Cancer Center

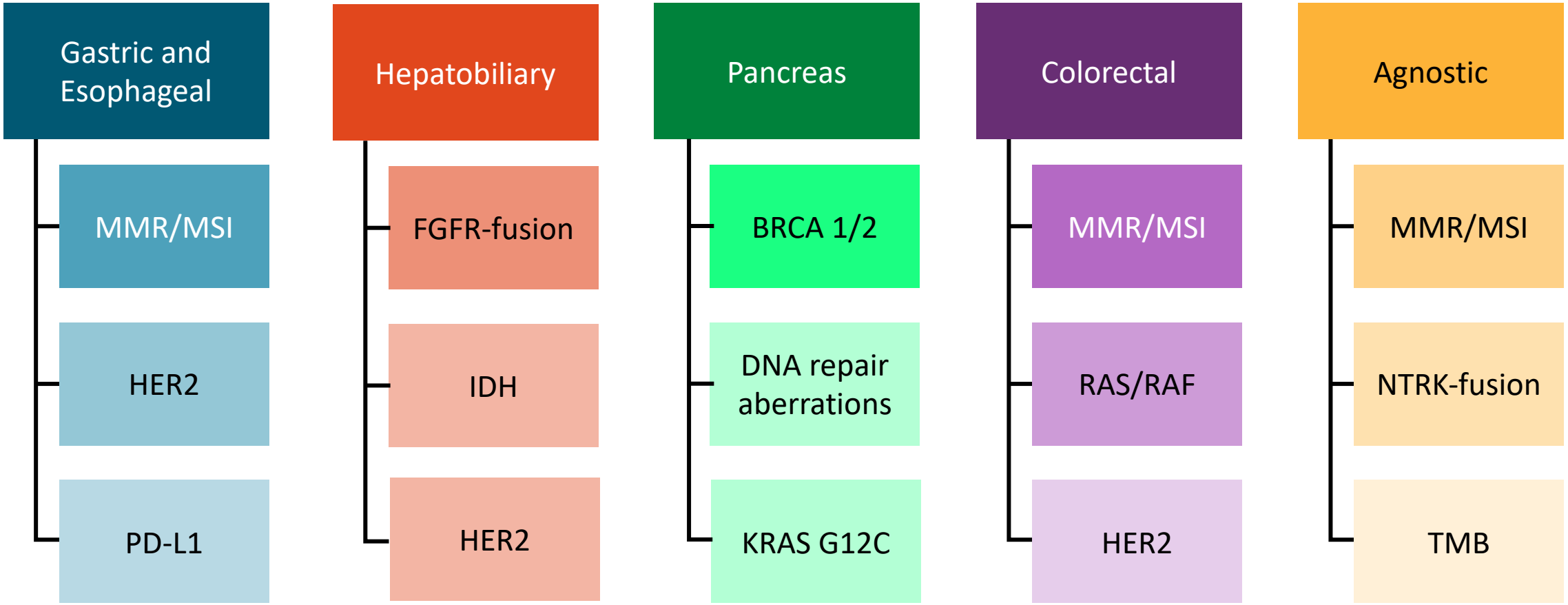
NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

PANCREAS, HEPATIC, AND CHOLANGIOCARCINOMA: *ADVANCES IN 2023*

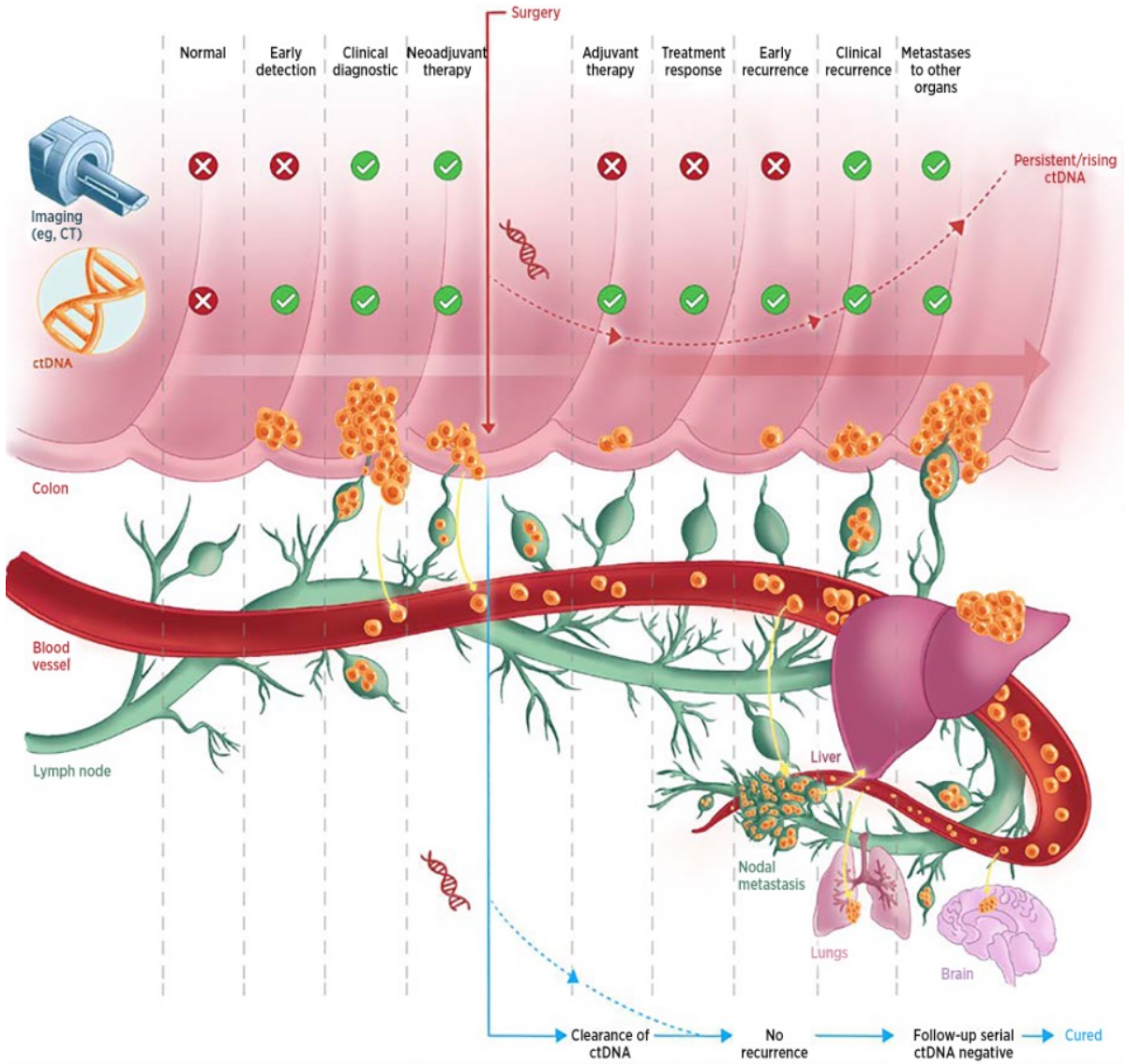
Christopher Lieu
University of Colorado

NOSCM™
NEW ORLEANS SUMMER CANCER MEETING

Key Biomarkers in GI Cancers



Potential Uses of ctDNA Assays



- Diagnosis
- Measurable Residual Disease
- Treatment Response
- Acquired Resistance

Kasi. ASCO Daily News 1.13.22. dailynews.ascopubs.org/do/10.1200/ADN.22.200792/full/.

Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

- Analysis of trial enrolment of patients with advanced GI cancers using ctDNA sequencing (GOZILA, n = 1687) vs tumor tissue sequencing (GI-SCREEN, n = 5621)

Key Findings

Outcome	GI-SCREEN (Tissue)	GOZILA (ctDNA)
Total screening duration, days	33	11
Pts enrolled in a trial, % (n/N)	4.1 (126/3055)	9.5 (60/632)
ORR, % (n/N)	16.7 (21/126)	20.0 (12/60)

Identification of Actionable Mutations

Success rate by tumor type, %	GI-SCREEN n = 5621	GOZILA n = 1687
CRC	92.3	100
GC	87.3	100
ESCC	86.2	99.1
PDAC	87.6	100
CCA	85.0	100
Others	84.7	100

Nakamura. Nat Med. 2020;26:1859.

Updates in Pancreas Cancer

Germline BRCA alterations in pancreas cancer

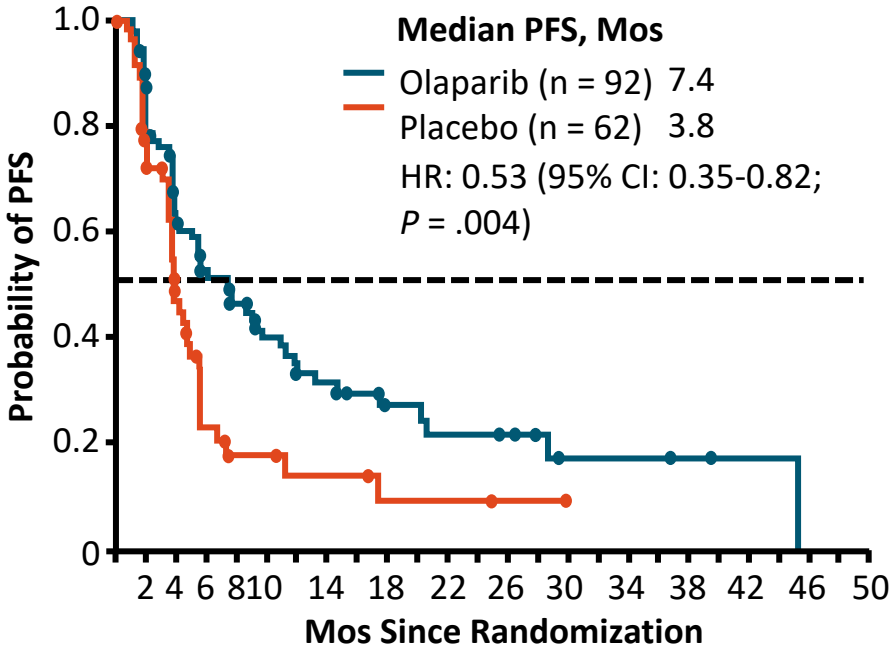
BRCA Mutations and Pancreas Cancer

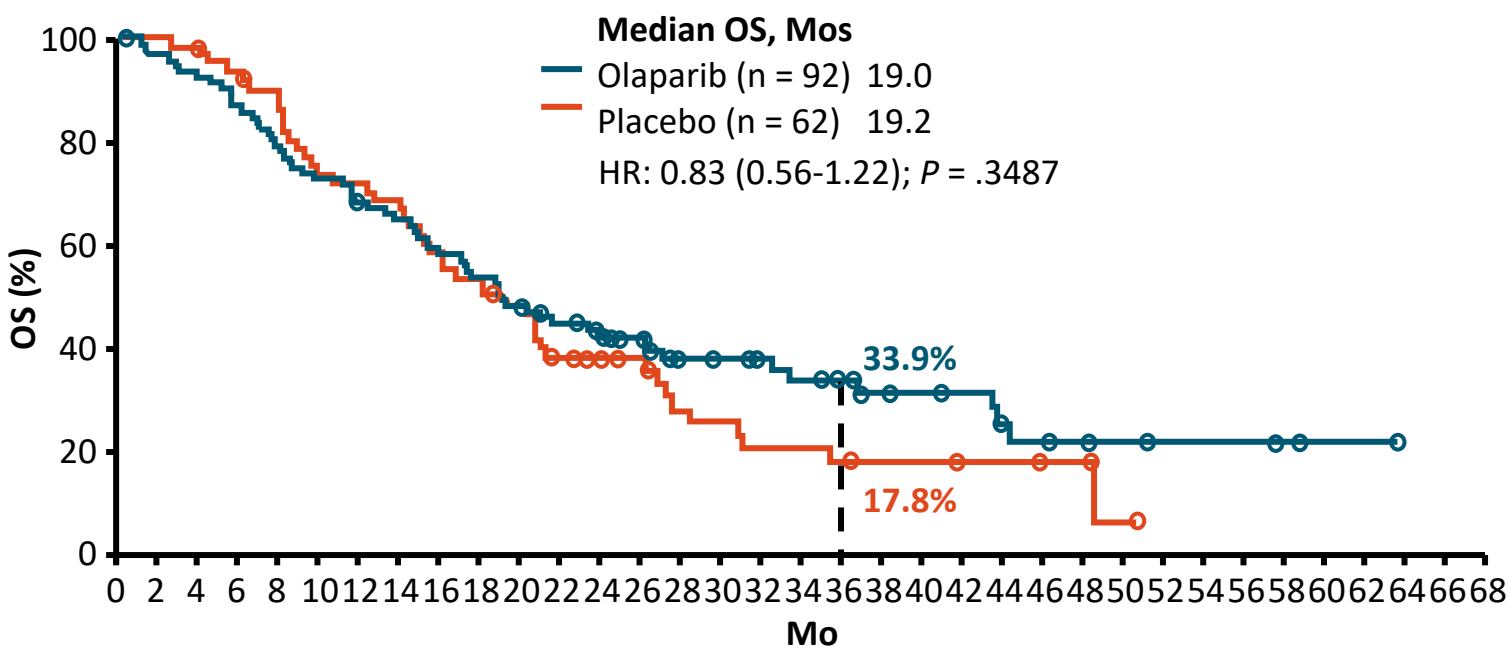
- Loss of function mutations in *BRCA1* and *BRCA2* are associated with an increased risk of pancreatic adenocarcinoma
  - 4% to 7% of patients have a germline *BRCA* mutation

- Clinical evidence suggests that platinum-based therapies may lead to improved outcomes
  - FOLFIRINOX or gemcitabine/cisplatin

POLO: Maintenance Olaparib vs Placebo After First-line Platinum-Based Therapy in Metastatic Pancreatic Cancer

- Randomized phase III trial of maintenance olaparib or placebo for patients with metastatic pancreatic cancer and deleterious/suspected deleterious g*BRCA1/2* mutation, ≥16 wk of first-line platinum-based therapy without progression (N = 154)



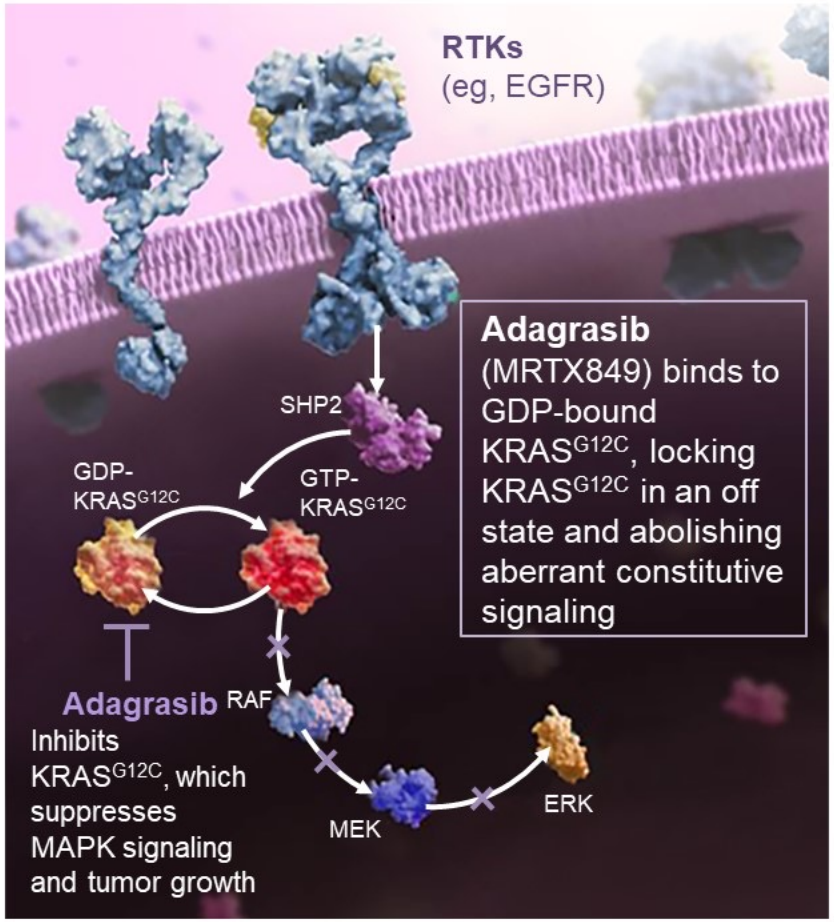


Golan. NEJM. 2019;381:317. Golan. ASCO GI 2021. Abstr 378.

KRAS G12C alterations in pancreas cancer

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

- KRAS mutations occur in approximately 90% of pancreatic cancer[1]; ~2% of these are KRAS^{G12C} mutations[2]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 hours[3,4]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor[5]:
  - Long half-life of ~24 hours
  - Dose-dependent PK
  - CNS penetration
- Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity

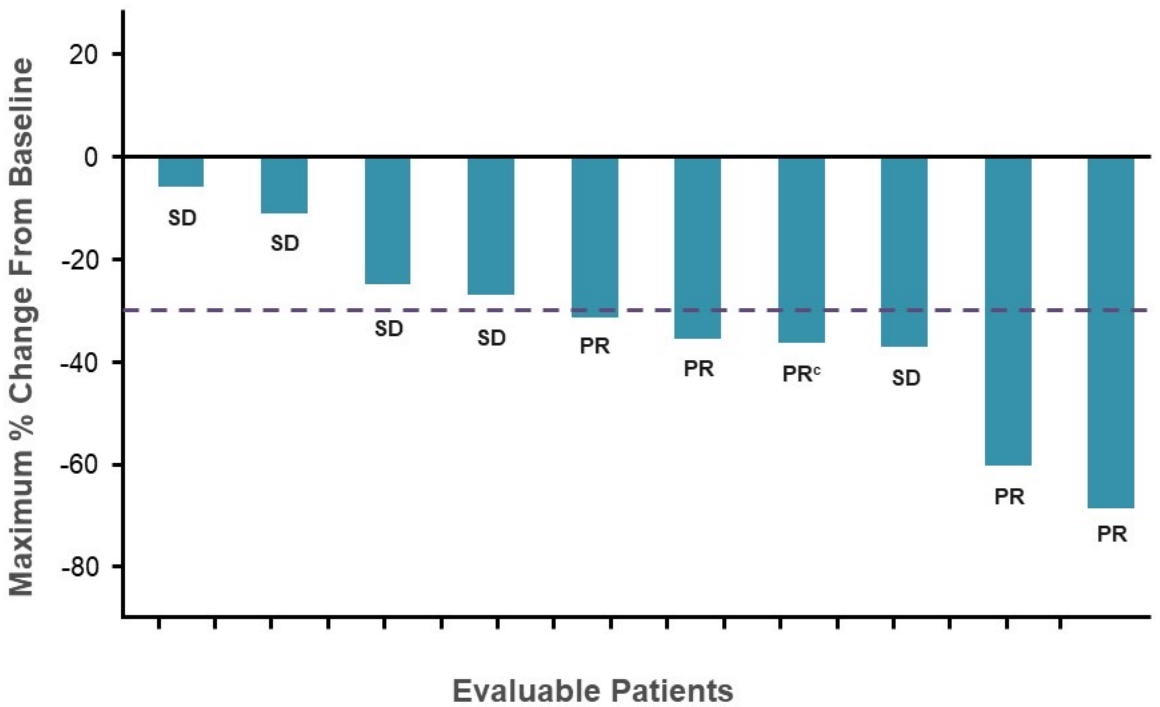


CNS, central nervous system; EGFR, epidermal growth factor receptor; PK, pharmacokinetics; RTK, receptor tyrosine kinase.

1. Prior IA, et al. *Cancer Res*. 2012;72(10):2457–2467. 2. Nollmann FI & Alexander Ruess D. *Biomedicines*. 2020;8(8):281. 3. Bos JL, et al. *Cell*. 2007;129:865–877. 4. Shukla S, et al. *Neoplasia*. 2014;16(2):115–128. 5. Hallin J, et al. *Cancer Discov*. 2020;10(1):54–71.

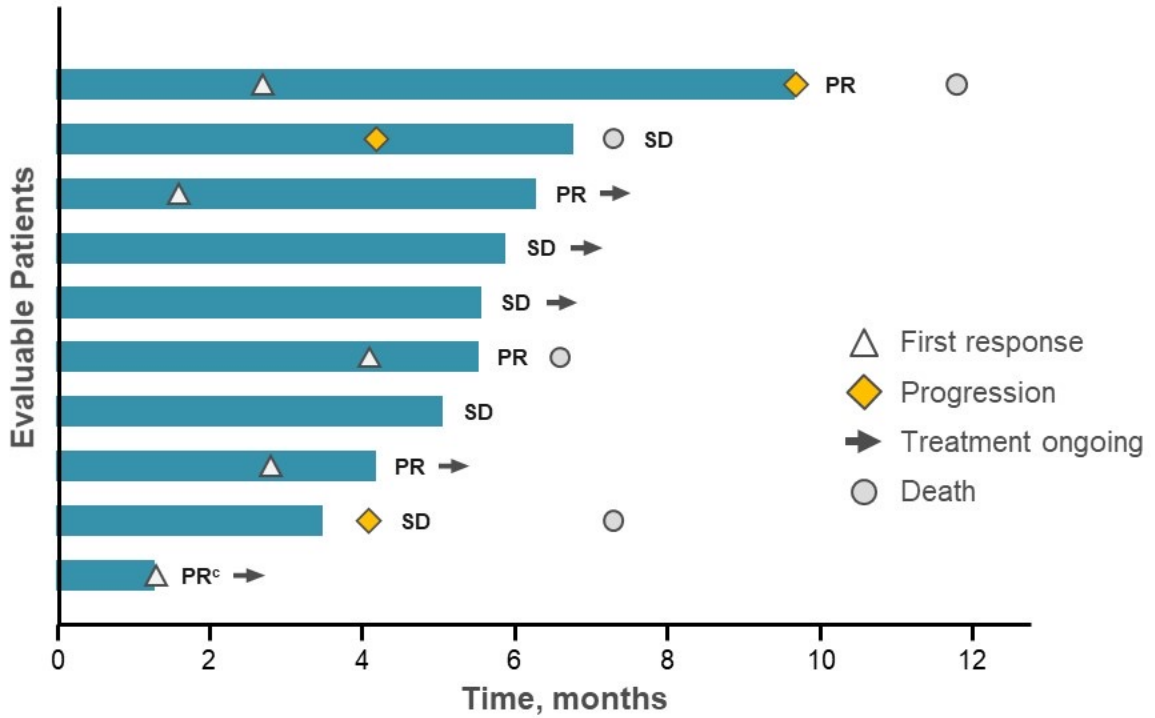
Adagrasib in Patients With Unresectable or Metastatic PDAC: Best Tumor Change From Baseline and Duration of Treatment

Best Tumor Change From Baseline (n=10)[a,b]



- Response rate: 50% (5/10), including 1 unconfirmed PR
- SD: 50% (5/10 patients)
- DCR: 100% (10/10 patients)

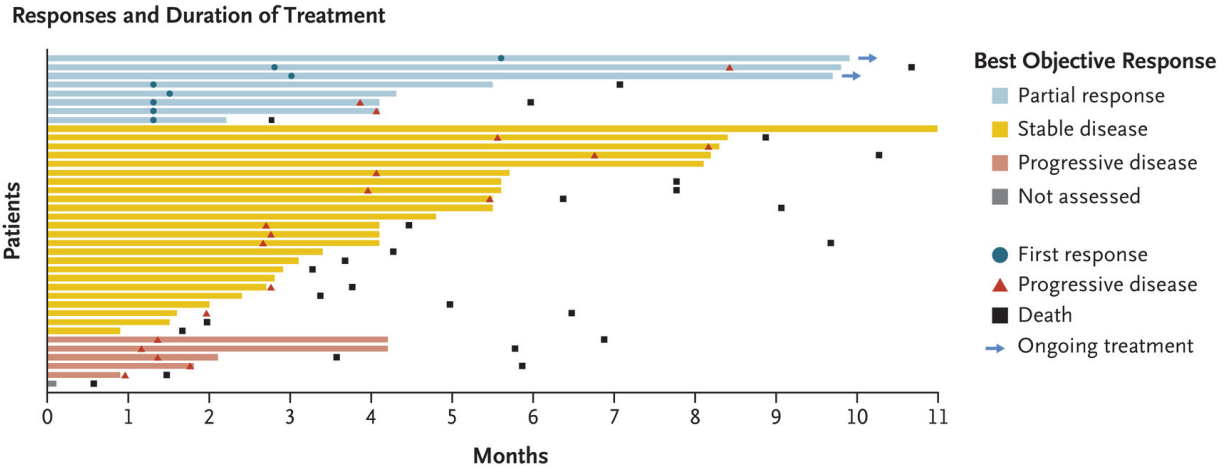
Duration of Treatment (n=10)[a,b]

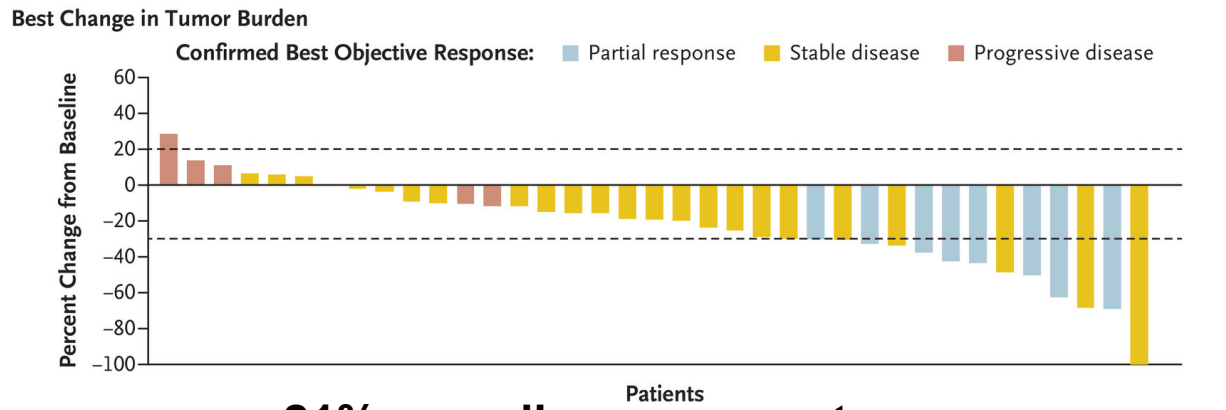


- Median TTR: 2.8 months
- Median DOR: 6.97 months
- Median PFS: 6.6 months (95% CI 1.0–9.7)
- Treatment ongoing in 50% (5/10) of patients

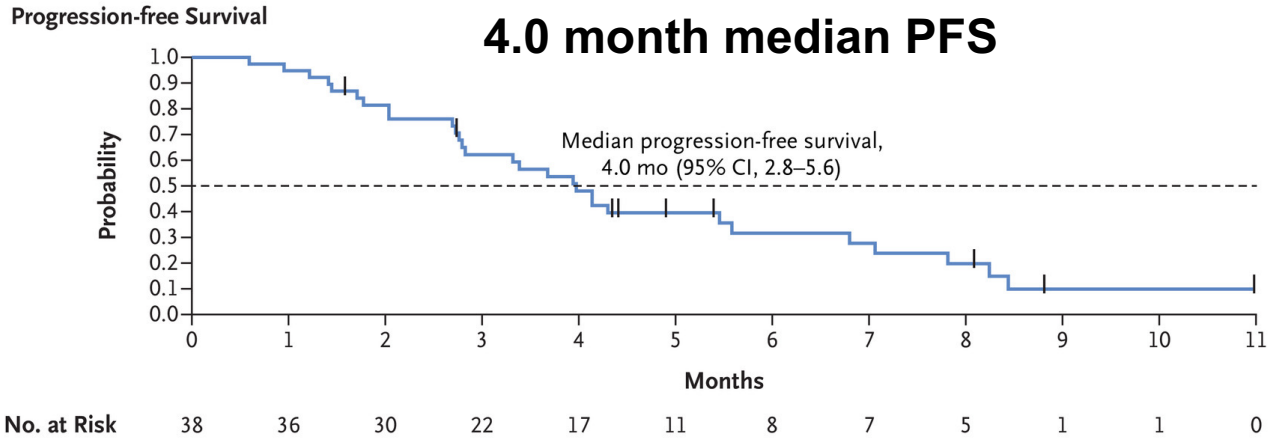
DCR, disease control rate; DOR, duration of response; PR, partial response; SD, stable disease; TTR, time to response.
[a]Evaluable population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; [b]All results are based on investigator assessments; [c]At data cut-off, 1 patient had unconfirmed PR.
Data as of 10 Sept 2021 (median follow-up: 8.1 months).

Sotorasib in KRAS G12C Pancreas Adenocarcinoma

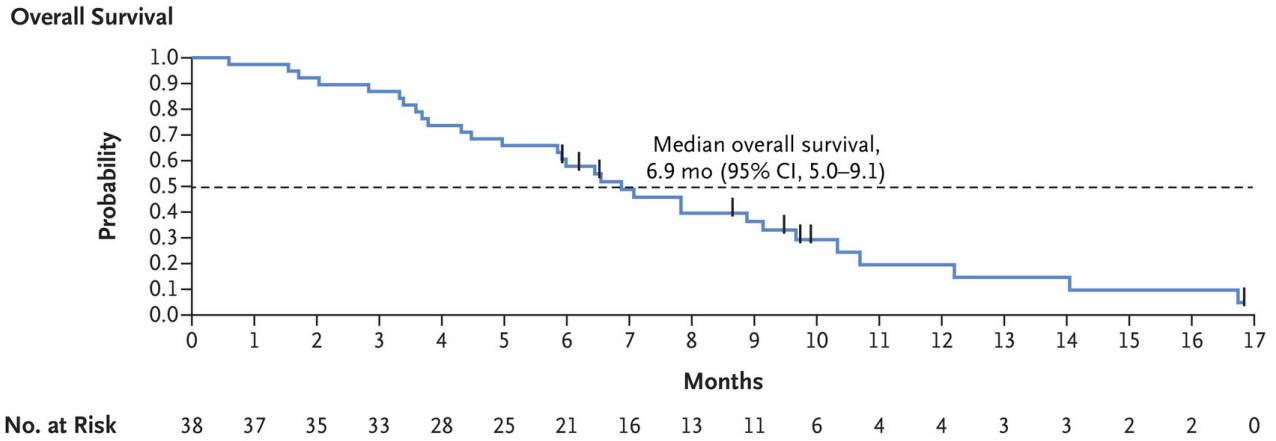




21% overall response rate



4.0 month median PFS



Strickler et al. N Engl J Med 2023

Prevent and conquer cancer. **Together.**

Take Home Points – Pancreas Cancer

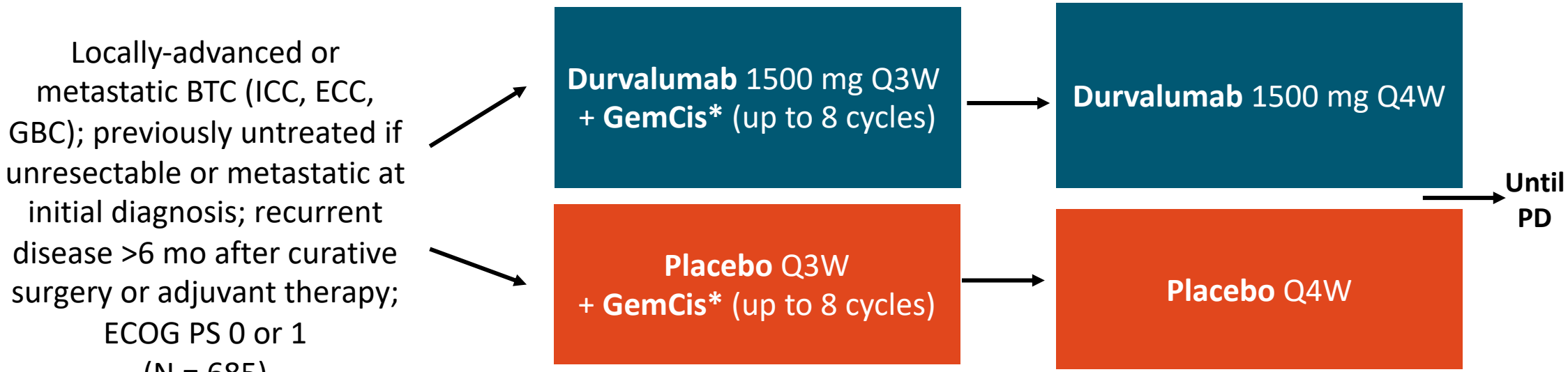
- Still a long way to go for pancreas cancer . . . BUT

- Emerging molecular targets highlight the importance of genetic testing and biomarker testing:
  - BRCA
  - KRAS G12C
  - *Tissue Agnostic: MSI-H, NTRK, BRAF V600E*

Updates in Biliary Cancers

TOPAZ-1: Durvalumab and Gemcitabine Plus Cisplatin in Patients With Advanced BTC

- Double-blind, global, multicenter phase III study of durvalumab + GemCis vs placebo + GemCis in BTC



*GemCis treatment: gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Days 1 and 8 Q3W administered up to 8 cycles.

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, ORR, and DoR, efficacy by PD-L1 status, and safety

Oh. NEJM Evid 2022;1.

TOPAZ-1: Baseline Characteristics

Characteristic	Durvalumab + GemCis (n = 341)	Placebo + GemCis (n = 344)
Median age, yr (range)	64 (20-84)	64 (31-85)
Female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
▪ Asian	185 (54.3)	201 (58.4)
▪ White	131 (38.4)	124 (36.0)
▪ African American	8 (2.3)	6 (1.7)
▪ AI or AN	0	1 (0.3)
▪ Other	17 (5.0)	12 (3.5)
Region, n (%)		
▪ Asia	178 (52.2)	196 (57.0)
▪ ROW	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)

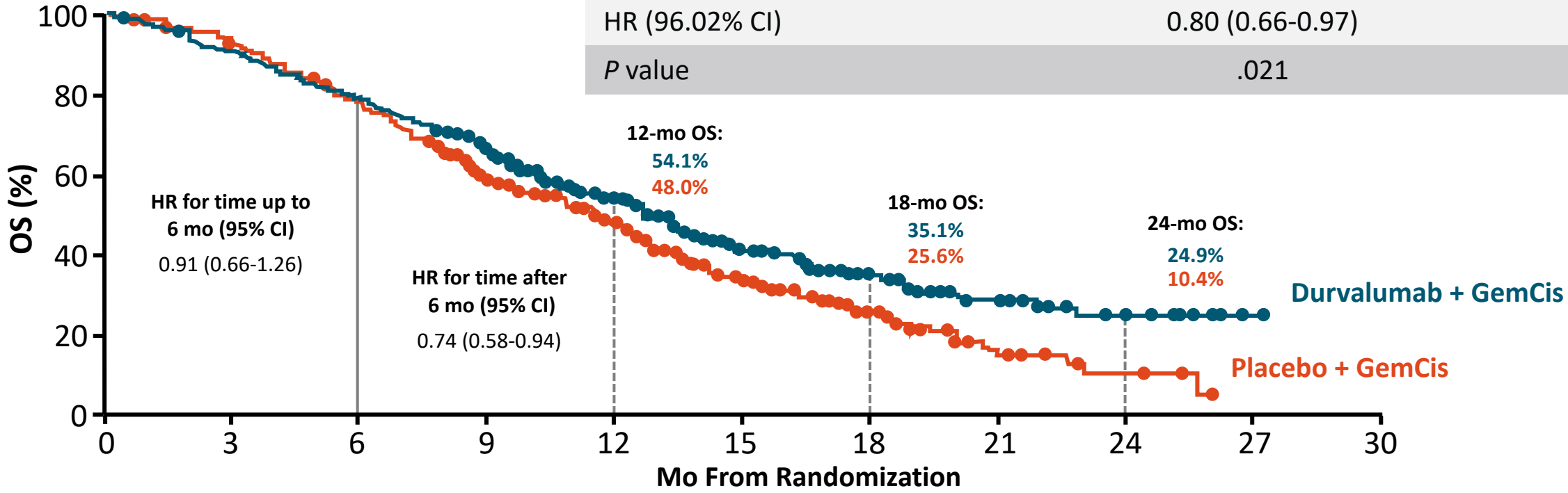
Characteristic, n (%)	Durvalumab + GemCis (n = 341)	Placebo + GemCis (n = 344)
Primary location at diagnosis		
▪ ICC	190 (55.7)	193 (56.1)
▪ ECC	66 (19.4)	65 (18.9)
▪ GBC	85 (24.9)	86 (25.0)
Disease status at randomization		
▪ Initially unresectable	274 (80.4)	279 (81.1)
▪ Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis*		
▪ Metastatic	303 (88.9)	286 (83.1)
▪ Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression*		
▪ TAP ≥1%	197 (57.8)	205 (59.6)
▪ TAP <1%	103 (30.2)	103 (29.9)

*Data missing for remaining patients. Unless otherwise indicated measurements taken at baseline.

Oh. ASCO GI 2022. Abstr 378. Oh. NEJM Evid 2022;1.

TOPAZ-1: Efficacy

Parameter	Durvalumab + GemCis (n = 341)	Placebo + GemCis (n = 344)
Median OS, mo (95% CI)	12.8 (11.1-14.0)	11.5 (10.1-12.5)
HR (96.02% CI)	0.80 (0.66-0.97)	
P value	.021	



- ORR: durvalumab + GemCis, 26.7%; placebo + GemCis, 18.7%; OR: 1.60 (95% CI: 1.11-2.31)
- Durvalumab + GemCis now FDA approved for patients with locally advanced or metastatic BTC

Oh. NEJM Evid 2022;1. Durvalumab PI.

TOPAZ-1: Safety Summary

AE	Durvalumab + GemCis (n = 338)	Placebo + GemCis (n = 342)
Median duration of exposure, mo (range)		
▪ Durvalumab/placebo	7.3 (0.1-24.5)	5.8 (0.2-21.5)
▪ Gemcitabine	5.2 (0.1-8.3)	5.0 (0.2-8.6)
▪ Cisplatin	5.1 (0.1-8.3)	4.9 (0.2-8.5)
Any AE, n (%)	336 (99.4)	338 (98.8)
Any TRAE, n (%)	314 (92.9)	308 (90.1)
Any grade 3/4 AE, n (%)	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE, n (%)	212 (62.7)	222 (64.9)
Any serious AE, n (%)	160 (47.3)	149 (43.6)
Any serious TRAE, n (%)	53 (15.7)	59 (17.3)
Any AE leading to discontinuation, n (%)	44 (13.0)	52 (15.2)
Any TRAE leading to discontinuation, n (%)	30 (8.9)	39 (11.4)
Any AE leading to death, n (%)	12 (3.6)	14 (4.1)
Any TRAE leading to death, n (%)	2 (0.6)	1 (0.3)
Any immune-mediated AE, n (%)	43 (12.7)	16 (4.7)

Oh. NEJM Evid 2022;1.

Cholangiocarcinoma: Target-Rich Disease

Target	~Frequency in CC	Drug(s)	Benefit	Status
MSI-H/dMMR	3%	Pembrolizumab	ORR: 40%[1]	Tumor agnostic approval
TMB >10 mut/Mb	2.4%	Pembrolizumab	ORR: 29%[1]	Tumor agnostic approval
NTRK fusion	1%	Entrectinib, larotrectinib	ORR: up to 75%[2,3]	Tumor agnostic approval
FGFR2 fusion	14% (intrahepatic)	Pemigatinib, infigratinib, futibatinib	ORR: 37% (pemigat); 42% (futibat)[4,5]	Cholangiocarcinoma approval
IDH1 mutation	10%-20% (intrahepatic)	Ivosidenib	PFS HR: 0.37[6]	Cholangiocarcinoma approval
BRAF V600E	4%	Dabrafenib/trametinib	ORR: 41% (ROAR)[7]	Tumor agnostic approval
RET	1%	Selpercatinib	Responses reported	Tumor agnostic approval
HER2	9% of BTC*†	Pertuzumab/trastuzumab	ORR: 23% (MyPathway)[8]	Open-label basket study
BRCA1/2, DDR	20%*	PARP inhibitor	Responses reported	Case reports
ROS1	1%	Crizotinib	Response reported	Case reports

Most common in *extrahepatic or †GB.

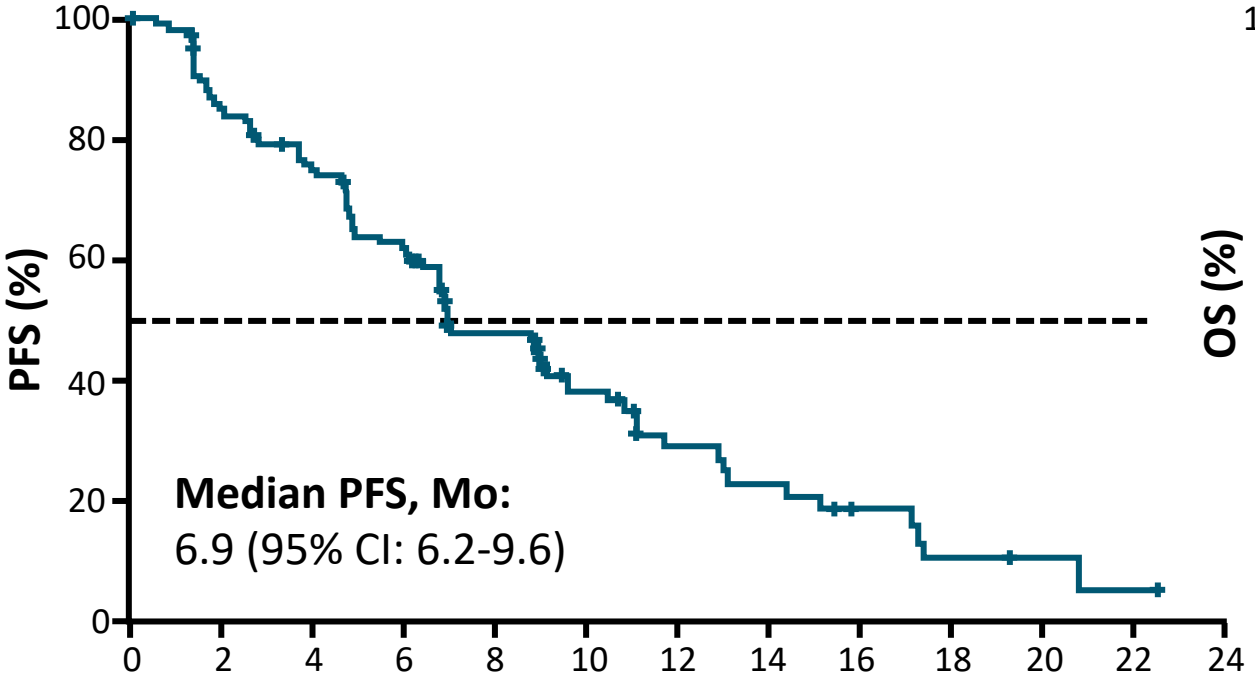
1. Pembrolizumab PI. 2. Entrectinib PI. 3. Larotrectinib PI. 4. Pemigatinib PI. 5. Futibatinib PI. 6. Ivosidenib PI.
7. Subbiah. Lancet Oncol. 2020;21:1234. 8. Javle. Lancet Oncol. 2021;22:1290. 9. Subbiah. ASCO 2020. Abstr 109.
Thornblade. Cancers (Basel). 2021;13:4062.

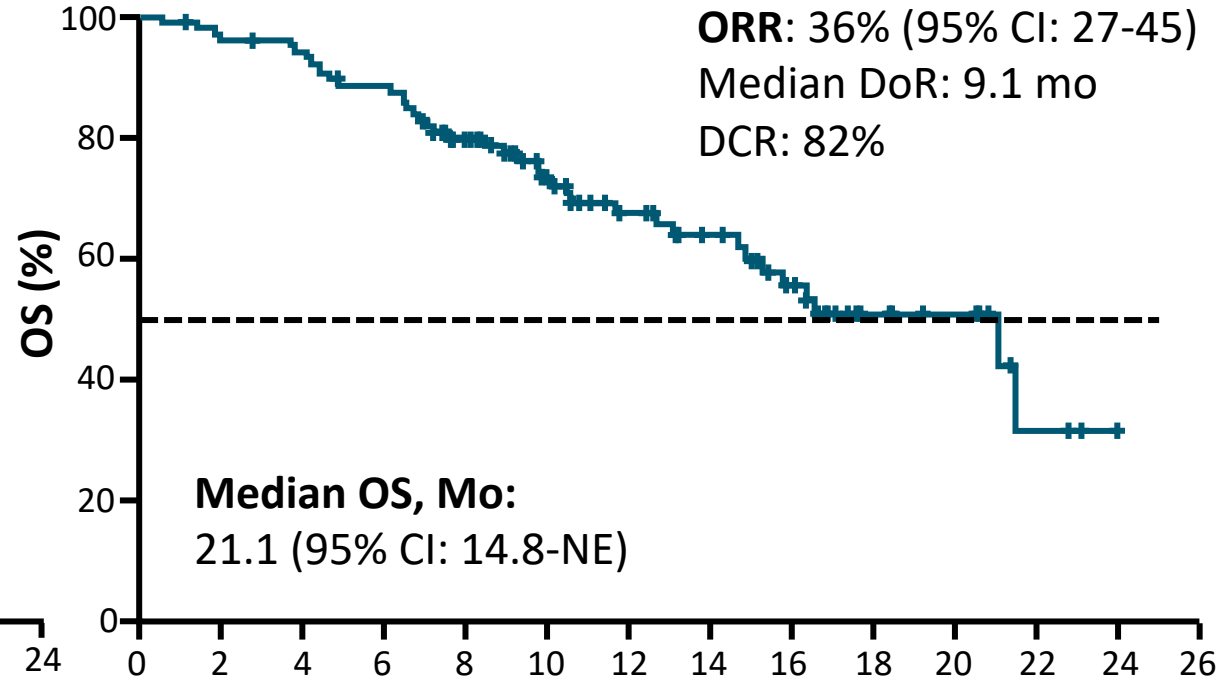
FGFR2 Fusions in Cholangiocarcinoma

14% of intrahepatic cholangiocarcinomas

FIGHT-202: Pemigatinib in Previously Treated Cholangiocarcinoma With *FGFR2* Fusions

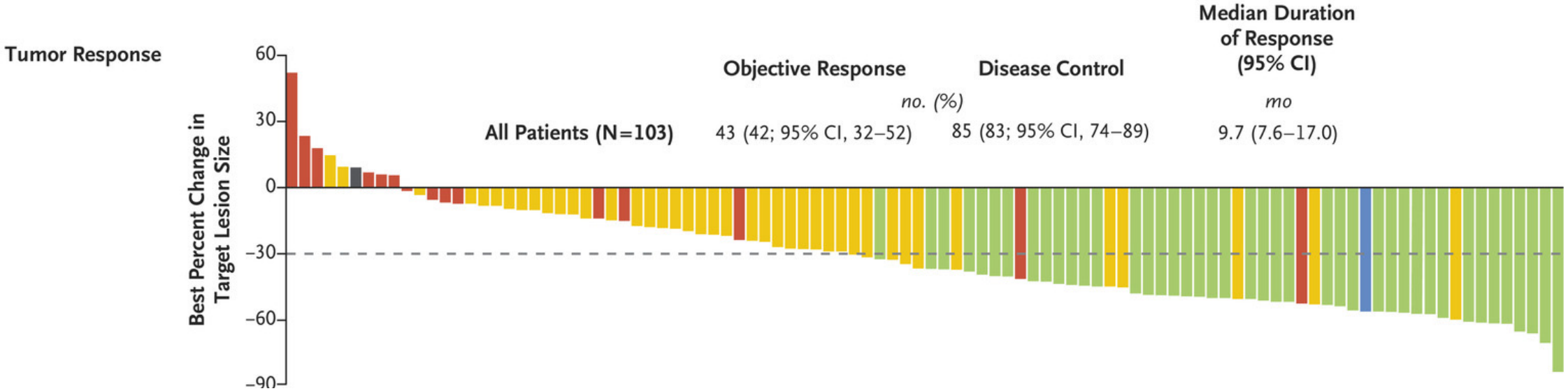
- Open-label, multicohort phase II trial of pemigatinib for patients with advanced cholangiocarcinoma and documented *FGF/FGFR2* status with progression on or after ≥1 prior line of systemic therapy (cohort A included patients with cholangiocarcinoma with *FGFR2* fusions; n = 107)

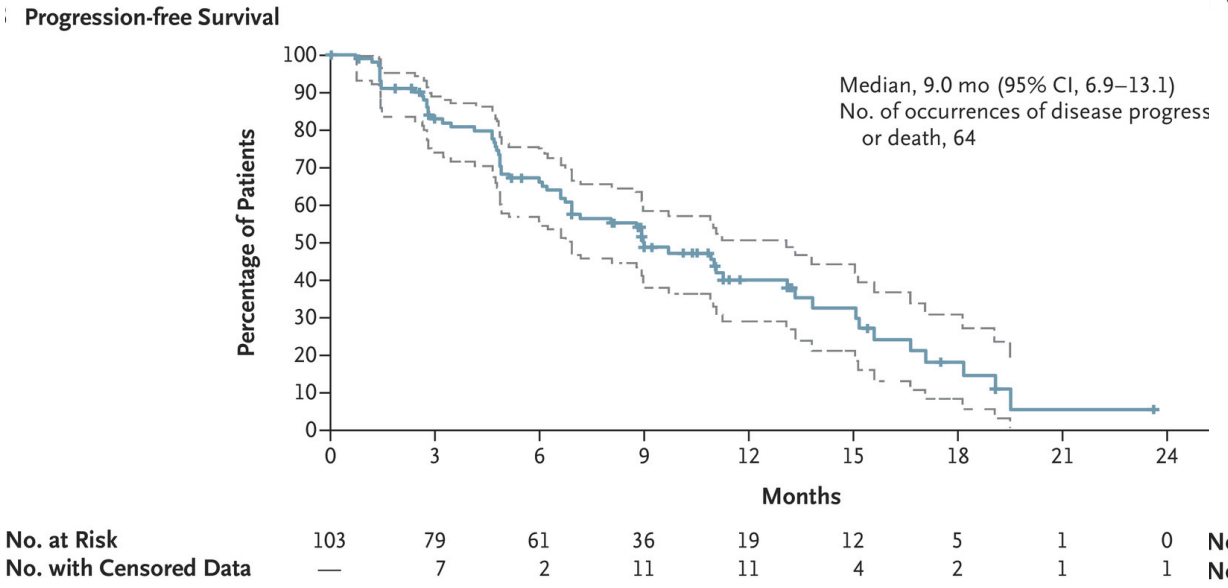


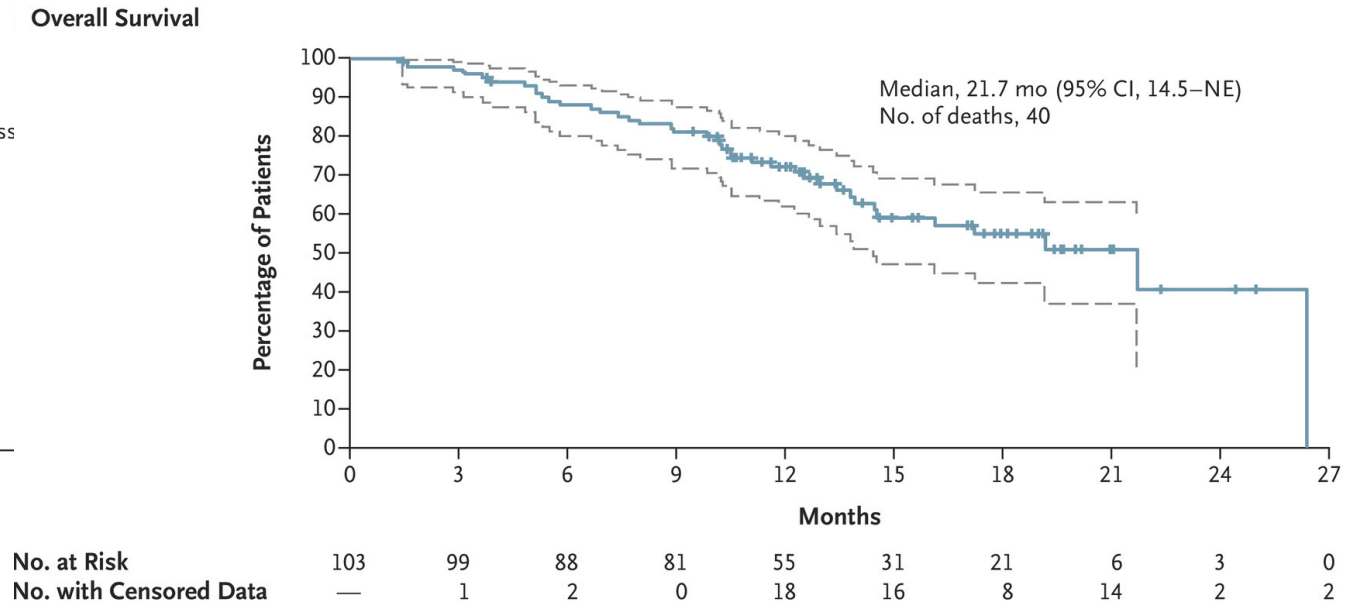


Abou-Alfa. Lancet Oncol. 2020;21:671.

Antitumor Activity of Futibatinib







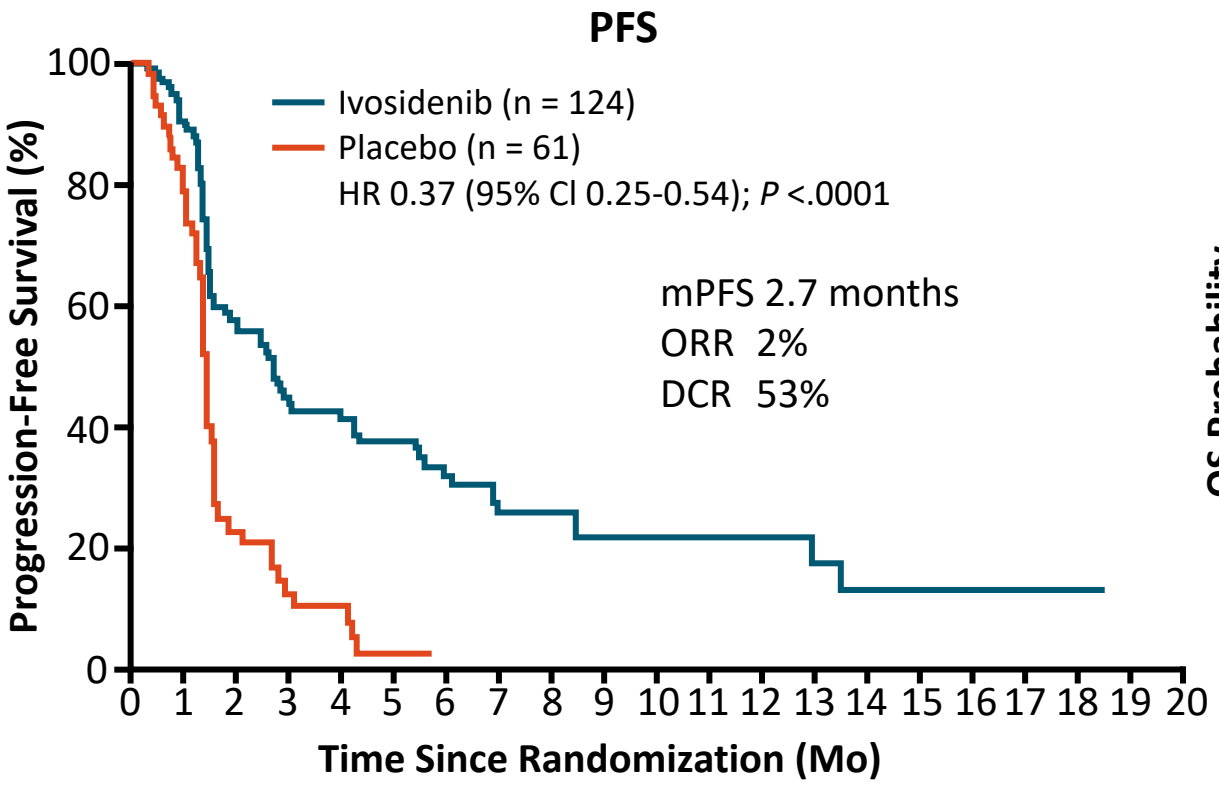
Goyal et al. *N Engl J Med* 2023.

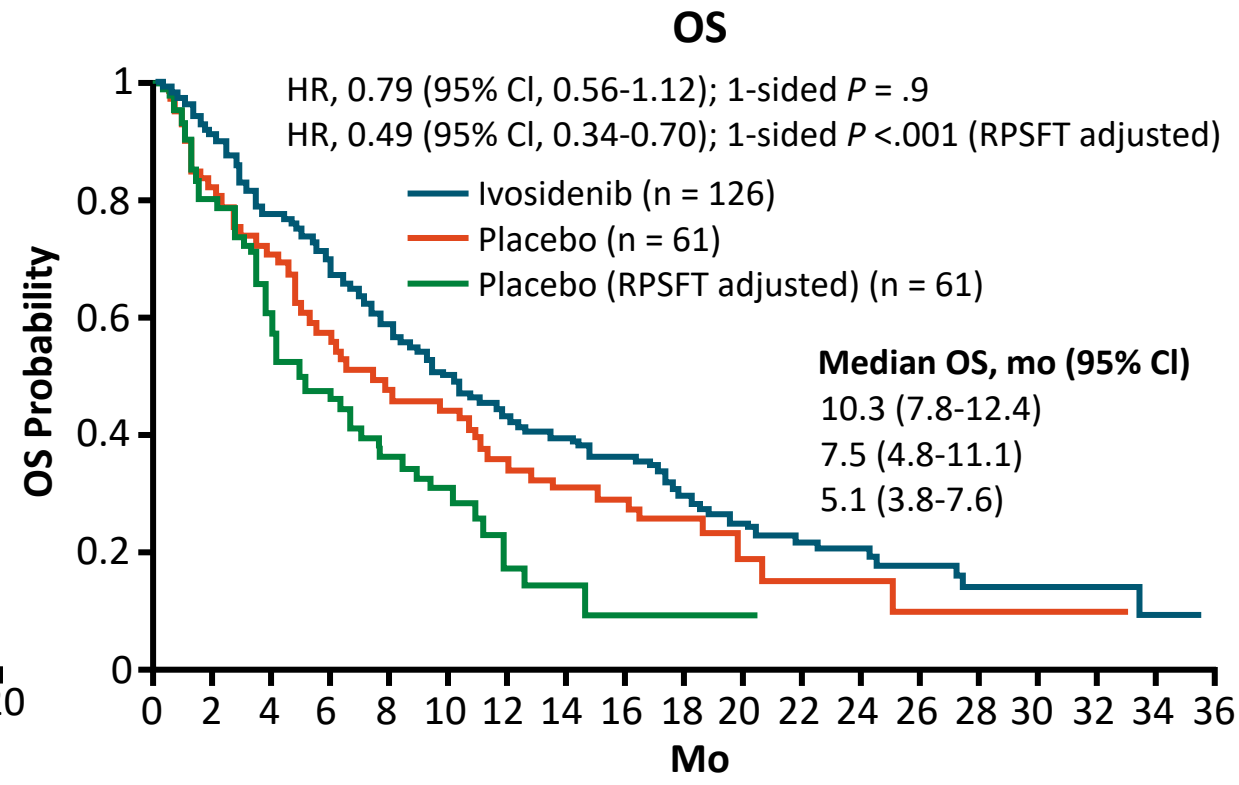
IDH1 Mutations in Cholangiocarcinoma

10-20% of intrahepatic cholangiocarcinomas

ClarIDHy: Ivosidenib vs Placebo in Previously Treated Cholangiocarcinoma With *IDH1* Mutation

- Double-blind, randomized phase III trial of ivosidenib vs placebo for patients with cholangiocarcinoma and *IDH1* mutation; 1-2 prior therapies (at least 1 gemcitabine- or 5-FU–containing regimen) (N = 187)





Abou-Alfa. Lancet Oncol. 2020;21:796. Zhu. JAMA Oncol. 2021;e213836. Zhu. ASCO GI 2021. Abstr 266.

HER2 amplifications in Cholangiocarcinoma

9% of cholangiocarcinomas

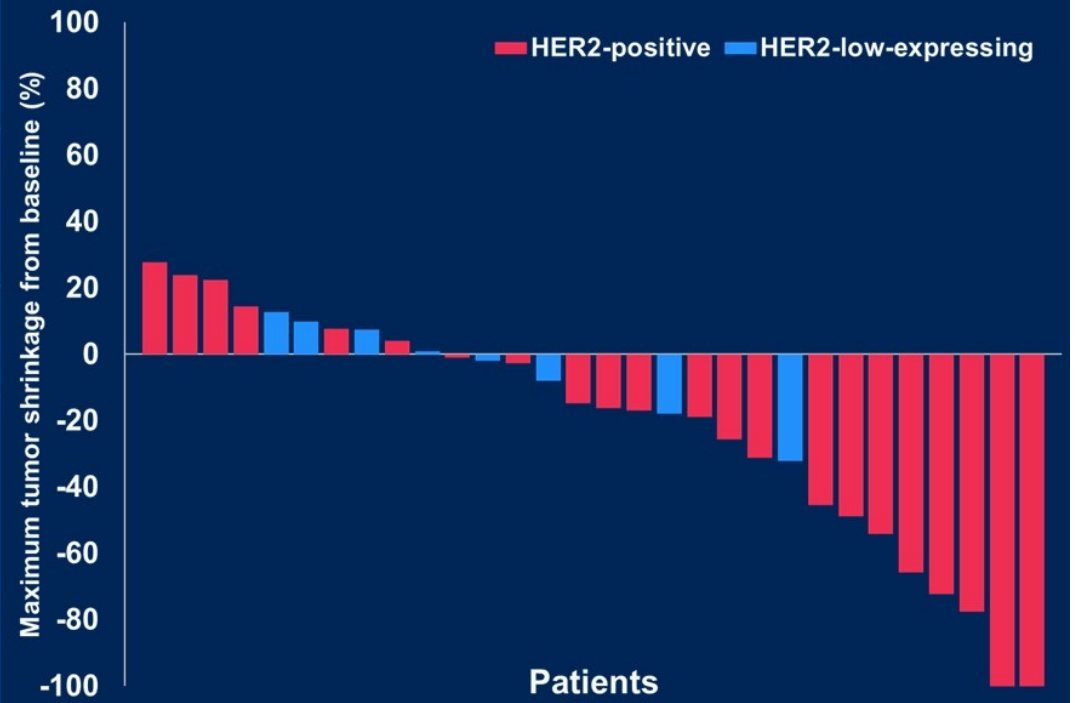
Trastuzumab deruxtecan in HER2-positive biliary tract cancer

- Tumor response

*: P =0.01

	HER2-positive (n=22)	HER2-low-expressing (n=8)	All pts (n=30)
Confirmed ORR (90% CI) (95% CI)	**36.4% (19.6-56.1)*** (17.2–59.3)	12.5% – (0.3–52.7)	30.0% – (14.7–49.4)
Confirmed DCR (95% CI)	81.8% (59.7–94.8)	75.0% (34.9–96.8)	80.0% (61.4–92.3)
Confirmed best response, n (%)			
CR	2 (9.1)	0 (0)	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)

- Best percentage change

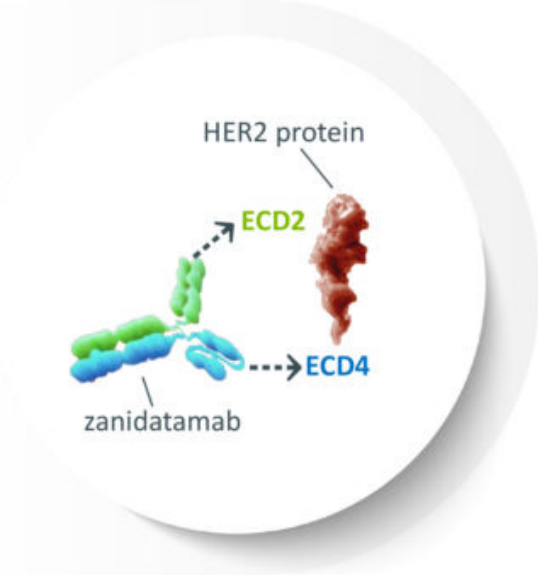


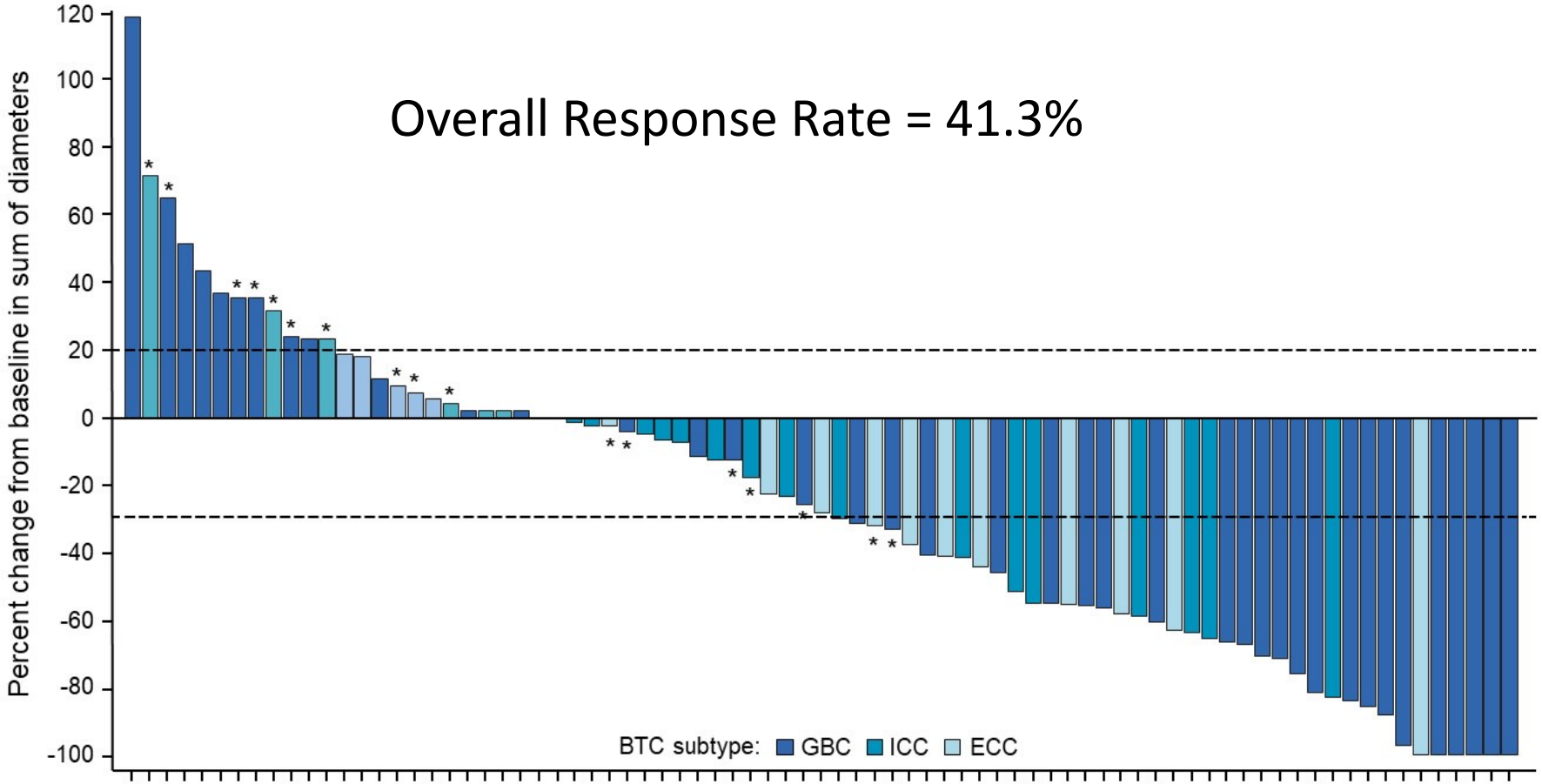
Overall Response Rate = 36.4%

Ohba et al. 2022 ASCO Annual Meeting

Zanidatamab in HER2 amplified Biliary Tract Cancers

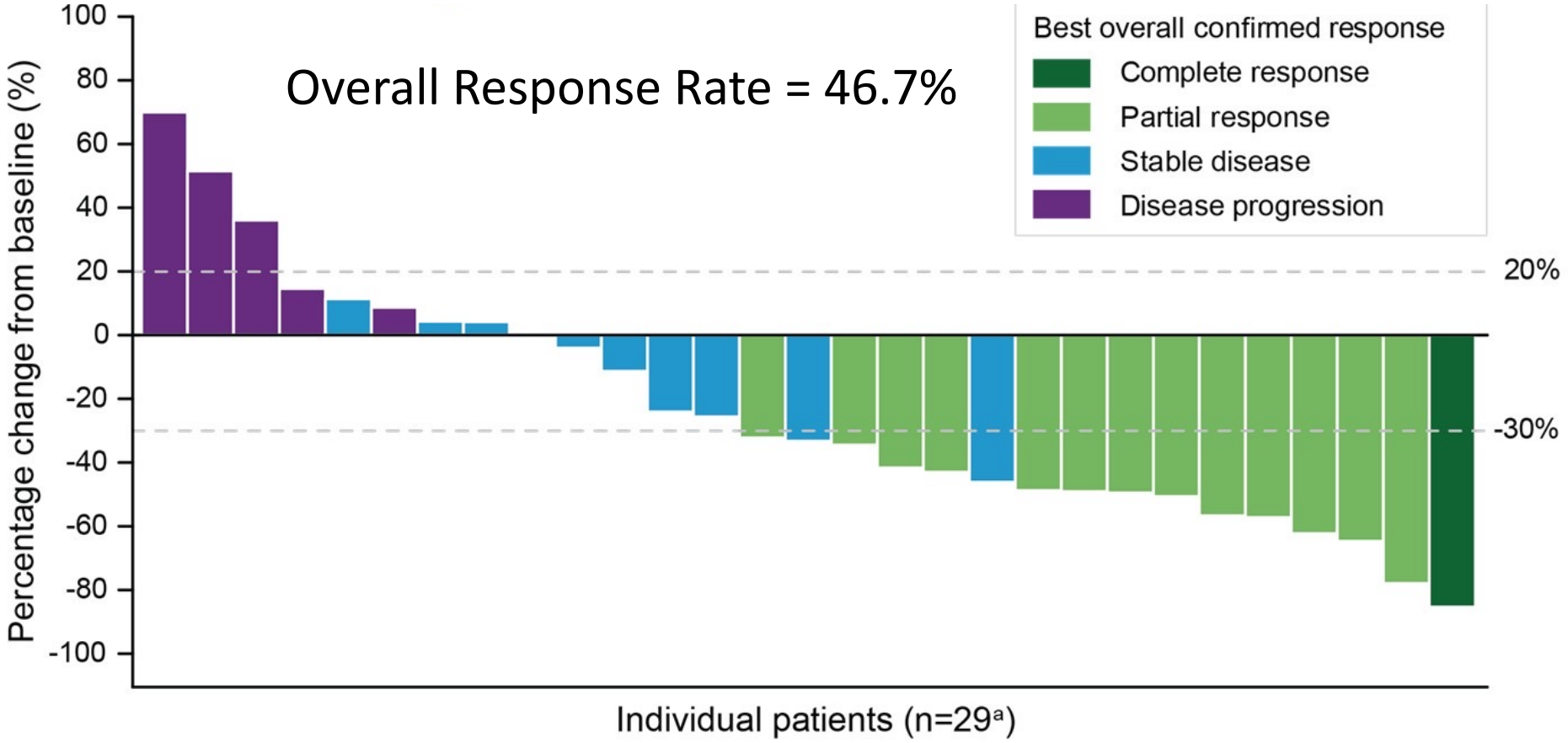
- Biparatropic: targets two distinct HER2 epitopes
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC





Pant et al. 2023 ASCO Annual Meeting

Tucatinib and Trastuzumab in HER2-amplified BTC



Twenty-one patients (70.0%[b]) had a reduction in tumor size
Median time to first response was 2.1 months (range, 1.2-4.3)

Nakamura, et al. 2023 ASCO Annual Meeting

Take Home Points – Biliary Cancers

- Gemcitabine and cisplatin in combination with durvalumab is the standard of care regimen for untreated metastatic biliary cancers

- FDA-approved targeted therapies highlight the importance of early biomarker testing in the metastatic setting
  - FGFR2 fusions
  - IDH1 mutations
  - MSI-H
  - BRAF V600E
  - HER2?

Updates in Hepatocellular Carcinoma

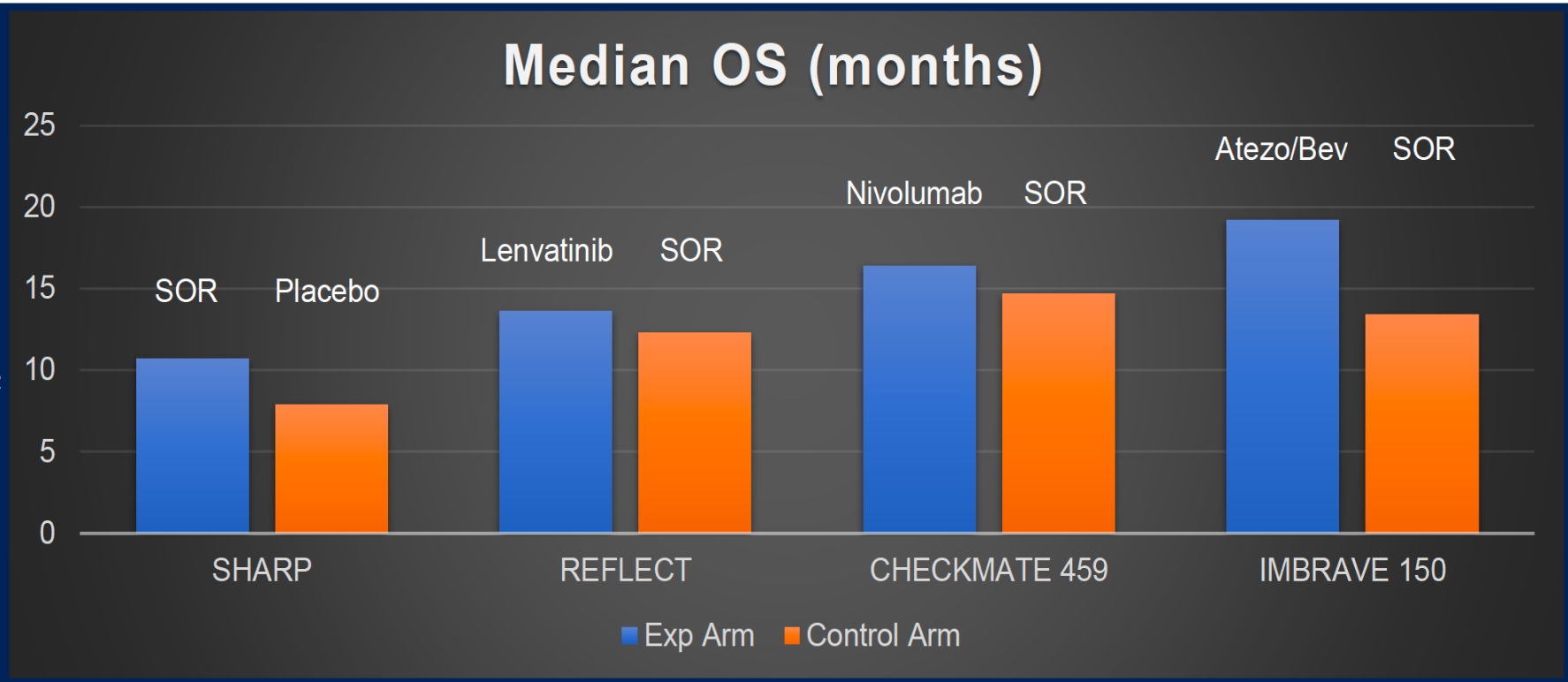
The Evolution of First Line Systemic Therapy for Hepatocellular Carcinoma

SHARP
Sorafenib
vs Placebo

REFLECT
Lenvatinib vs
Sorafenib

CHECKMATE
459
Nivolumab vs
Sorafenib

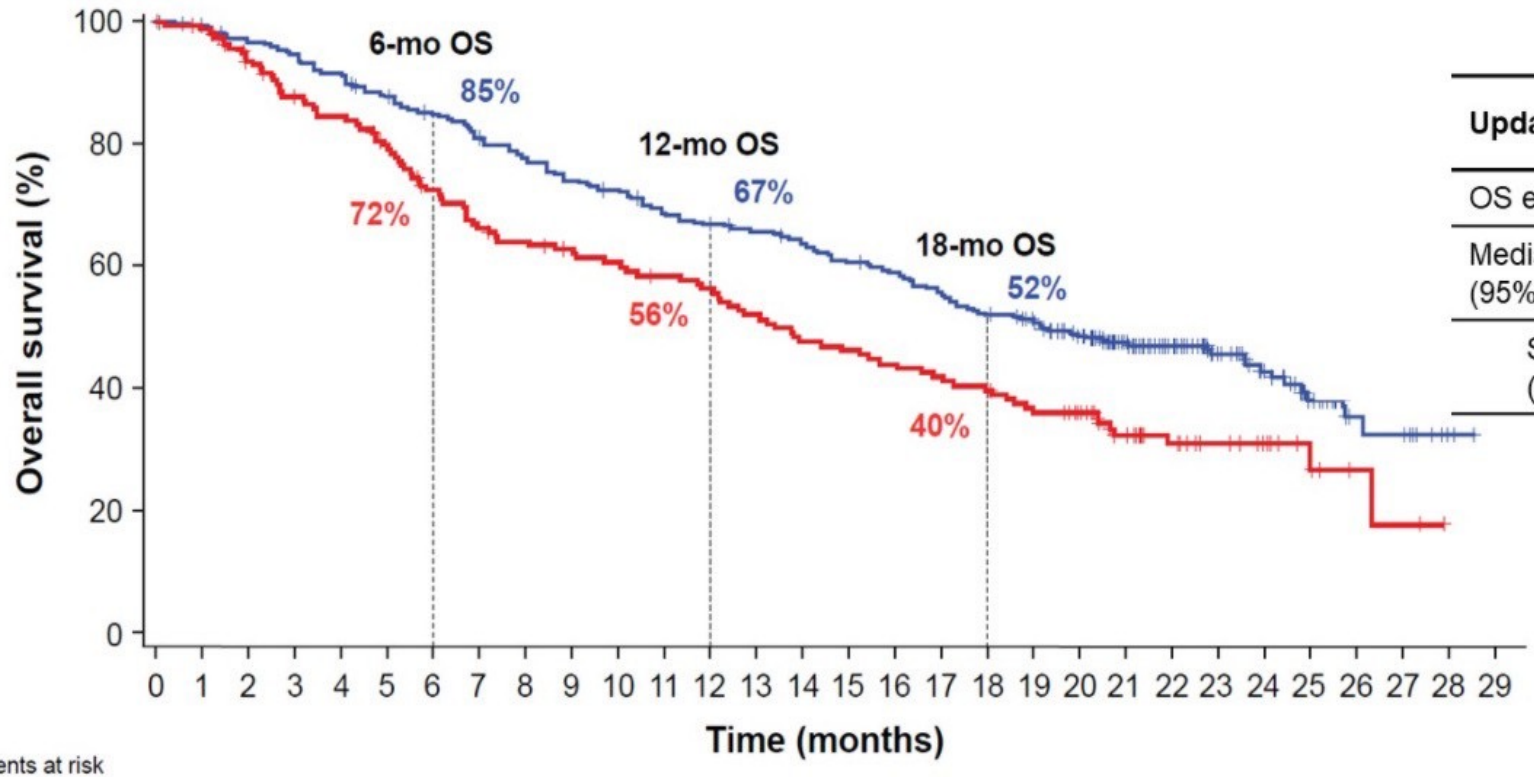
IMBRAVE 150
Atezo/Bev vs
Sorafenib



Anthony El-Khoueiry; ASCO GI 2022

Llovet JM et al. N Engl J Med. 2008; Kudo M et al, Lancet 2018; El-Khoueiry, A et al, Lancet 2017; Yau T et al, Lancet Oncol. 2022; Finn RS et al, J. Clin. Oncol. 39, (2021)

IMbrave150 OS: Atezolizumab and Bevacizumab versus sorafenib



No. of patients at risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

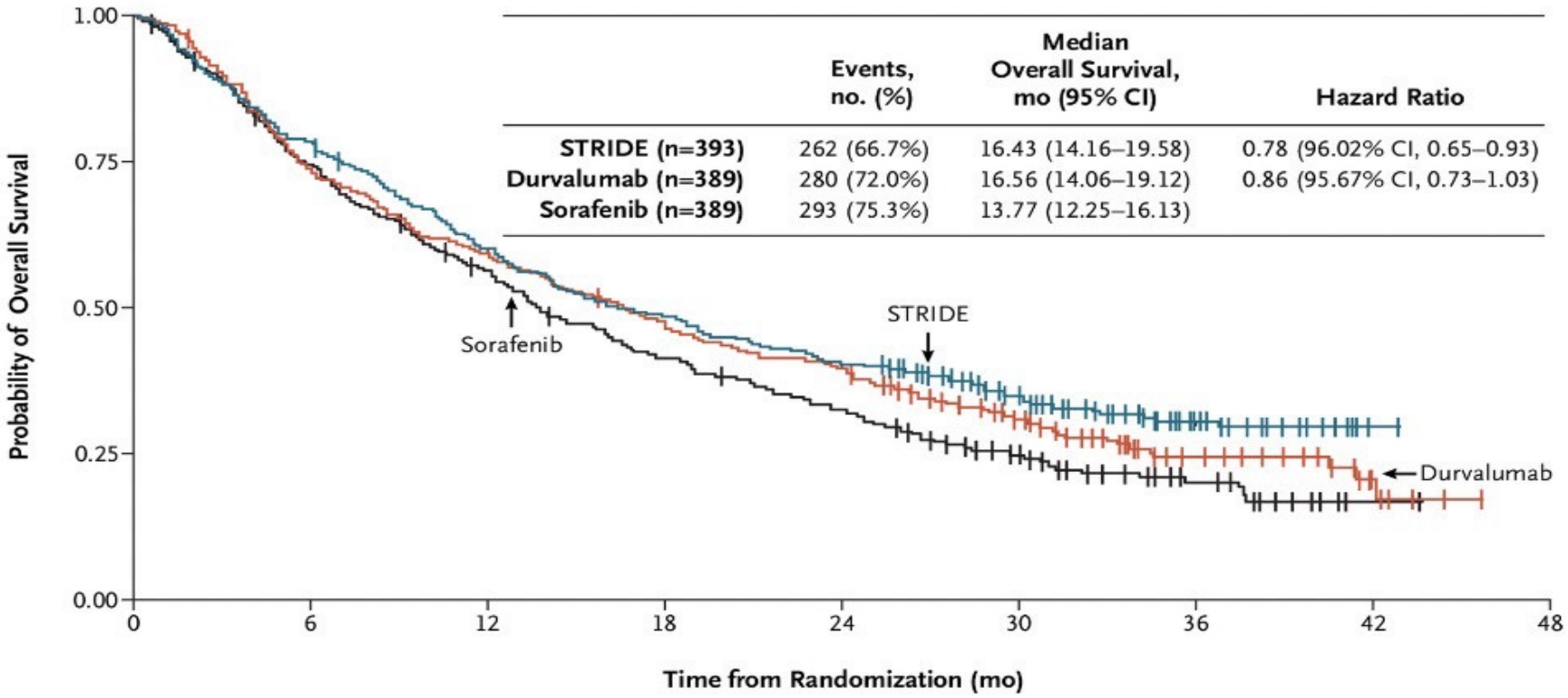
Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Finn, RS, et al. *J Clin Oncol*. 2021;39(3_suppl):267.

HIMALYA OS for Durvalumab + Tremelimumab 300 mg and Durvalumab versus sorafenib

A



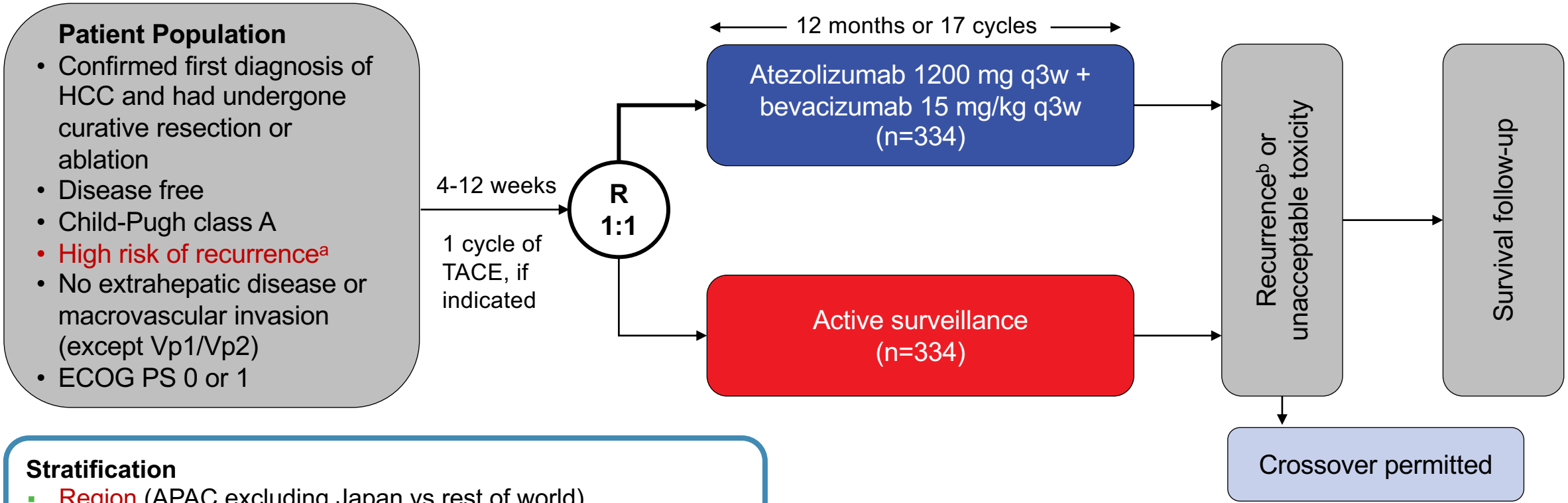
	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

No. at Risk									
STRIDE	393	308	235	190	158	98	32	1	0
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Abou-Alfa GK, et al. Accessed February 27, 2023.
https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070.

Adjuvant Therapy for High-Risk Resected HCC?

IMbrave050 study design
adjuvant atezo/bev for resected high-risk HCC



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.

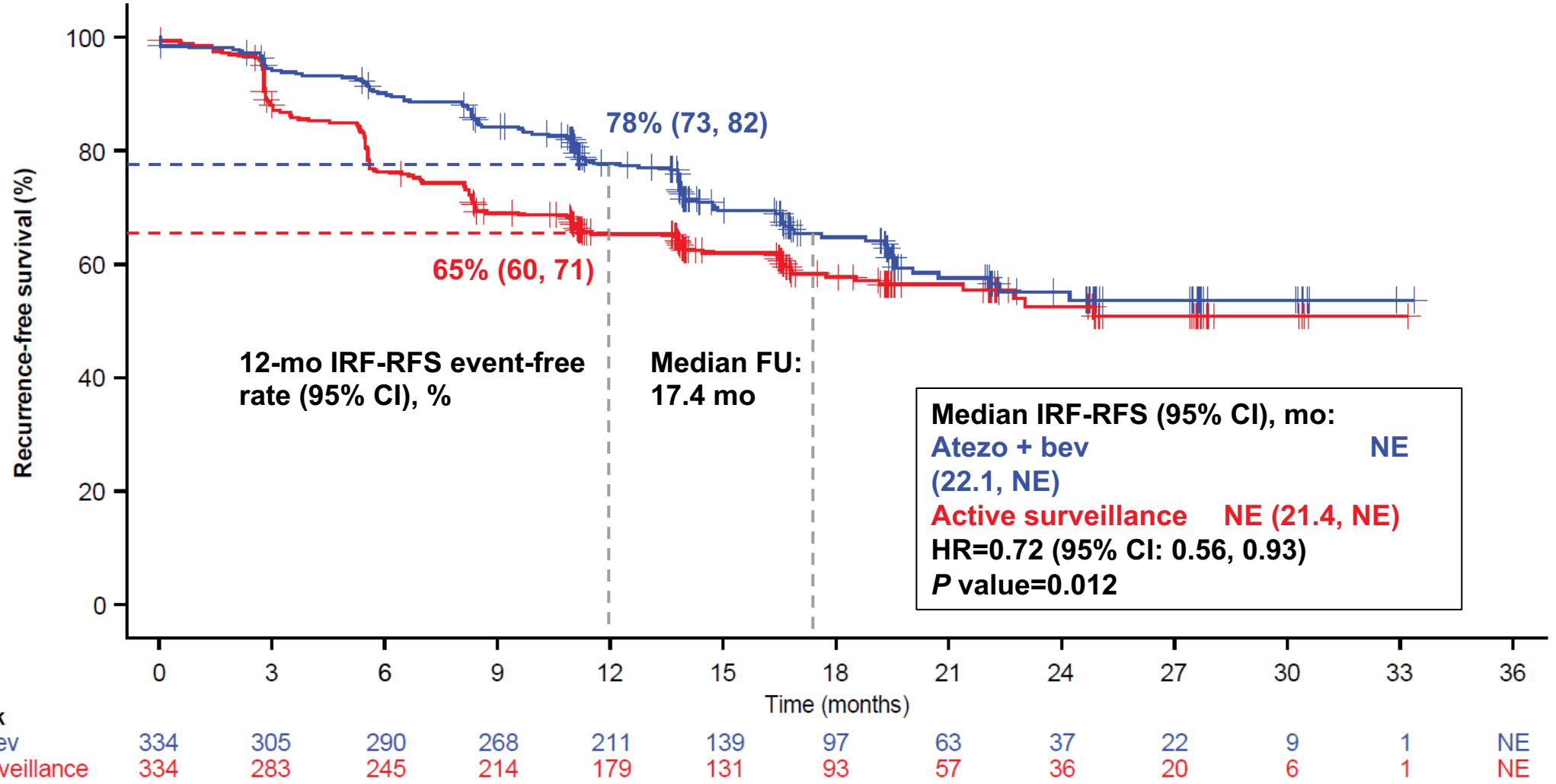
Baseline characteristics—curative procedures

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm[a]	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
Adjuvant TACE following resection, n (%)	32 (10.9)	34 (11.6)
Any tumors >5 cm, n (%)	152 (51.9)	175 (59.9)
Microvascular invasion present, n (%)	178 (60.8)	176 (60.3)
Minor macrovascular invasion (Vp1/Vp2) present, n (%)	22 (7.5)	17 (5.8)
Poor tumor differentiation (Grade 3 or 4), n (%)	124 (42.3)	121 (41.4)
Ablation, n (%)	41 (12.3)	42 (12.6)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumors, n (%)		
1	29 (70.7)	31 (73.8)
2	11 (26.8)	8 (19.0)
3	1 (2.4)	3 (7.1)

- Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.

[a] 1 patient in the atezo + bev arm was excluded from the calculation due to data entry error.

Primary endpoint: IRF-assessed RFS



- 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.

Chow et al IMbrave050
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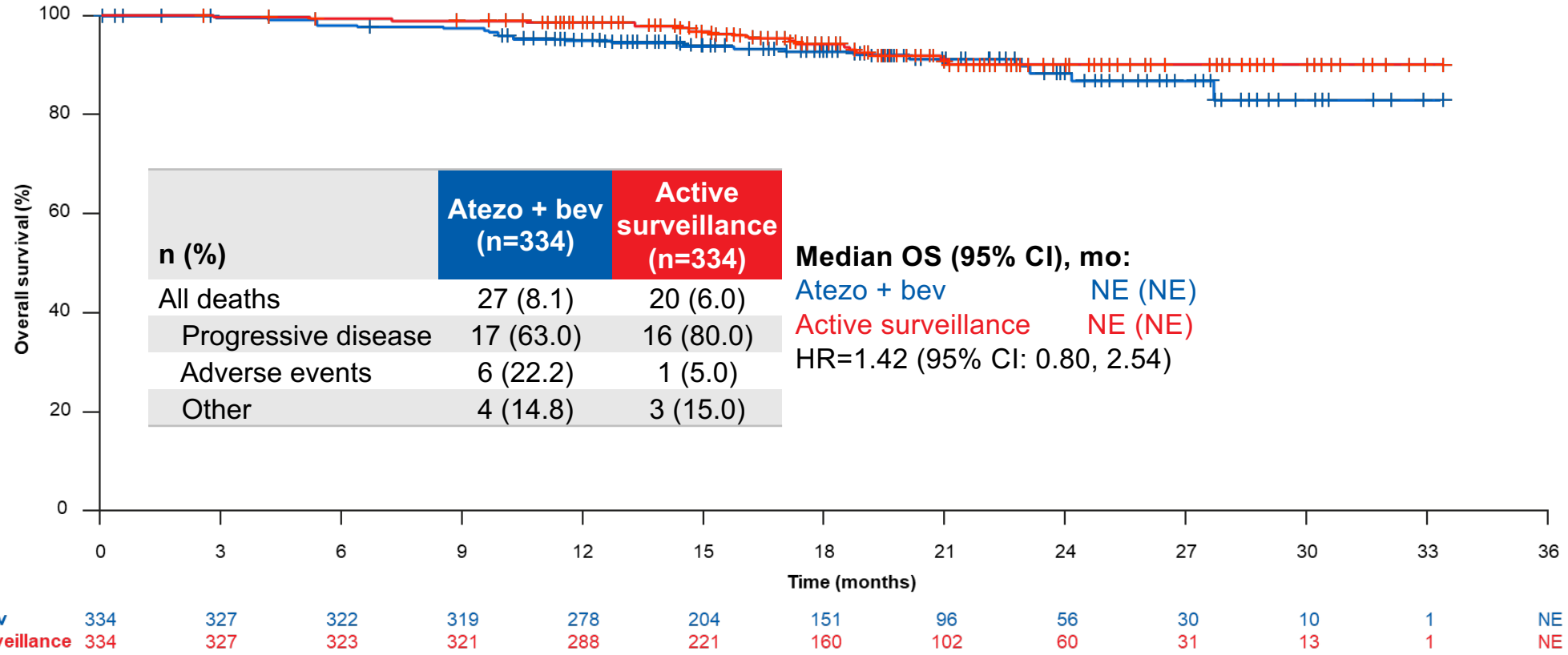
Overall survival was highly immature



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	27 (8.1)	20 (6.0)
Progressive disease	17 (63.0)	16 (80.0)
Adverse events	6 (22.2)	1 (5.0)
Other	4 (14.8)	3 (15.0)

Median OS (95% CI), mo:
Atezo + bev NE (NE)
Active surveillance NE (NE)
HR=1.42 (95% CI: 0.80, 2.54)

- **OS is highly immature, with a 7% event-patient ratio (n=47).** There were:
  - 7 more deaths in the atezo + bev arm (27 vs 20)
  - Similar number of deaths due to HCC recurrence

- Clinical cutoff: October 21, 2022. Median follow-up duration: 17.4 mo. NE, not estimable. HR is stratified.

Wrap Up

- Evolving biomarker directed therapies for pancreas and hepatobiliary cancers
- Pancreas cancer
  - BRCA, KRAS G12C
- Biliary cancers
  - Durvalumab in combination with chemotherapy should be considered
  - Numerous biomarkers, though a majority of patients will still have no actionable alterations
- Hepatocellular carcinomas
  - Immunotherapy now the standard of care in the frontline setting

Thank you!

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