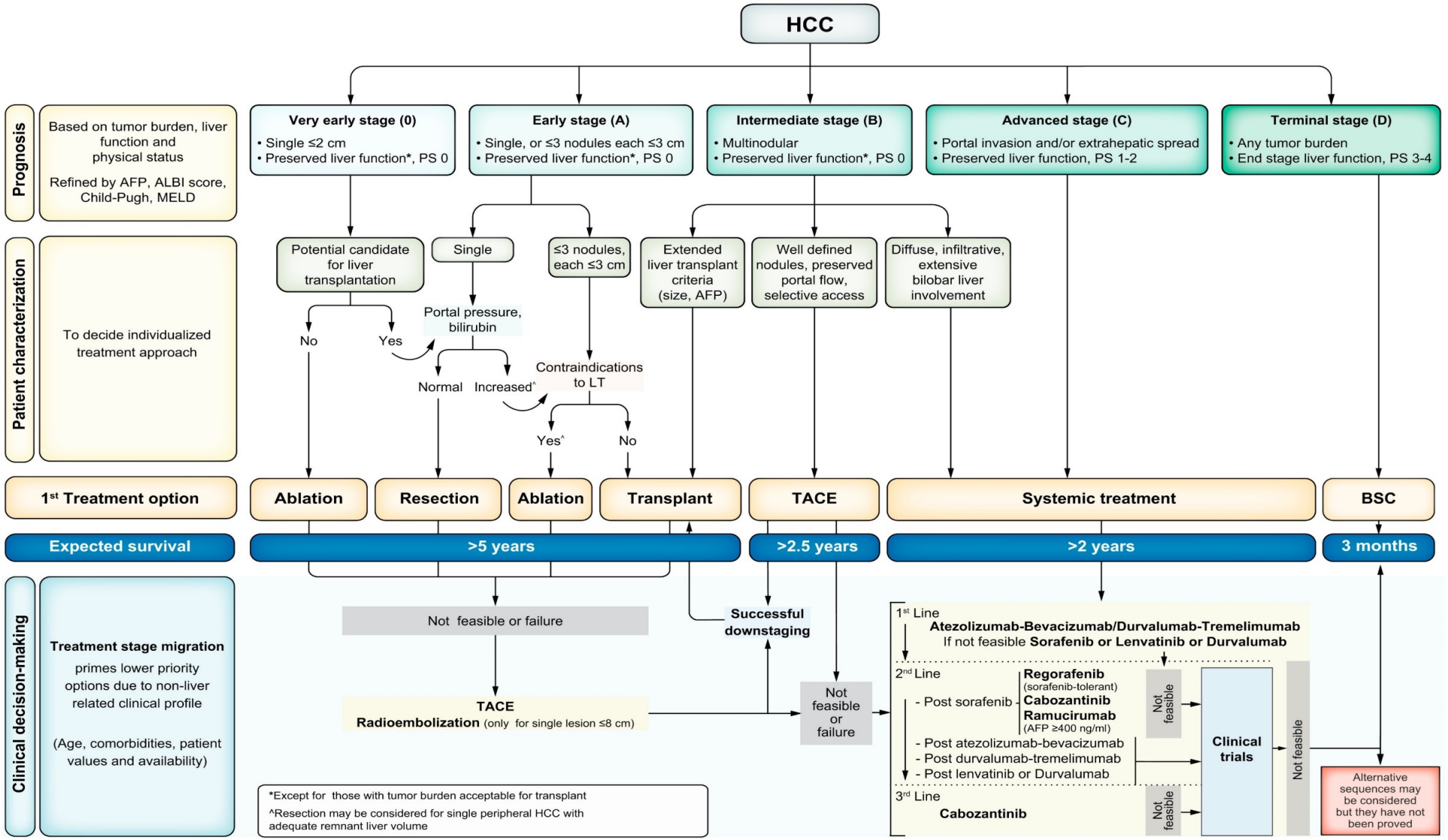


Conclusions

- Direct inhibition of mutant RAS through allele- specific inhibitors provides the best therapeutic approach
- Both Adagrasib and Sotorasib are well tolerated with a manageable safety profile
- Further exploration of Adagrasib is ongoing in the KRYSTAL-1 trial (NCT03785249)
- Next steps :
  - Combination with Chemotherapy?
  - Combination with Cetuximab ? KRYSTAL-1
  - Combination with other targets ? IO?
  - G12 D and others on the way

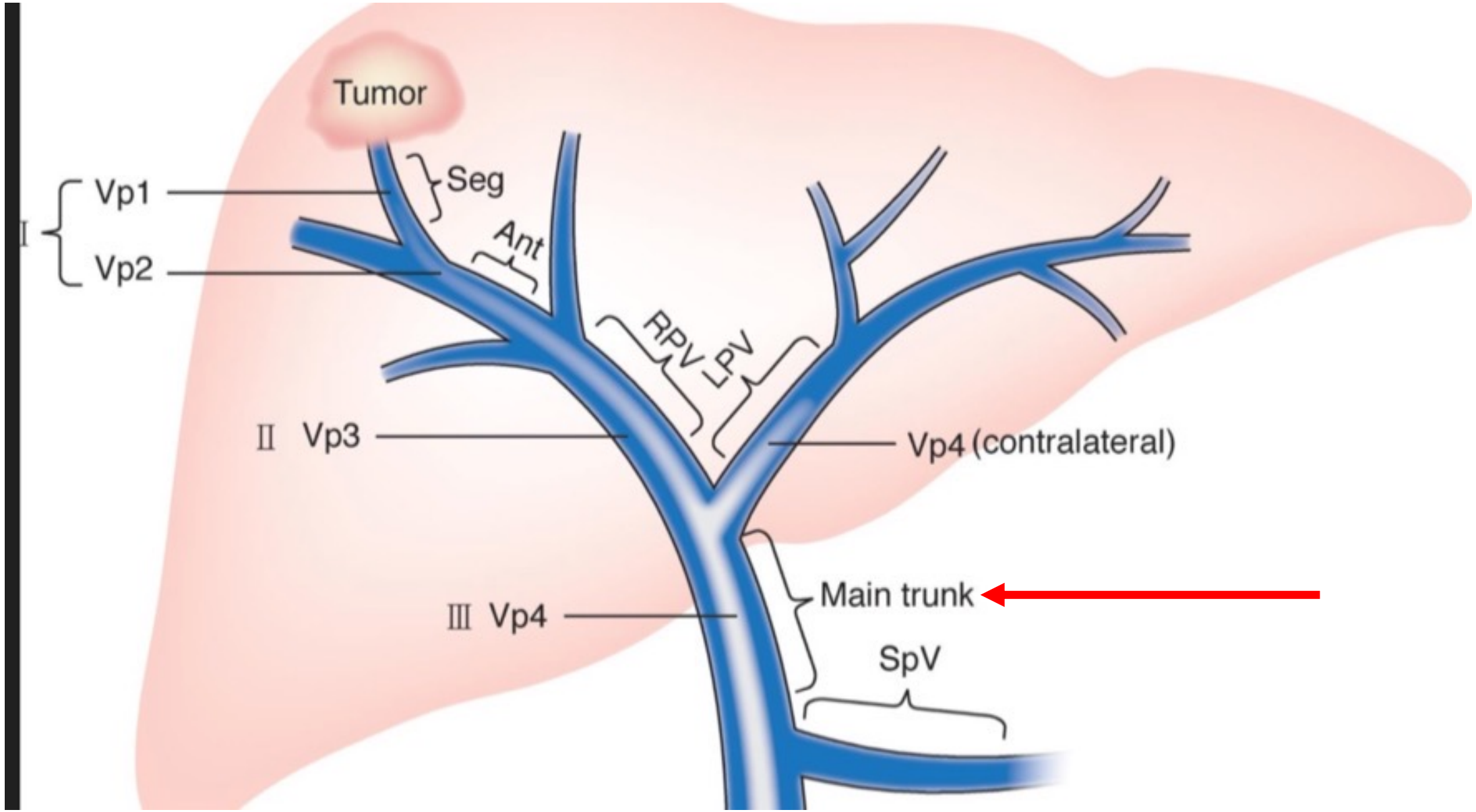
Hepatocellular Carcinoma

When is systemic therapy indicated for HCC ?



Reig M et al, J of Hepatology 2022

IO BASED COMBINATIONS


Tumor
Seg
Ant
Vp1
Vp2
I
RPV
LPV
II Vp3
Vp4 (contralateral)
III Vp4
Main trunk
SpV

Phase III Approved IO Combination Studies in HCC

	IMBRAVE 150		HIMALAYA	
	Atezo/Bev	Sorafenib	STRIDE	Sorafenib
mOS (mo)	19.2 HR 0.66 (0.52,0.85)	13.4	16.4 HR 0.78 (0.65-0.92)	13.8
mPFS (mo)	6.9 HR 0.65(0.53, 0.81)	4.3	3.78 HR 0.9 (0.77-1.05)	4.07
ORR (RECIST 1.1)	30%	11%	20.1%	5.1%
CR	8%		3.1%	
PD	19%		39.9%	
Median DoR (months)	18.1	14.9	22.3	18.4
DCR	74%	55%	60.1%	60.7%
IMAEs requiring steroids	12.2%		20.1%	
All grade bleeding events	25%	17.3%	1.8%	4.8%
Grade 3/4 bleeding events	6.4%	5.8%	0.5%	1.6%

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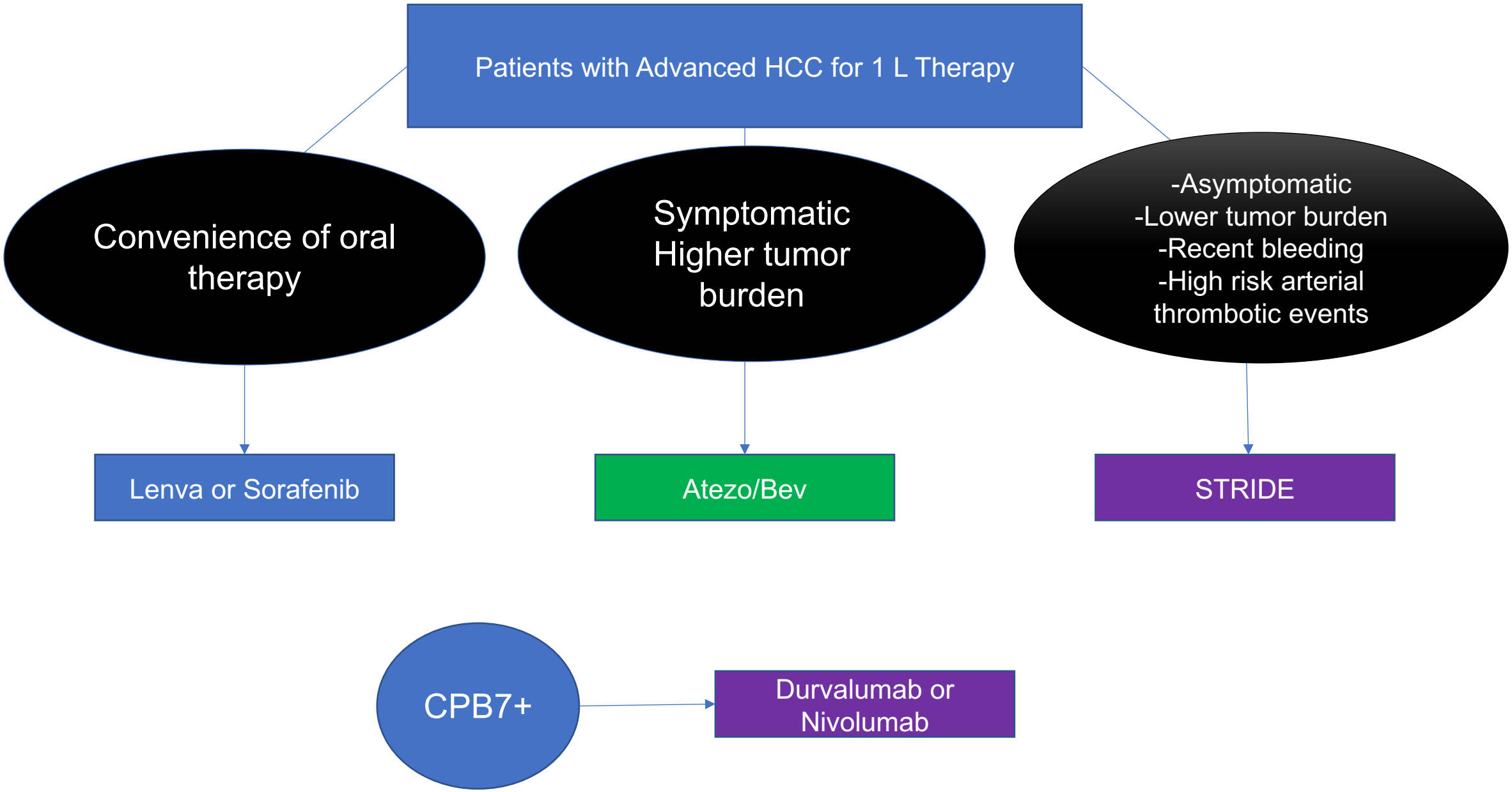
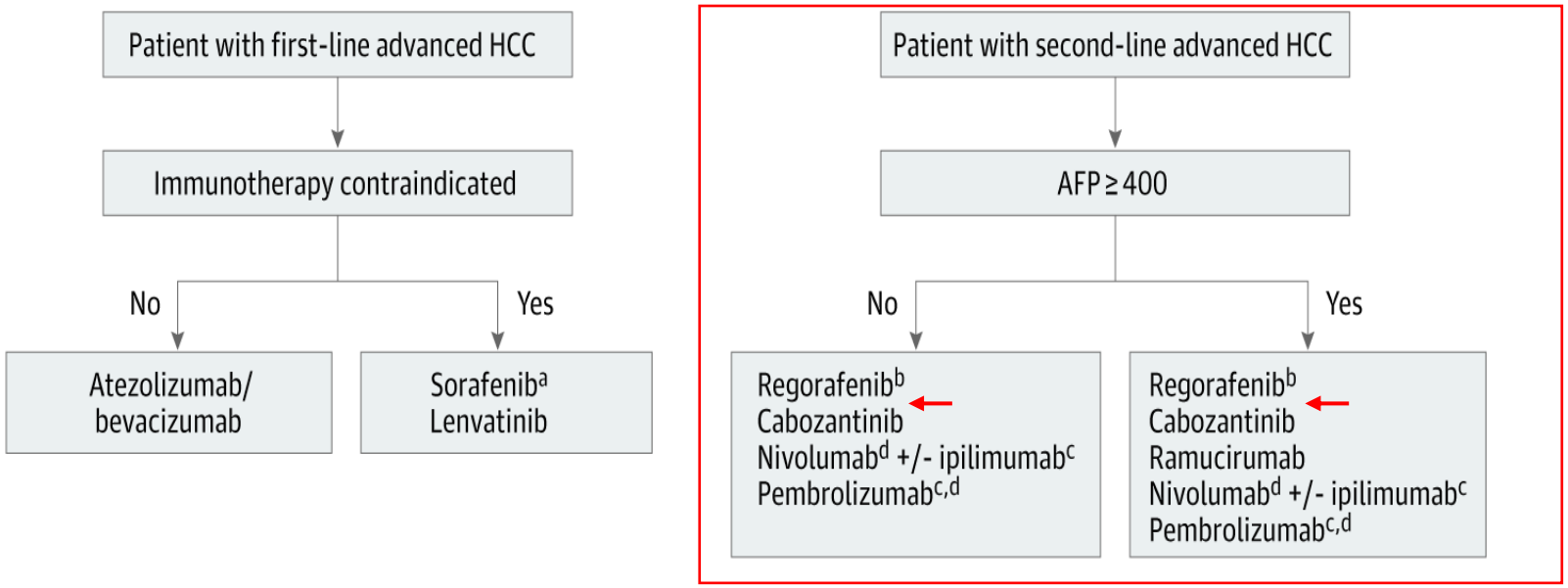
IO + MKI = Mixed Bag

- LEAP-002 Lenva +/- Pembro **Negative for OS/PFS**
- COSMIC 312 Cabo + Atezo **Negative for OS / Positive for OS**
- Rivoceranib (Apatinib) + Camrelizumab vs. Sorafenib **Positive for OS/PFS**


Patients with Advanced HCC for 1 L Therapy
Convenience of oral therapy
Symptomatic Higher tumor burden
-Asymptomatic
-Lower tumor burden
-Recent bleeding
-High risk arterial thrombotic events
Lenva or Sorafenib
Atezo/Bev
STRIDE
CPB7+
Durvalumab or Nivolumab

From: Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis

Sonbol and Bekaii-Saab et al . JAMA Oncol. 2020;6(12):e204930. doi:10.1001/jamaoncol.2020.4930



Suggested Treatment Algorithms for Patients With Advanced Hepatocellular Carcinoma (HCC)AFP indicates α-fetoprotein.

[a]Consider lower starting dose of 200 mg and escalate as tolerated.

[b]Consider starting dose-escalation strategy starting with 80-mg dose.

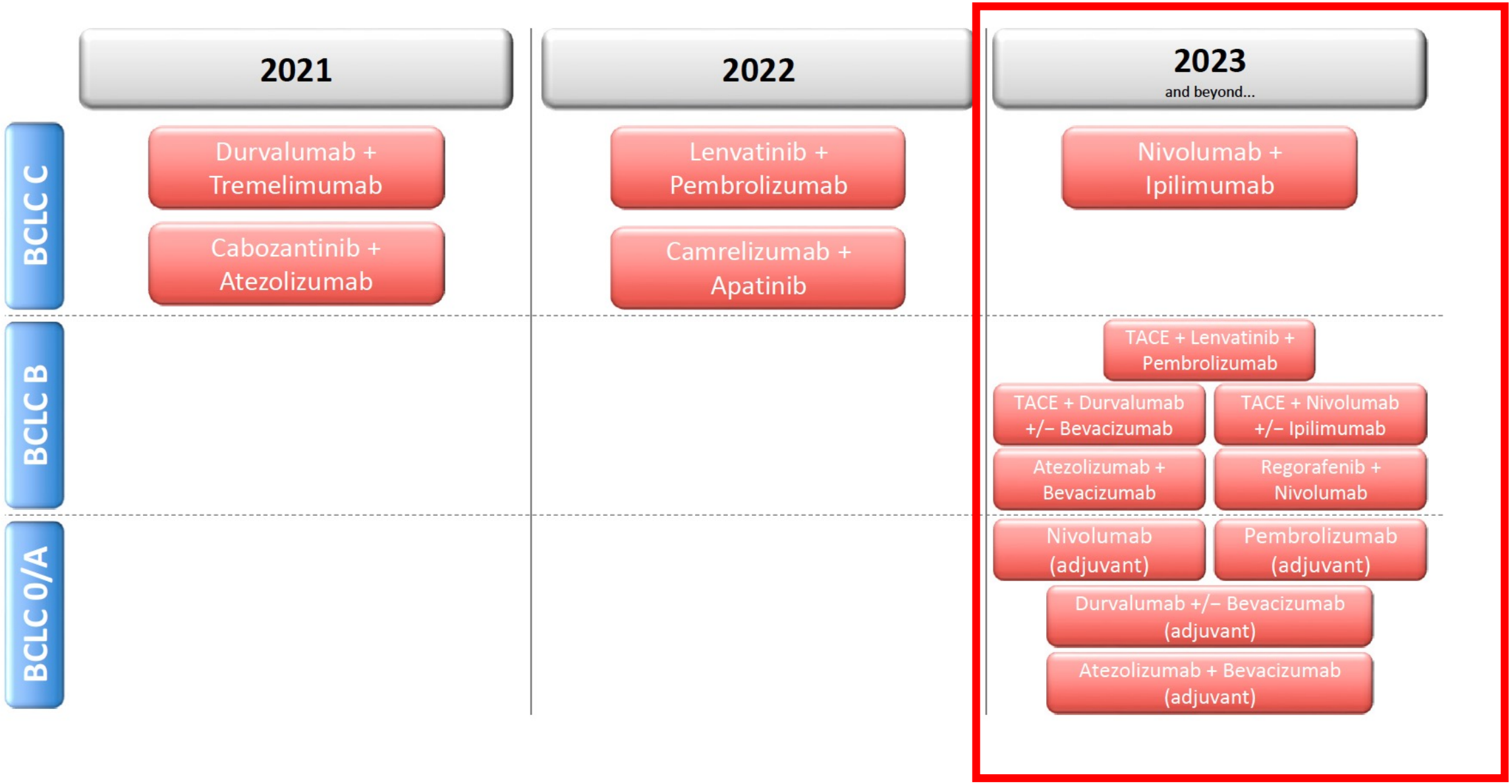
[c]Not supported by level 1 evidence.

[d]If no prior programmed cell death-1 or programmed cell death ligand-1 failure.

Future Practical Considerations

- Optimal sequencing of all agents is not well-established
- Biomarker Discovery is key to better selection of patients with HCC
- Explore in earlier disease stages: LR combination, adjuvant and neoadjuvant settings etc …

Future Directions



IMbrave050 study design

Patient Population
- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1

4-12 weeks

1 cycle of TACE, if indicated

R 1:1

12 months or 17 cycles

Atezolizumab 1200 mg q3w + bevacizumab 15 mg/kg q3w (n=334)

Active surveillance (n=334)

Recurrence[b] or unacceptable toxicity

Survival follow-up

Crossover permitted

Stratification
- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

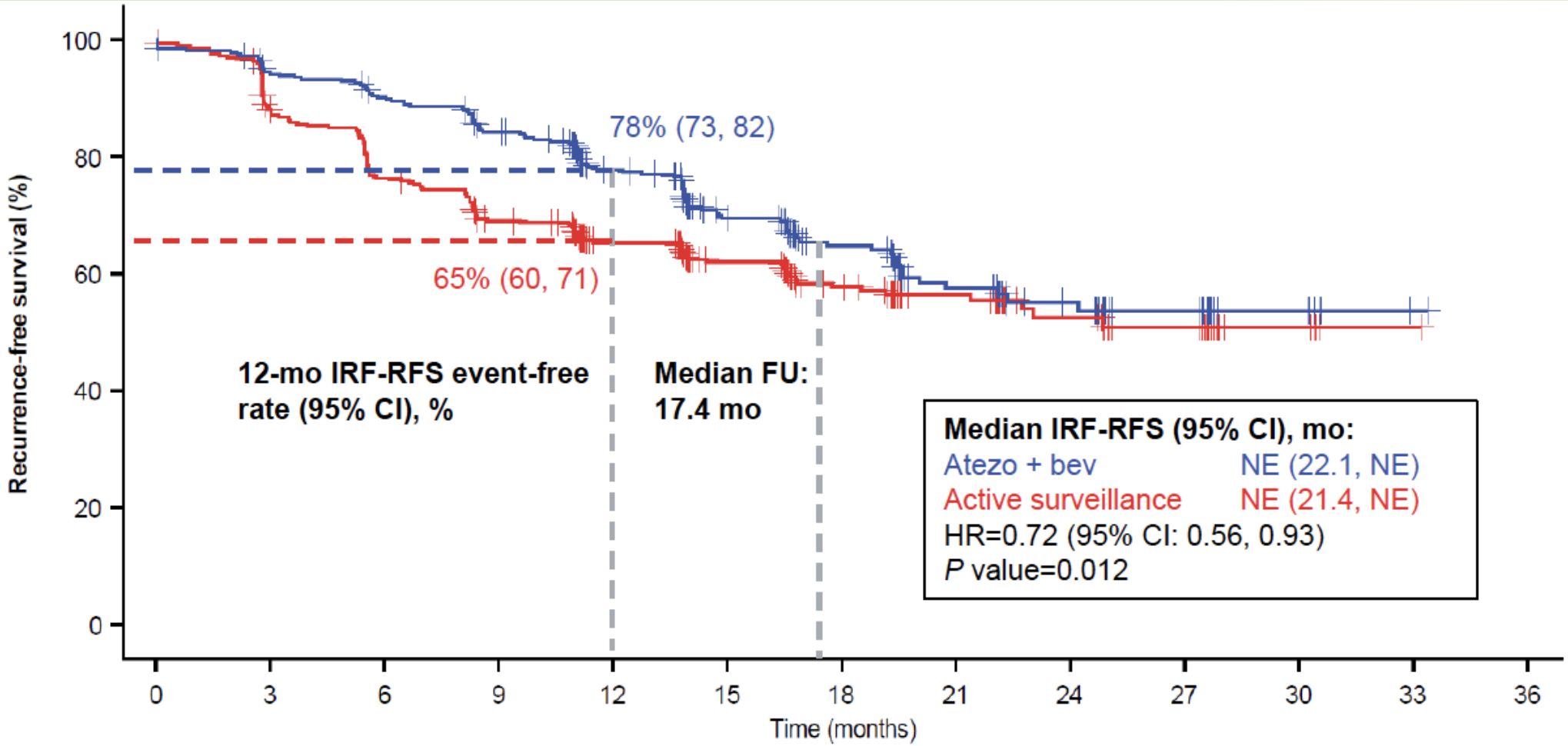
Primary endpoint
- Recurrence-free survival assessed by the independent review facility[b]

ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[a] **High-risk features** include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

[b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance

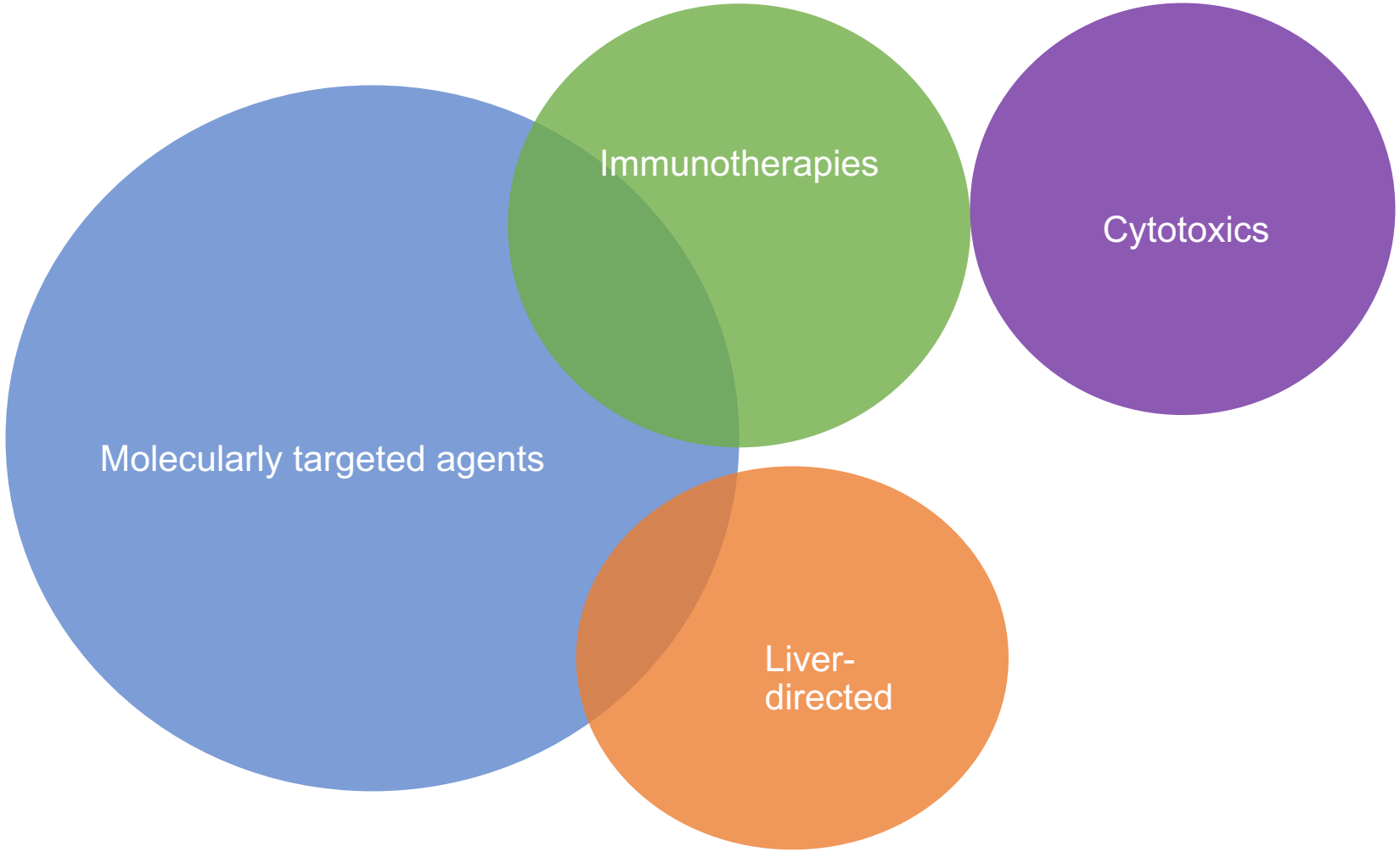


No. at risk													
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

Cholangiocarcinoma

Classes of novel therapeutics under investigation for BTC



TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1) N=685

Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → **Durvalumab 1500 mg Q4W until PD**

Placebo Q3W + GemCis (up to 8 cycles) → **Placebo Q4W until PD**

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

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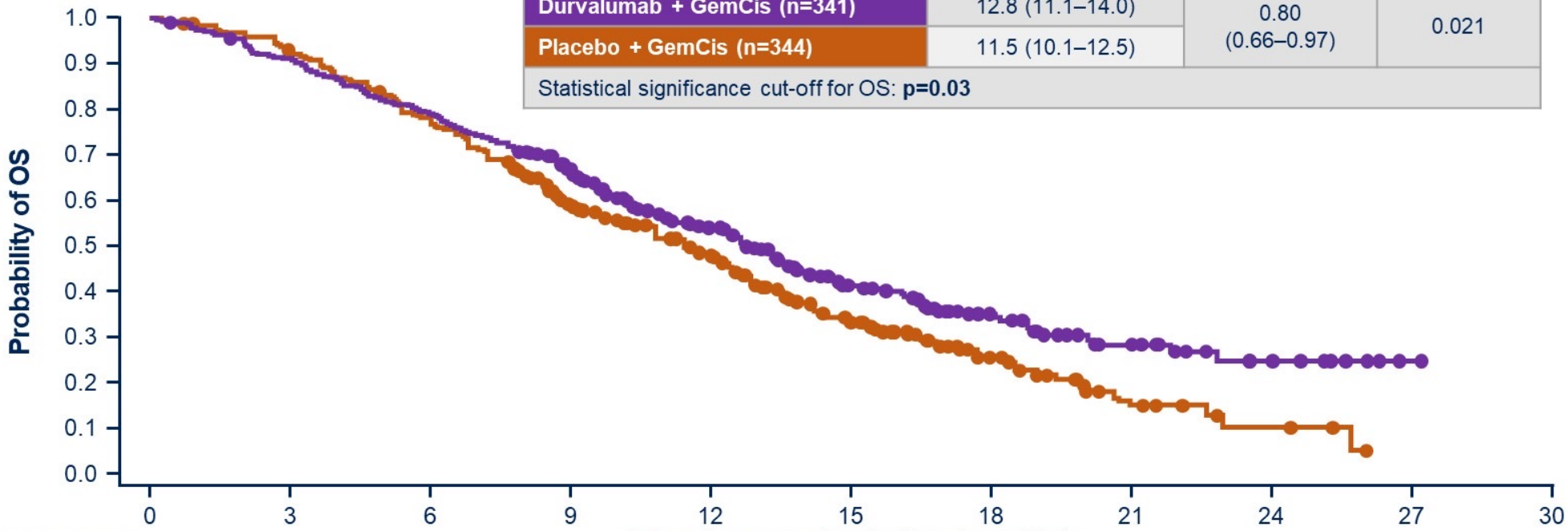
Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

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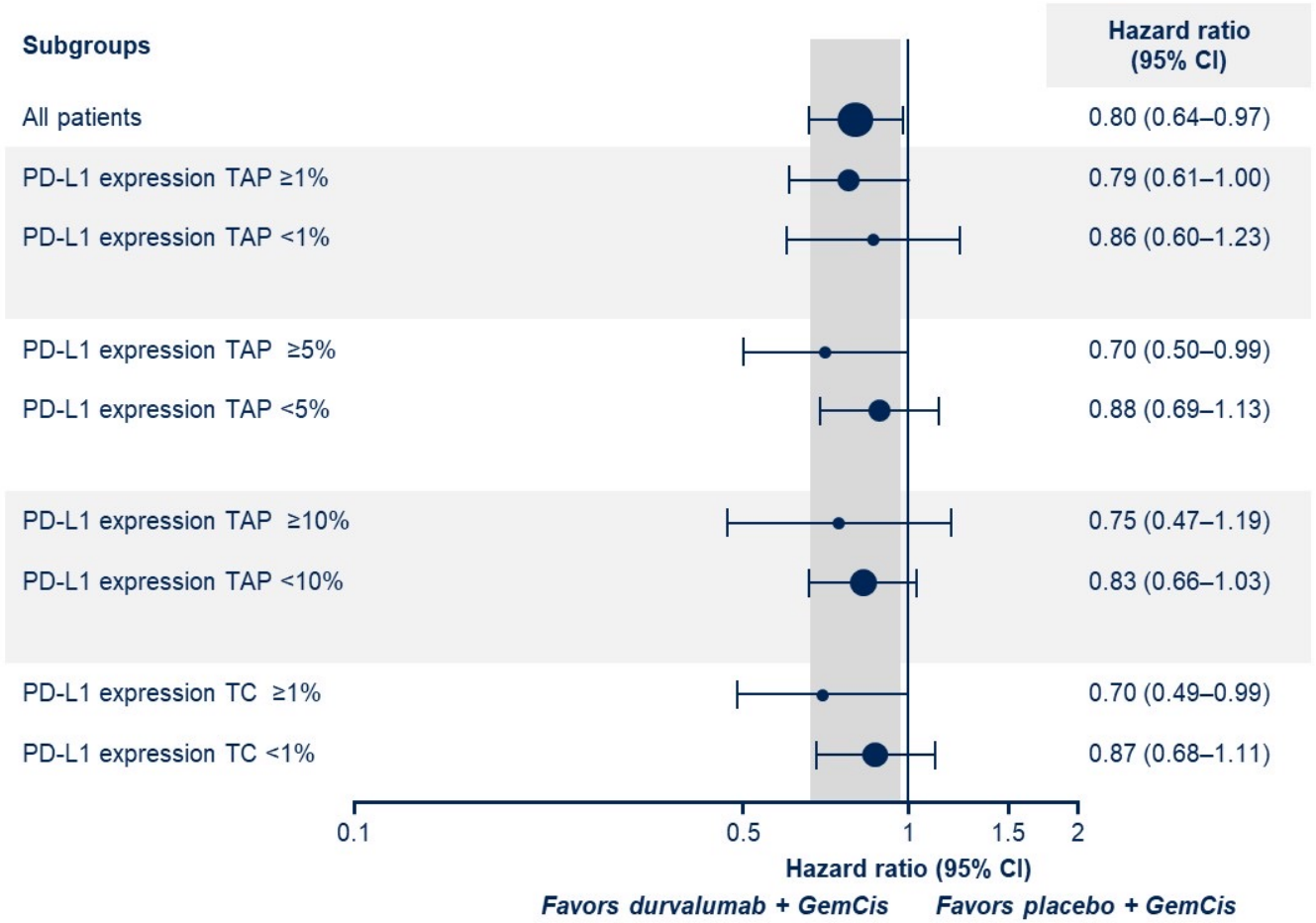
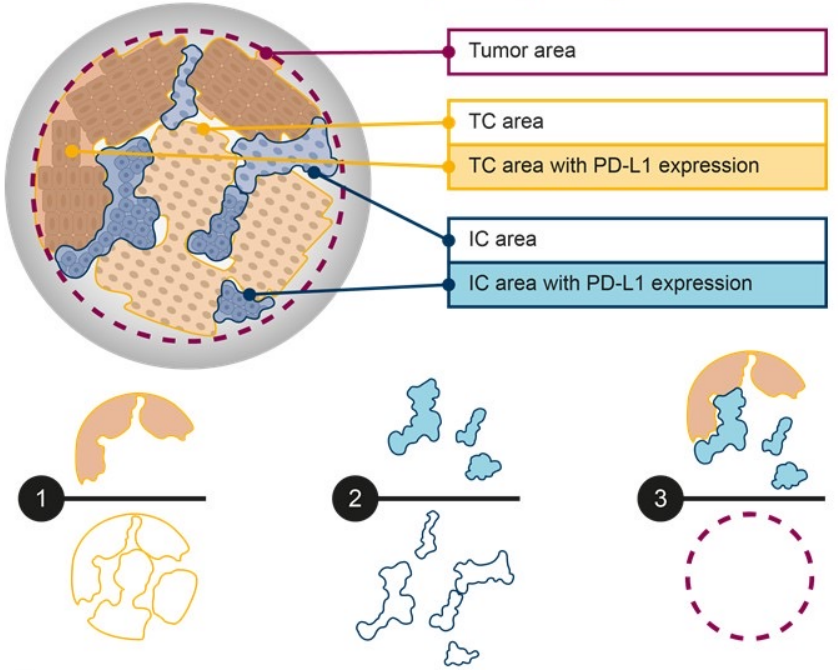
OS in subgroups by PD-L1 expression



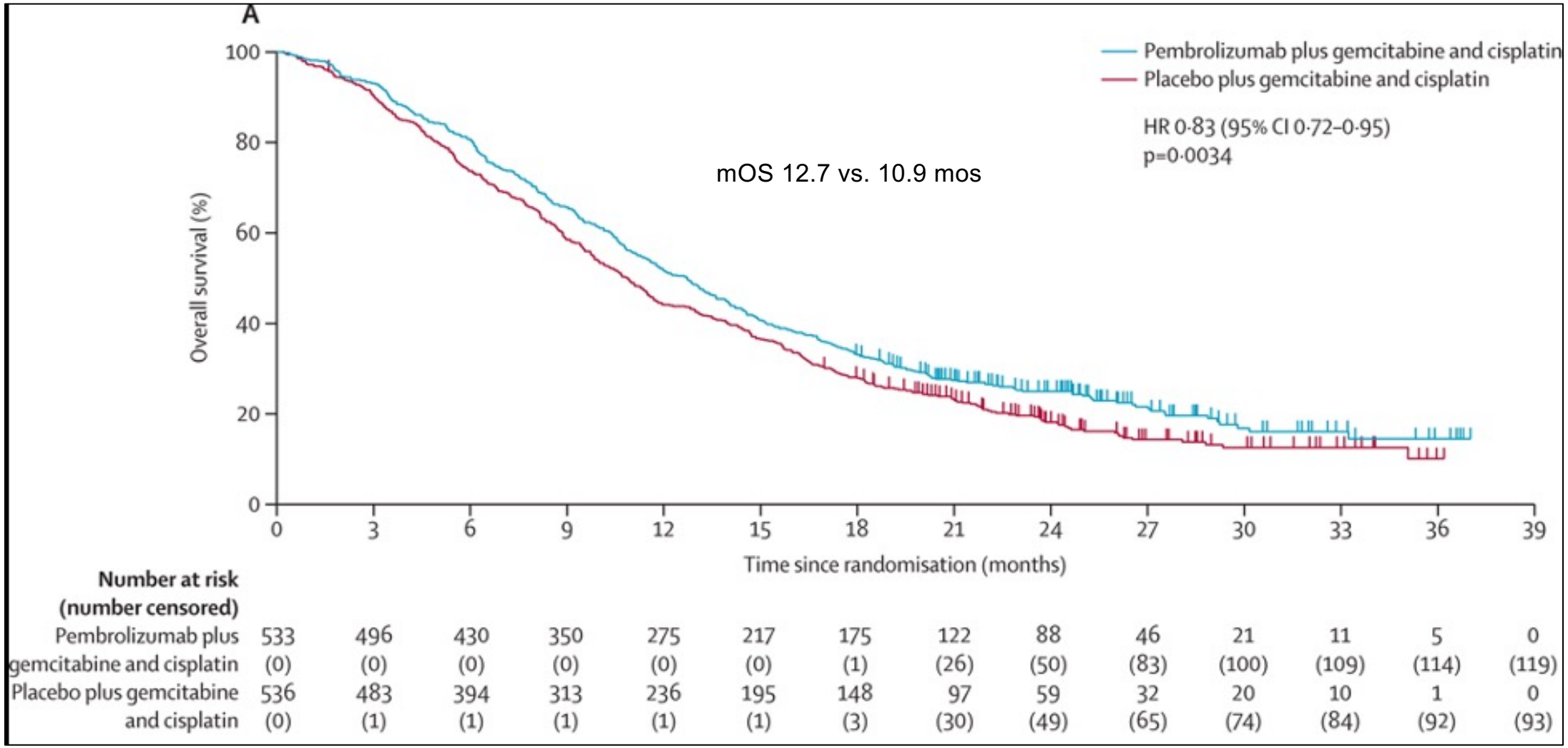
Tumor Area Positivity (TAP) score using the Ventana PD-L1 (SP263) Assay



1. TC: proportion of TCs with PD-L1 membrane staining at any intensity
2. IC: proportion of tumor-associated ICs with PD-L1 cytoplasmic/membrane staining at any intensity
3. **Combined TCs and ICs:** Proportion of tumour area occupied by TCs with membrane and ICs with cytoplasmic/membrane PD-L1 staining at any intensity (TAP score)

CI, confidence interval; IC, immune cell; OS, overall survival; PD-L1, programmed cell death ligand-1; TC, tumor cell; TAP, tumor area positivity

Keynote 966 GC +/- Pembrolizumab
Primary Endpoint : OS



Kelley K, April 2023 . Lancet Oncology.

Study Design

Prespecified stratifications factors: tumor type, PS, locally-advanced vs. metastatic

Key Inclusion/Exclusion:
- Newly diagnosed, histologically proven untreated BTCs
- ECOG PS 0-1
- Adequate laboratories

First line, advanced cholangiocarcinoma and gallbladder cancer → R 2:1

- Gemcitabine 800 mg/m2 + Cisplatin 25 mg/m2 + Nab-Paclitaxel 100 mg/m2 IV Days 1, 8 of a 21-day cycle
- Gemcitabine 1000 mg/m2 + Cisplatin 25 mg/m2 IV Days 1, 8 of a 21-day cycle

Restage every 3 cycles until progression

N = 441

FIRST PATIENT IN: 2/2019

CLOSED TO ACCRUAL 2/15/2021

Primary EP: OS; **Target HR 0.7**
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

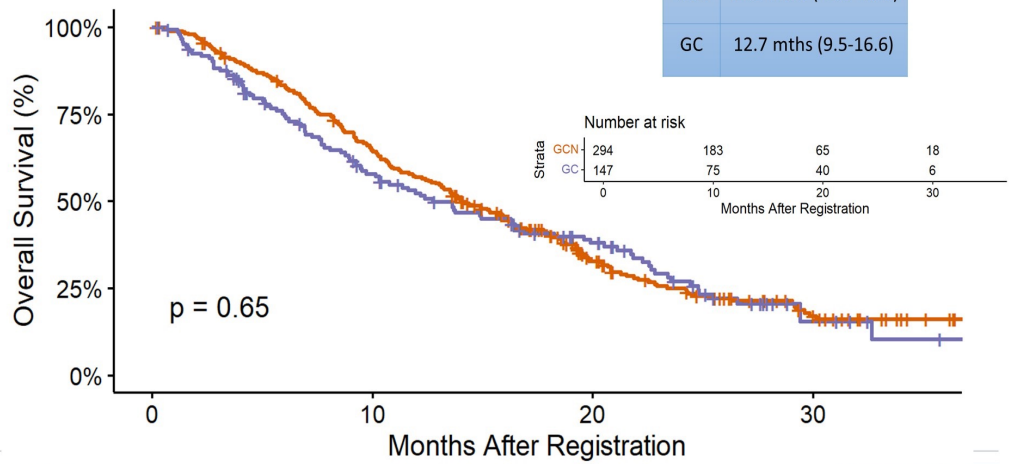
Archival blood and tissue specimens to be banked

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Overall Survival

Arm	Median (CI)
GCN	14.0 mths (12.6-16.3)
GC	12.7 mths (9.5-16.6)



SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Gr 3-4 Treatment-Related Adverse Events

Treatment-Related Adverse Event	GCN Grade 3-4 N (%)	GC Grade 3-4 N (%)
Anemia	95 (33%)	30 (22%)
Neutropenia	105 (37%)	37 (28%)
Thrombocytopenia	56 (20%)	20 (15%)
Leukopenia	72 (25%)	14 (10%)
Diarrhea	13 (5%)	1 (0.7%)
Fatigue	26 (9%)	8 (6%)
Sepsis	12 (4%)	3 (2%)
Peripheral Sensory Neuropathy	10 (4%)	1 (0.7%)

*Included if incidence ≥5% of patients.

Additional all grade AE's seen in ≥25% of patients:
Alopecia, ALT increase, Anorexia, Constipation, Edema, Hypomagnesemia, Nausea, Vomiting
Gr 5 events on GCN (N): Cardiac Arrest (1), Sepsis (3), SVC Syndrome (1), Thromboembolic Event (1), Upper GI Hemorrhage (1)

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Conclusions

- Biomarker Discovery is key to better selection of patients with BTC
- The role of immunotherapy in cholangiocarcinoma remains to be fully defined;
  - TOPAZ-1 with Gem/Cis +/- Durvalumab positive
  - KEYNOTE 966 (G/C +/- Pembro) positive
- Adding Nab-Paclitaxel to Gem/Cis did not improve outcome
- Molecularly targeted agents such as those targeting FGFR and IDH1 are providing patients with advanced cholangiocarcinoma new treatment options
  - Ongoing efforts to expand the role of targeted therapies to IDH2, BRAF V600E, Her2 amplifications and others.
  - Ongoing trials with first line strategies in iCCA and FGFR2 fusions vs. standard gemcitabine/cisplatin

Pancreatic Cancer

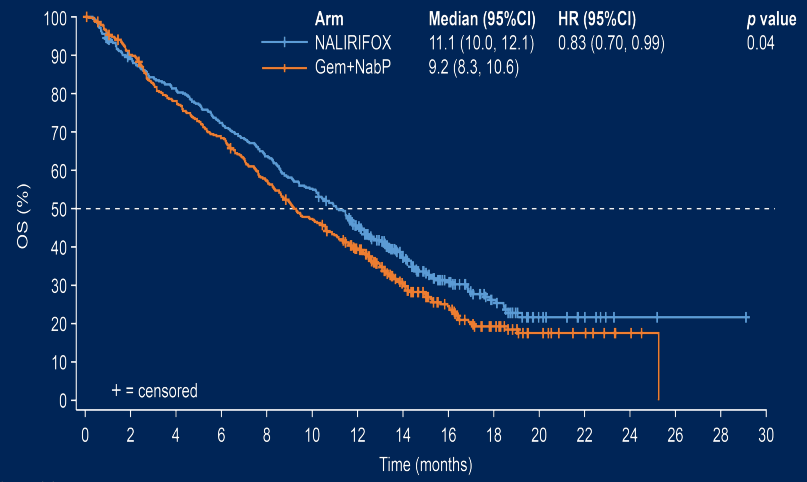
ASCO® Gastrointestinal Cancers Symposium

NAPOLI 3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma

Zev A Wainberg,[1] Davide Melisi,[2] Teresa Macarulla,[3] Roberto A Pazo Cid,[4] Sreenivasa R Chandana,[5] Christelle De La Fouchardière,[6] Andrew Dean,[7] Igor Kiss,[8] Woo Jin Lee,[9] Thorsten O Goetze,[10] Eric Van Cutsem,[11] Scott Paulson,[12] Tanios Bekaii-Saab,[13] Shubham Pant,[14] Richard Hubner,[15] Zhimin Xiao,[16] Huanyu Chen,[16] Fawzi Benzaghou,[16] Eileen M O'Reilly[17]

[1]University of California, Los Angeles, CA, USA; [2]Azienda Ospedaliera Universitaria Integrata and University of Verona, Verona, Italy; [3]Vall d'Hebrón University Hospital, Vall d´Hebrón Institute of Oncology (VHIO), Barcelona, Spain; [4]Hospital Universitario Miguel Servet, Zaragoza, Spain; [5]Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [6]Centre Leon Berard, Lyon, France; [7]St John of God Subiaco Hospital, Subiaco, WA, Australia; [8]Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czechia; [9]National Cancer Center, South Korea; [10]Krankenhaus Nordwest, Frankfurt, Germany; [11]University Hospital, University of Leuven, Leuven, Belgium; [12]Texas Oncology - Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [13]Mayo Clinic, Scottsdale, AZ, USA; [14]MD Anderson Cancer Center, Houston, TX, USA; [15]Christie NHS Foundation Trust, Manchester, UK; [16]Ipsen, Cambridge, MA, USA; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA

NAPOLI 3: mOS (ITT population)

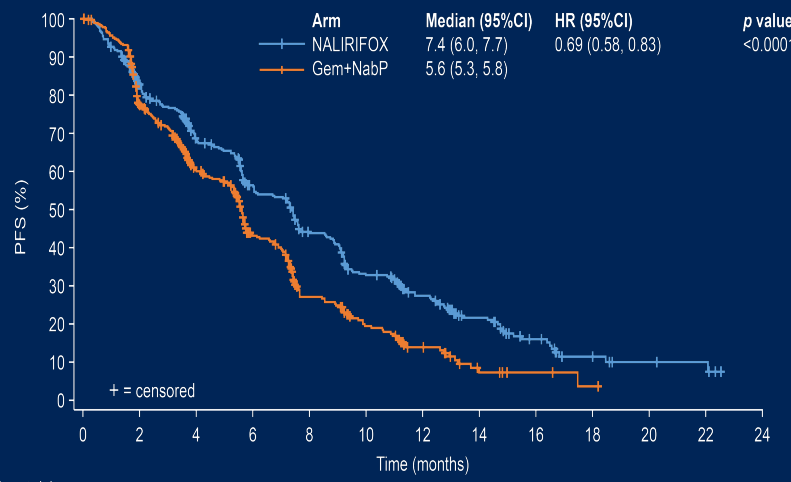


No. at risk:

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
Gem+NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0

Stratified by ECOG PS (0 vs 1), region (North America vs ROW), live metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; mOS, median overall survival; NabP, nab-paclitaxel.

NAPOLI 3: mPFS per investigator (ITT population)



No. at risk:

NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
Gem+NabP	387	267	182	112	60	38	19	6	3	1	0	0	0

Stratified by ECOG PS (0 vs 1), region (North America vs ROW), live metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; mPFS, median progression-free survival; NabP, nab-paclitaxel; PFS, progression-free survival; ROW, rest of world.

NAPOLI 3: Selected any-cause TEAEs in ≥10% of patients

	NALIRIFOX (N = 370)		Gem+NabP (N = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	Any grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Neutropenia / neutrophil count decreased / febrile neutropenia	29.5 / 20.5 / 2.4	14.1 / 9.7 / 2.4	31.9 / 18.7 / 2.6	24.5 / 13.5 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia / platelet count decreased	13.5 / 10.5	0.8 / 0.8	22.7 / 17.9	3.7 / 2.4
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy	17.8	3.2	17.4	5.8
Peripheral sensory neuropathy	15.1	3.5	13.5	2.9
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

[a]Grouped by system organ class (safety population).
Gem, gemcitabine; NabP, nab-paclitaxel; TEAE, treatment-emergent adverse event.

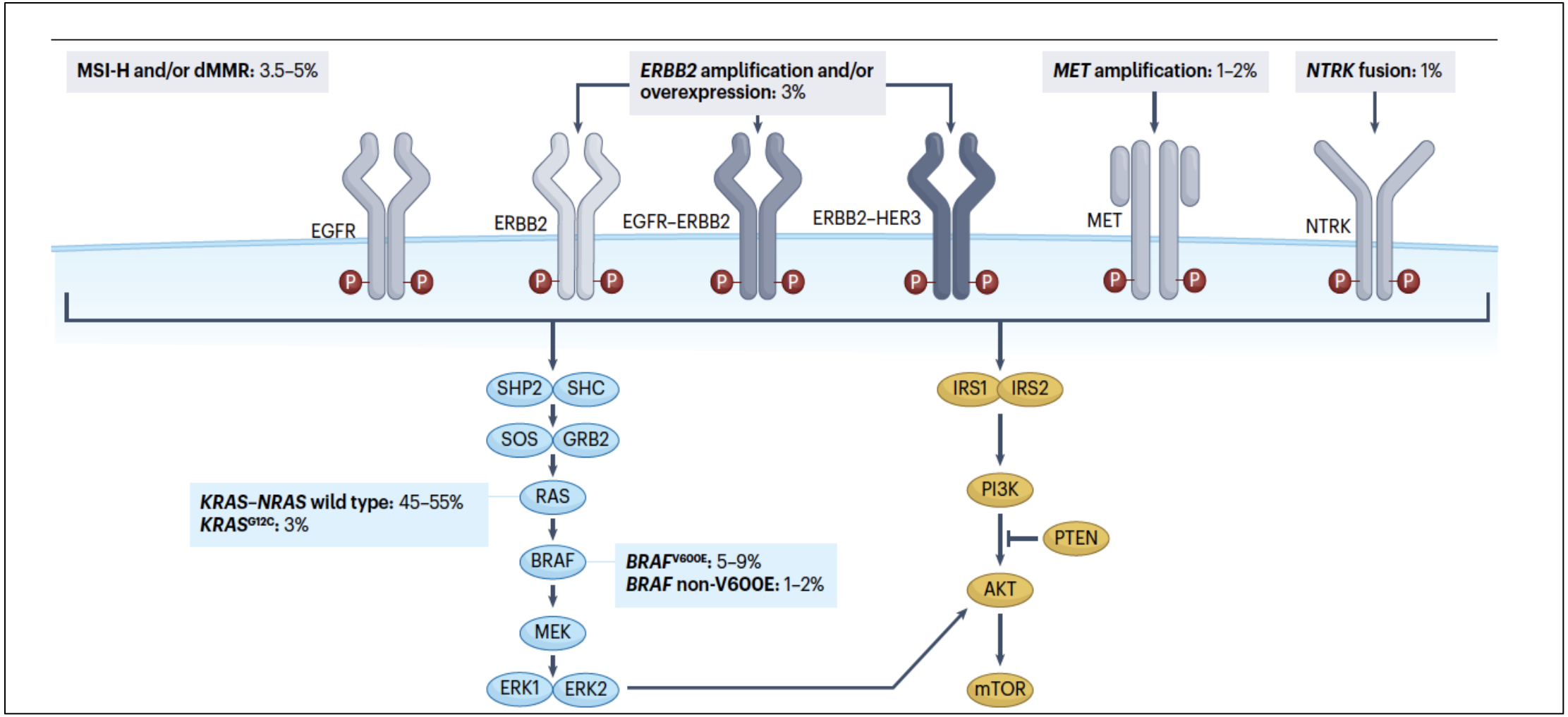
PRESENTED BY: Professor Zev A Wainberg

Conclusions

- Frontline NALIRIFOX has demonstrated survival benefit vs. gemcitabine/nab-paclitaxel in a phase III study for patients with metastatic pancreatic cancer
  - ? FOLFIRINOX ?
- Maintenance (Switch) therapy with PARP inhibitor olaparib can be considered in select patients with germline *BRCA1/2* mutation
- Novel therapies, including immunotherapeutic approaches and molecularly and metabolic targeting agents, are currently under active investigation

Colorectal Cancer

Relevant Targets in mCRC



Bando H et al et al . *Nature Rev Gastro & Hepatol.* 2023

Recent data of HER2-targeted therapies in patients with advanced or metastatic colorectal cancer

Regimen	Trial (n) – year	ORR	PFS	OS	Most common Grade 3+ AEs
Trastuzumab + lapatinib	HERACLES-A (n=32) – 2016	28%	4.7m	10m	Fatigue 16% Decreased LVEF 6%
Trastuzumab + pertuzumab	MyPathway (n=84; 57 evaluable) – 2019	32%	2.9m	11.5m	Hypokalemia 5% Abdominal pain 5%
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab deruxtecan	DESTINY-CRC01 (N=78; 53 HER2+) – 2021	45.3%	6.9m	15.5m	Neutropenia 15% Anemia 13% ILD 5+%
Tucatinib + trastuzumab	MOUNTAINEER (n	38.1%	8.2m	24.1m	Hypertension 7% Diarrhea 3.5%

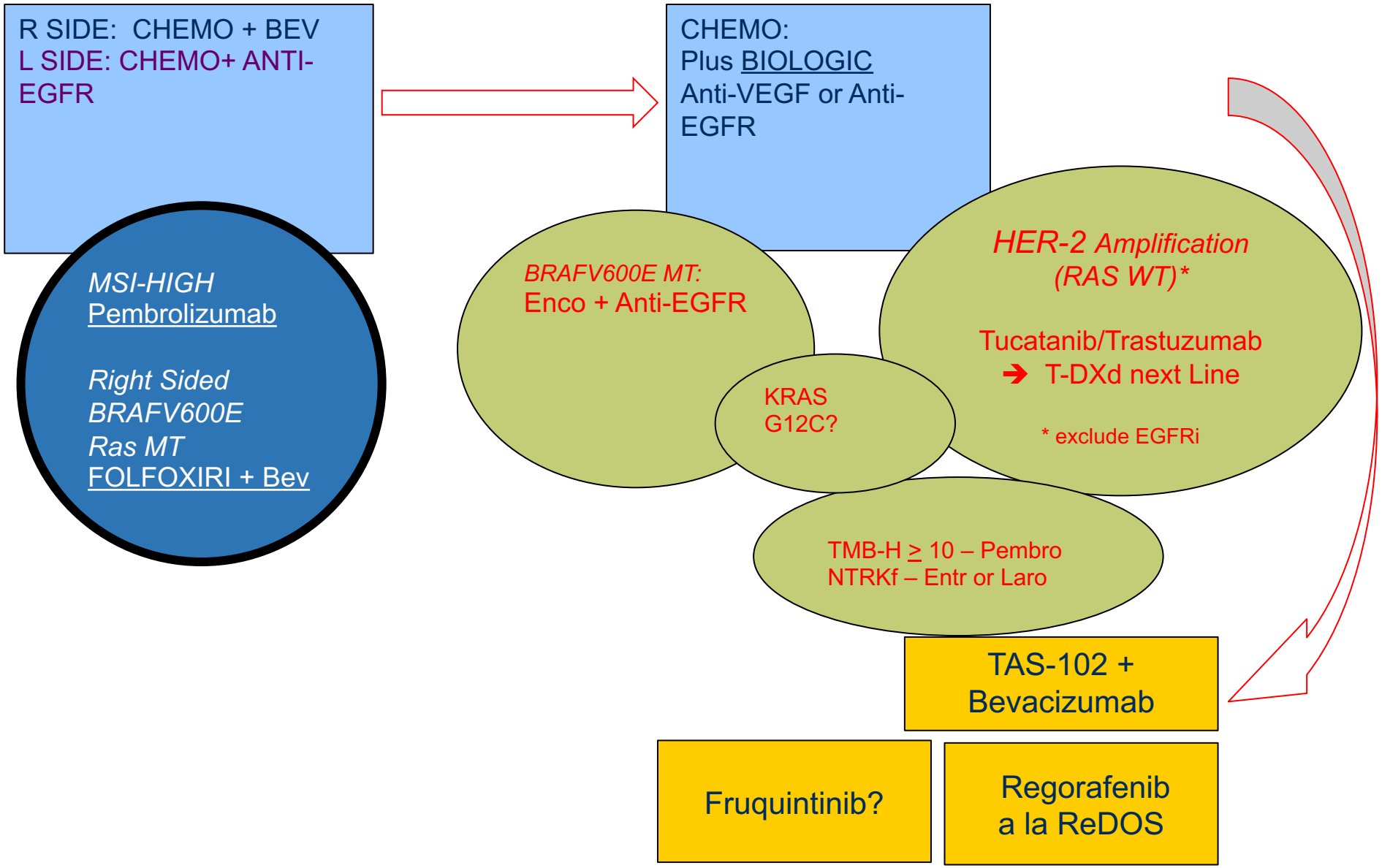
FDA Approval 1/2023

Tosi F, Sartore-Bianchi A, et al. Long-term Clinical Outcome of Trastuzumab and Lapatinib for HER2-positive Metas… e2. doi: 10.1016/j.clcc.2020.06.009. Epub 2020 Jun 27. PMID: 32919890.
Meric-Bernstam F, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from … phase 2a, multiple basket study. Lancet Oncol. 2019 Apr;20(4):518-530. doi: 10.1016/S1470-2045(18)30904-5. Epub 2019 Mar 8. PMID: 30857956; PMCID: PMC6781620.
Sartore-Bianchi A, et al. Pertuzumab and trastuzumab emtansine in patients with HER2-amplified metastatic colorectal cancer: the phase II HERACLES-B trial. ESMO Open. 2020 Sep;5(5):e000911. doi: 10.1136/esmoopen-2020-000911. PMID: 32988996; PMCID: PMC7523198.
Siena S, et al; DESTINY-CRC01 investigators. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2021 Jun;22(6):779-789. doi: 10.1016/S1470-2045(21)00086-3. Epub 2021 May 4. PMID: 33961795.
https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.3004
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.4_suppl.119

Comparison of Modern Studies with Regorafenib, TAS-102/Bev and Fruquintinib in mCRC

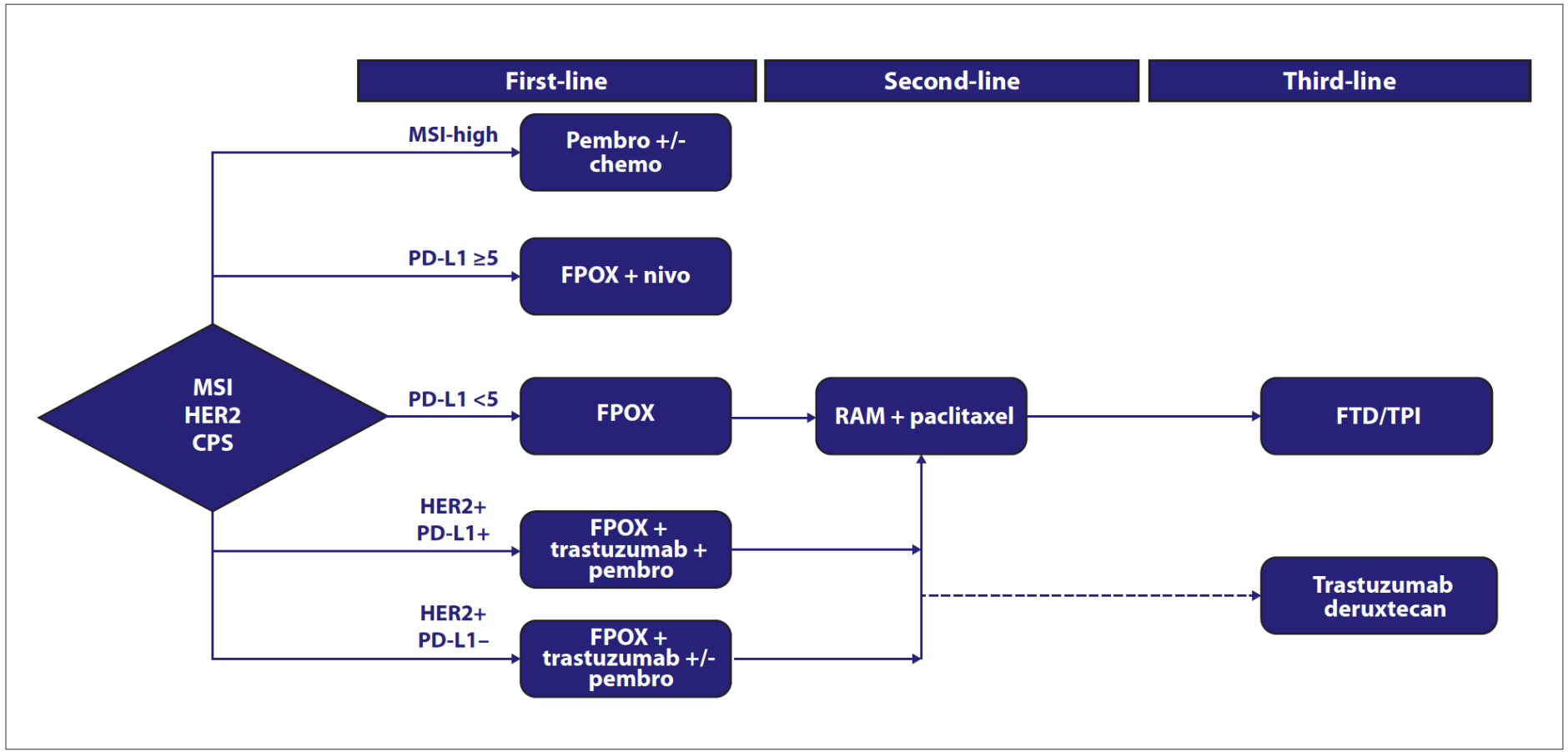
Agent	Regorafenib		Fruquintinib		TAS-102 +/-Bevacizumab			
Trial	ReDOS		FRESCO 2		SUNLIGHT + Prior Bev		SUNLIGHT – Prior Bev	
Prior biologics	100% BEV 100% EGFR mAbs		100% BEV 100% EGFR mAbs		Prior Bevacizumab (72%) ?? EGFR		No Prior Bevacizumab (28%) ?? EGFR	
	REGO (n = 54)	REGO 160 (n = 62)	FRUQ (n = 136)	BSC + PL (n = 68)	TAS 102 + Bev n = 178	TAS 102 n = 177	TAS 102+ Bev n = 68	TAS102 n = 69
Prior lines ≤2 >3	0% 100%	0% 100%	0% 100%	0% 100%	100% 0%		100% 0%	
Median OS, mo	10	6	7.4	4.8	9.0	7.1	15.1	8.1

CRC: Rx PARADIGM 2023



Gastro-Esophageal Cancers

Suggested treatment algorithm in advanced/metastatic gastroesophageal adenocarcinoma

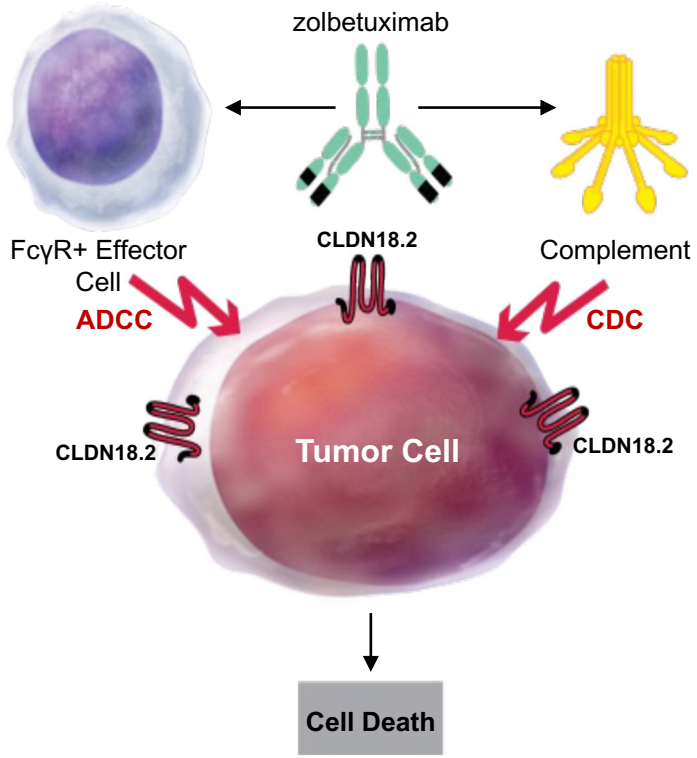


Sonbol B and Bekaii-Saab T HO , 2023

Introduction: Zolbetuximab Targets CLDN18.2

- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1–8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[4–8]
- In the phase 2b FAST study, EOX ± zolbetuximab prolonged survival in a subgroup of patients with higher expression of CLDN18.2 in tumor cells[8]
  - mPFS: 9.0 vs 5.7 months with zolbetuximab + EOX vs EOX alone
  - mOS: 16.5 vs 8.9 months with zolbetuximab + EOX vs EOX alone

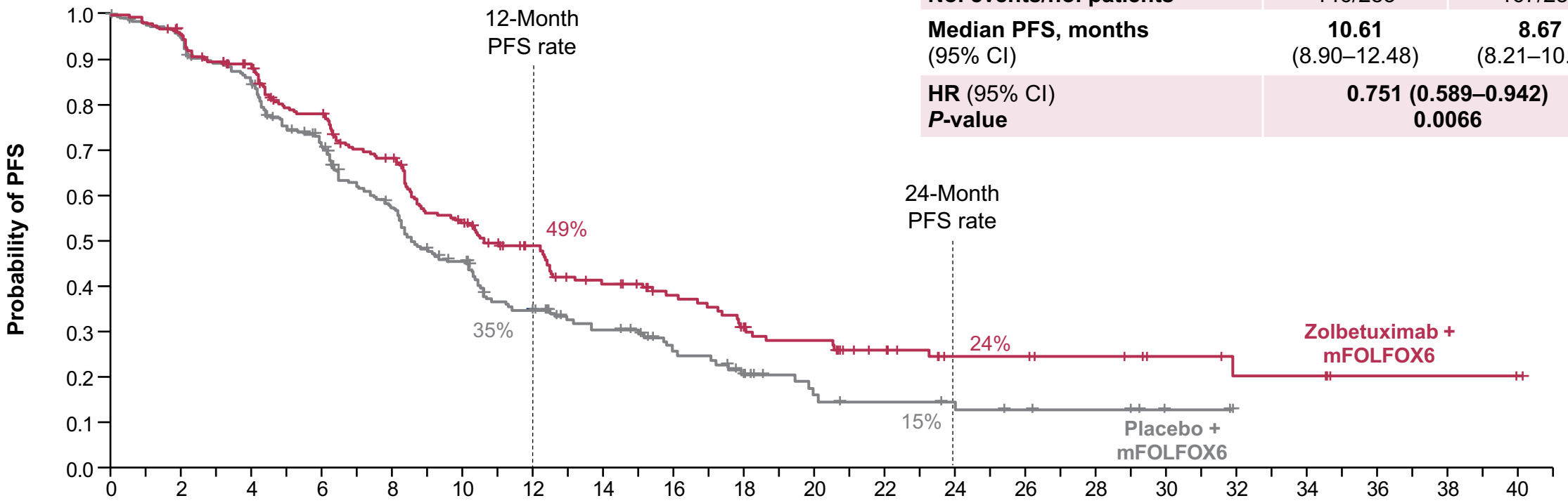
Mechanism of Action of Zolbetuximab



1. Niimi T et al. *Mol Cell Biol.* 2001;21:7380–90; 2. Sahin U et al. *Clin Cancer Res.* 2008;14:7624–34; 3. Moran D et al. *Ann Oncol.* 2018;29:viii14-viii57; 4. Sahin U et al. *Eur J Cancer.* 2018;100:17–26; 5. Rhode C et al. *Jpn J Clin Oncol.* 2019;49:870–6; 6. Türeci Ö et al. *Ann Oncol.* 2019;30:1487-95. 7. Pellino A et al. *J Pers Med.* 2021; 11(11):1095; 8. Sahin U et al. *Ann Oncol.* 2021;32:609–19.

Primary End Point: PFS by Independent Review Committee[a]

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

Dr. Kohei Shitara

Biomarker selection in esophageal & gastric adenocarcinoma

Biomarker	Prevalence in metastatic gastric cancer	Therapeutic agent(s)
ERBB2/HER2	20%	Trastuzumab + pembrolizumab
MSI-high	5% in Stage IV, 20% in Stage I-III	Pembrolizumab or nivolumab
EBV-positive	3%	Pembrolizumab or nivolumab
PD-L1 CPS	CPS ≥ 1 80%/ CPS ≥ 5 60%	Nivolumab or pembrolizumab
FGFR2b overexpression	30%	Bemarituzumab
CLDN18.2	35%	Zolbetuximab
Tumor sequencing	NTRACK , EGFR, MET, RAS amp	Larotrectinib/Entrectenib, afatinib etc
Plasma DNA	Monitoring for response and resistance	Broad application

IO

All patients with a diagnosis of a gastrointestinal cancer should be offered germline testing, as well as somatic tumor profiling to look for actionable molecular findings

QUESTIONS & ANSWERS