Wake Forest®
School of Medicine

Pancreatic, HCC, and Biliary Cancers
Hope is in the Horizon!

Caio Max S. Rocha Lima, M.D.

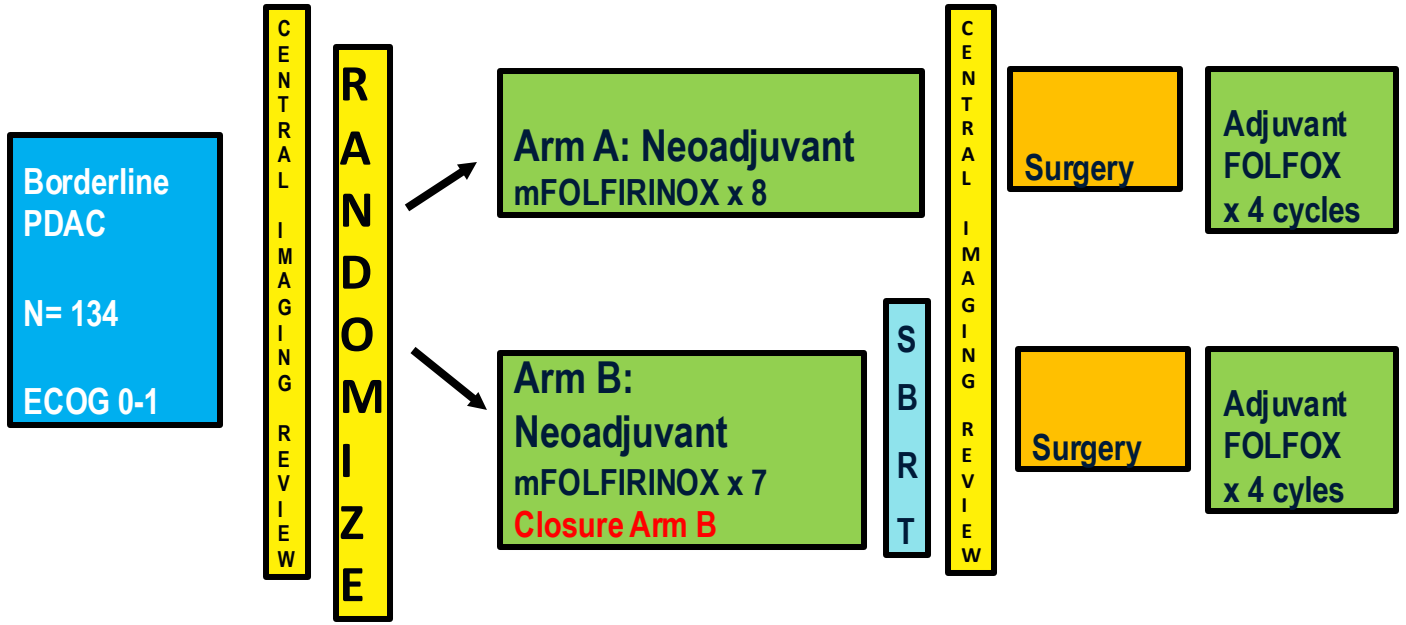
M. Robert Cooper Professor in Medical Oncology

Co-leader GI Oncology and Co-leader Phase I Program

Wake Forest School of Medicine

A021501 BORDERLINE RESECTABLE PDAC

Randomized Phase II mFOLFIRINOX +/- SBRT



Interim analysis: R0 after
N= 30/arm → early closure of SBRT arm (<11 R0/ 30)

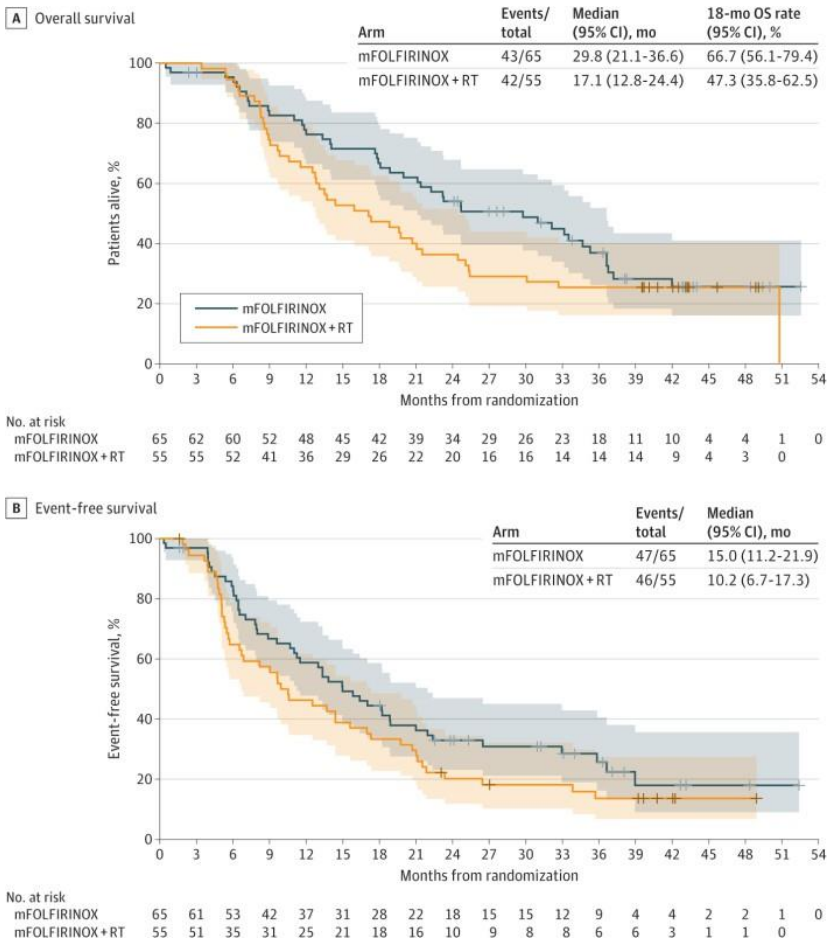
Primary endpoint: 18-month OS in each arm (no comparison)

*Alternative to SBRT – HIGRT

NCT02839343 M. Katz, PI

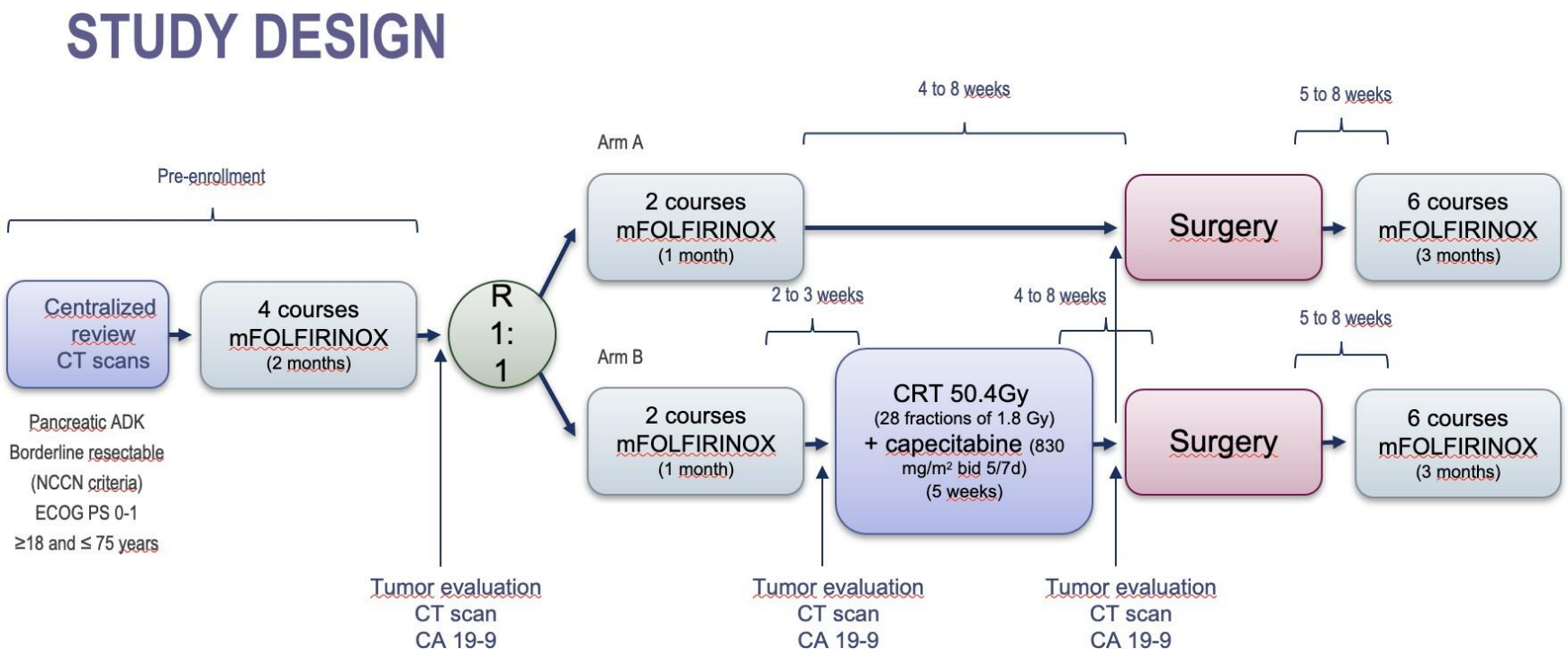
A021501 BORDERLINE RESECTABLE PDAC

- ARM A FOLFIRINOX;
  - **Median OS (95): 29.8 (21.1 – NE) mo**
  - 18-mo OS rate: 66.4**% CI** (55.6 – 79.2%)
- ARM B FOLFIRINOX→RT
  - **Median OS (95% CI): 17.1 (12.8 – 24.4) mo**
  - 18-mo OS rate: 47.3 (35.8 – 62.5%)



Katz et al, JAMA Oncol 2022

ESMO 2024 PANDAS/PRODIGE 44 trial



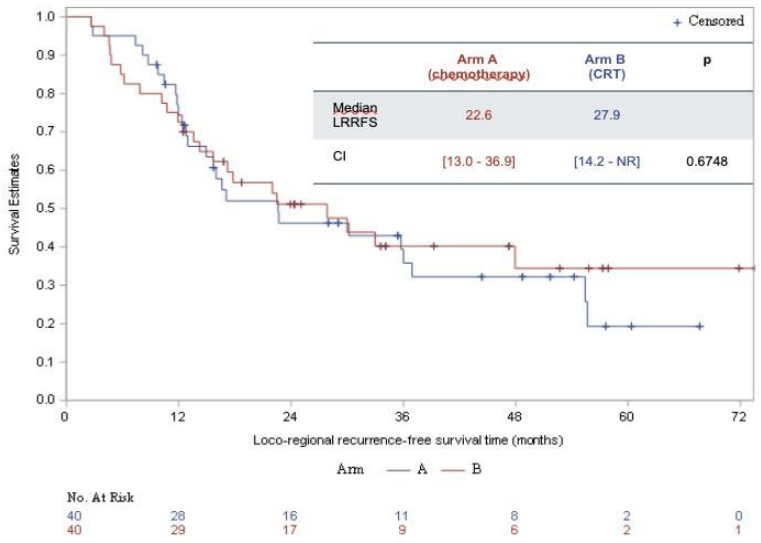
Primary objective: R0 resection rate

Lambert A ESMO 2024

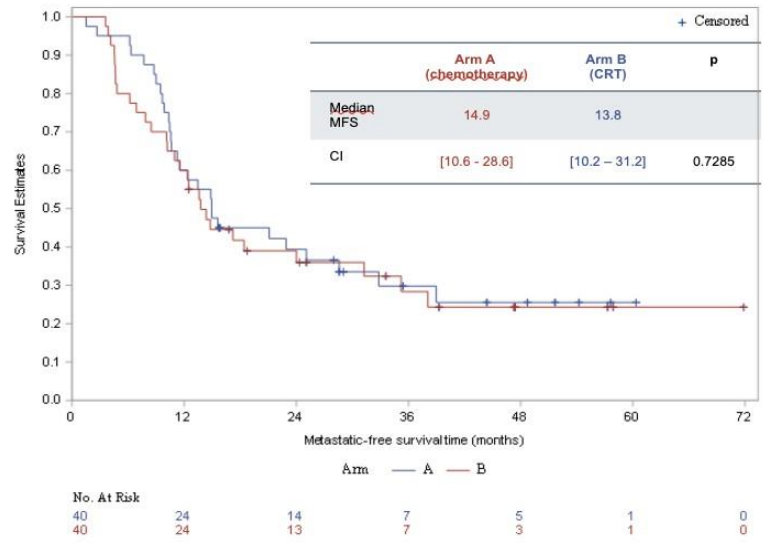
		Arm A (chemotherapy) N=40	Arm B (CRT) N=40	p-value
R0 Resection rate	**Yes** / No N (%)	**20 (50)** / 20 (50)	**18 (45)** / 22 (55)	0.8230
Resection (R0 or R1)	Yes / No N (%)	37 (92.5) / 3 (7.5)	31 (77.5) / 9 (22.5)	0.1149
ypCR	No N (%)	37 (100) (3 missing)	31 (100) (9 missing)	

Loco-regional recurrence-free survival

ITT population



Metastasis-free survival

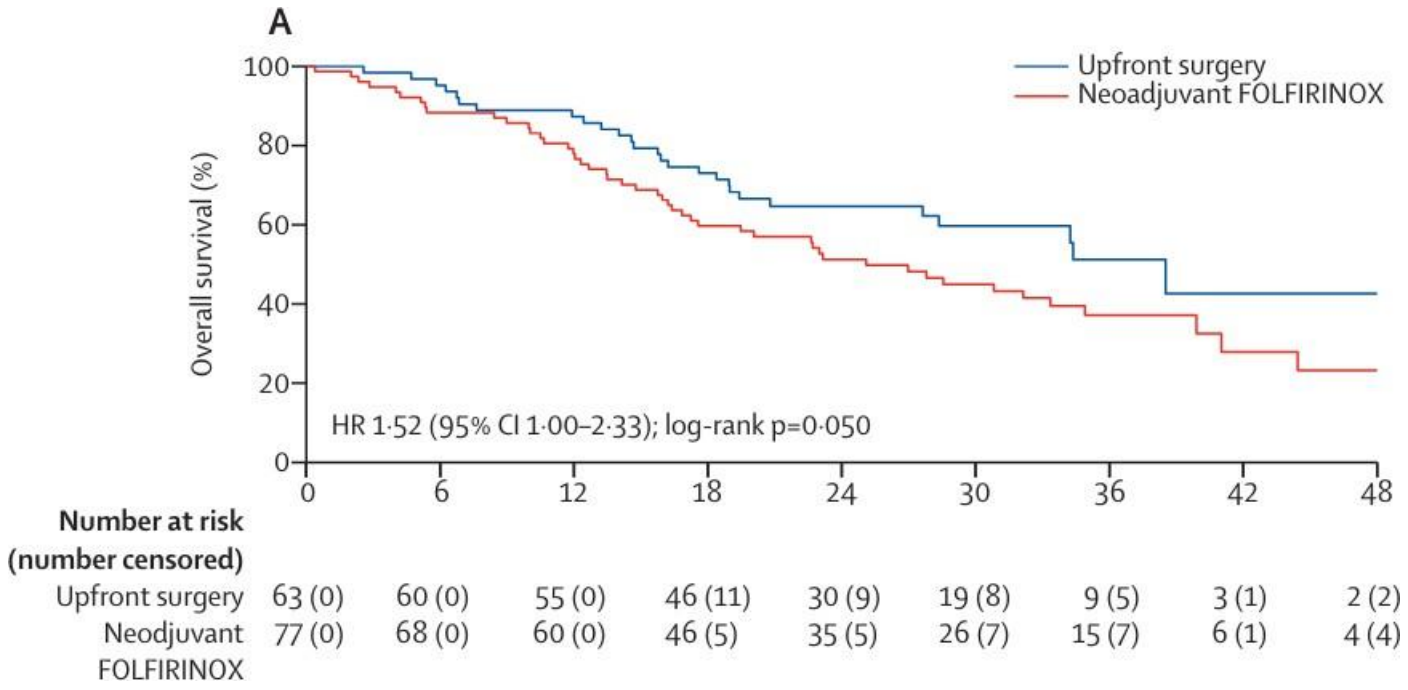


Lambert A ESMO 2024

Randomized Phase III

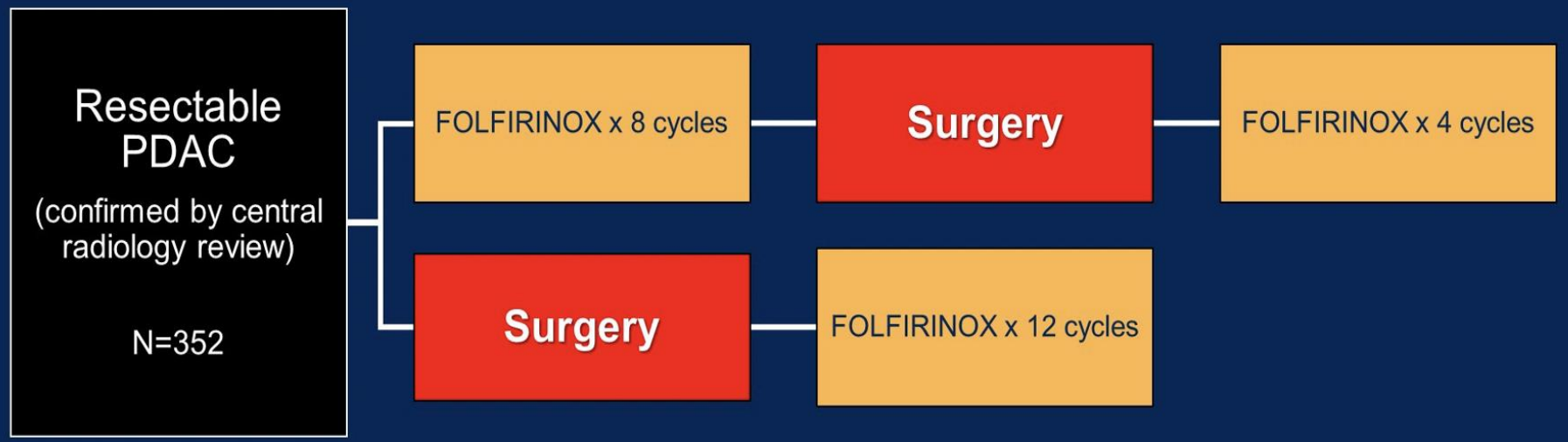
Study	Randomization	Resectablitiy	# Patients	OS in months	Other Endpoints
PREOPERATIVE					
PREOPANC-1 Versteijne E JCO 40: 11 ,2022	G+XRT-S 119 pts S- G 127 pts	Resectable or borderline resectable	119 x 127	15.7 (N) x 14.3 (S) 5-y OS 20.5% x 6.5% (HR 0.73, p=0.025)	R0 71% (N) x 40% (S) (p<.001)
Preop-02/JSA 05 JCO 37 S4;A189, 2019	GS1 x 2-S –GS1 x 6 S- GS1 x 6	Resectable	182 x 180	36.7 (9N) x 26.6(S) HR 0.72 p=0.015	No reported change in resection rates

NORPAC-1 DIFFERENT RESULTS



Labori, et al. Lancet Gastronterol Hepatol 2024

Alliance A021806: Perioperative vs. adjuvant therapy for resectable pancreatic cancer

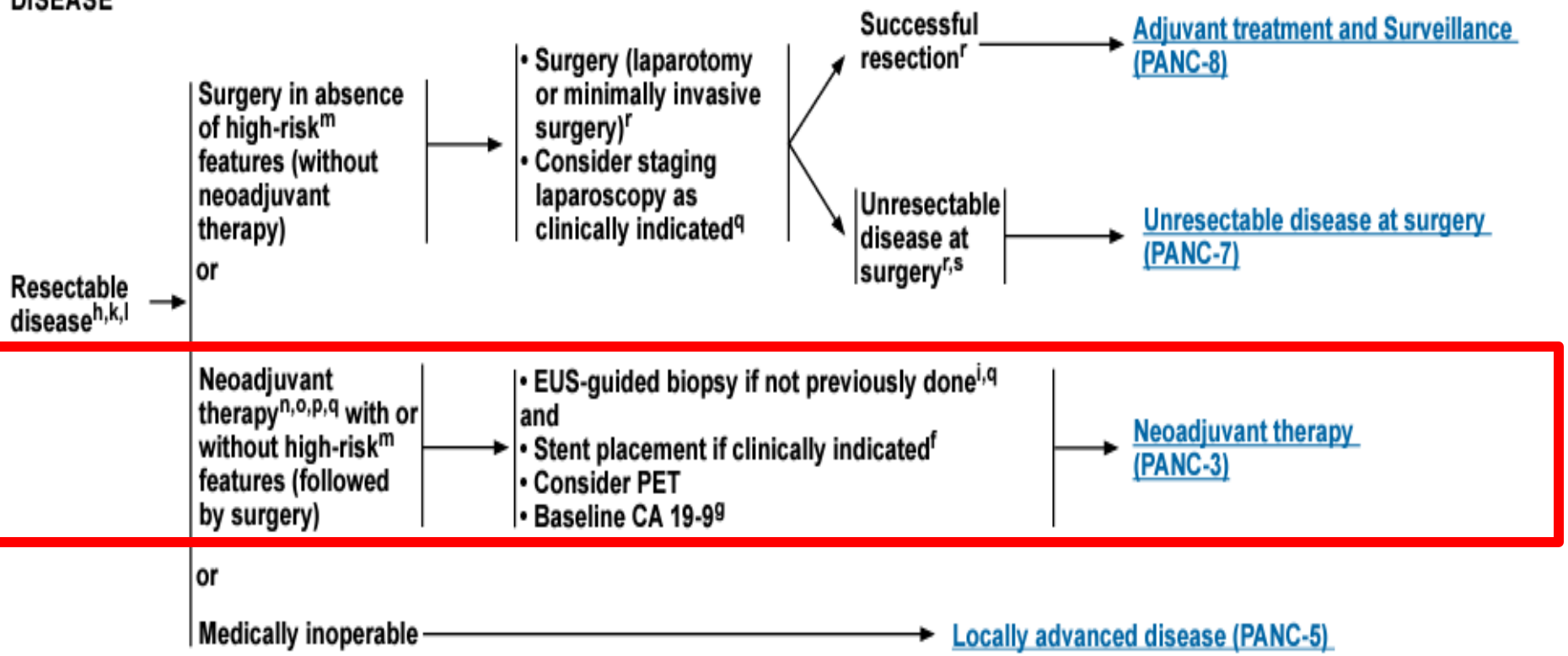


ClinicalTrials.gov Identifier: NCT04340141
P.I., Cristina Ferrone

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion



METASTATIC PANCREAS CANCER

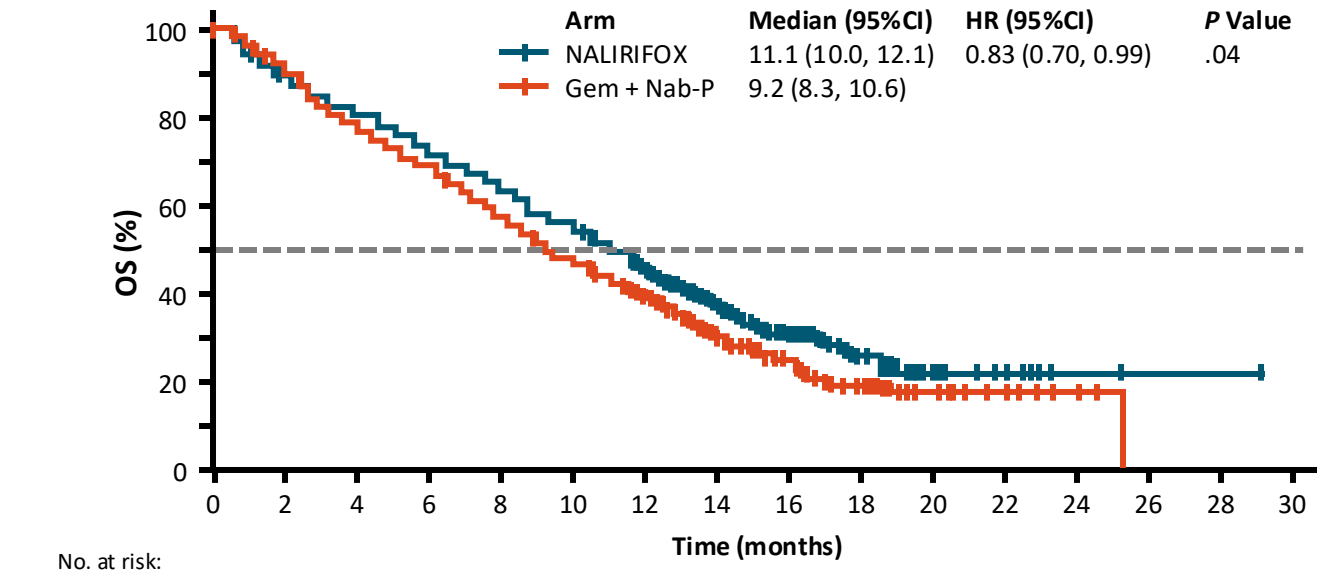
We Have Made Progress in the 1st-Line Pancreas Adeno in the Metastatic Setting

Trial[1]	Date	Patients (n)	Treatment	Median survival (mo)	P value
Burris et al[2]	1997	126 (unresectable, LA or metastatic pancreatic cancer)	5-FU vs. gemcitabine	4.41 5.65*	Log-Rank Test 0.0025
NCIC[3]	2007	569 (unresectable, LA or metastatic pancreatic cancer)	gemcitabine vs. gemcitabine + erlotinib	5.91 6.24	0.038 (HR = 0.82 [95% CI, 0.69–0.99])
PRODIGE[4]	2011	342 (metastatic)	gemcitabine vs. FOLFIRINOX	6.8 11.1	<0.001 (HR = 0.57 [95% CI, 0.45–0.73])
Ueno, et al[5]	2013	834 (LA, or metastatic pancreatic cancer)	gemcitabine vs. S-1 vs. gemcitabine + S-1	8.8 9.7 10.1	gemcitabine vs. S-1: <0.001 (non-inferiority; HR = 0.96 [97.5% CI, 0.78–1.18]) gemcitabine vs. gemcitabine + S-1: 0.15 (superiority; HR = 0.88 [97.5% CI, 0.71–1.08])
MPACT[6]	2013	861 (metastatic)	gemcitabine vs. gemcitabine + nab-paclitaxel	6.7 8.5	<0.001 (HR = 0.72 [95% CI, 0.62–0.83])

1. Ryan DP, et al. N Engl J Med 2014;371:1039;
2. Burris HA, et al. J Clin Oncol 1997;15:2403;
3. Moore MJ, et al. J Clin Oncol 2007;25:1960;

4.Conroy T, et al. N Engl J Med 2011;364:1817;
5. Ueno H, et al. J Clin Oncol 2013;31:1640;
6. Von Hoff DD, et al. N Engl J Med 2013;369:1691.

NAPOLI: OS (Primary Endpoint)



Wainberg ZA, Melisi D, Macarulla T, et al. Lancet. 2023

NALIRIFOX x FOLFIRINOX

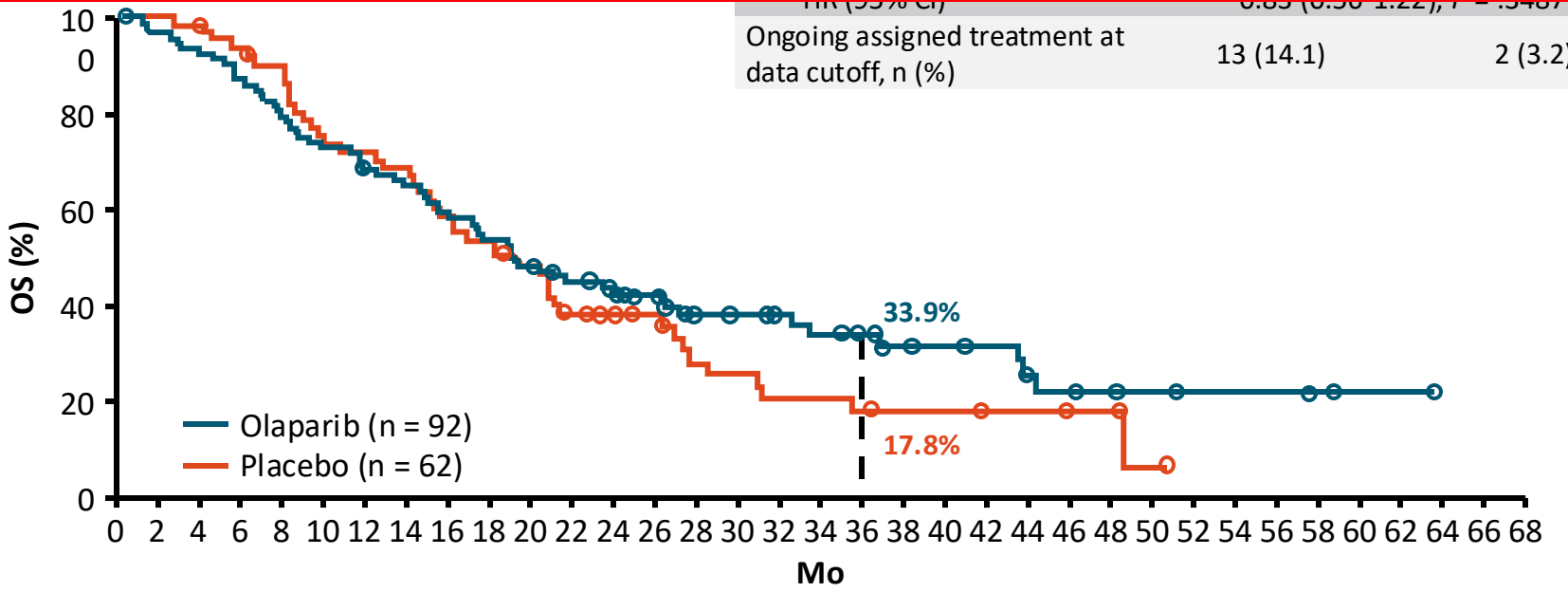
	NALIRIFOX	FOLFIRINOX (PRODIGE)
Median OS	11.2 Months	11.1 Months
Median PFS	7.4 Months	6.4 Months
ORR	41.8%	31.6%
Toxicity	Myelotoxicity, peripheral neuropathy, and GI Toxicity	

O'Reilly et al. Abstract 4006.PASCO 2023

Conroy T, et al. N Engl J Med 2011;364:1817

POLO: Final OS

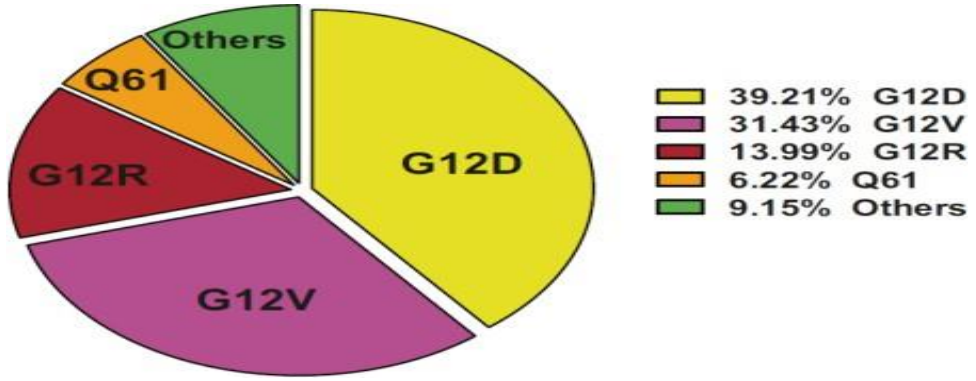
	Olaparib (n = 92)	Placebo (n = 62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, mo	19.0	19.2
HR (95% CI)	0.83 (0.56, 1.22); P = .3487	
Ongoing assigned treatment at data cutoff, n (%)	13 (14.1)	2 (3.2)

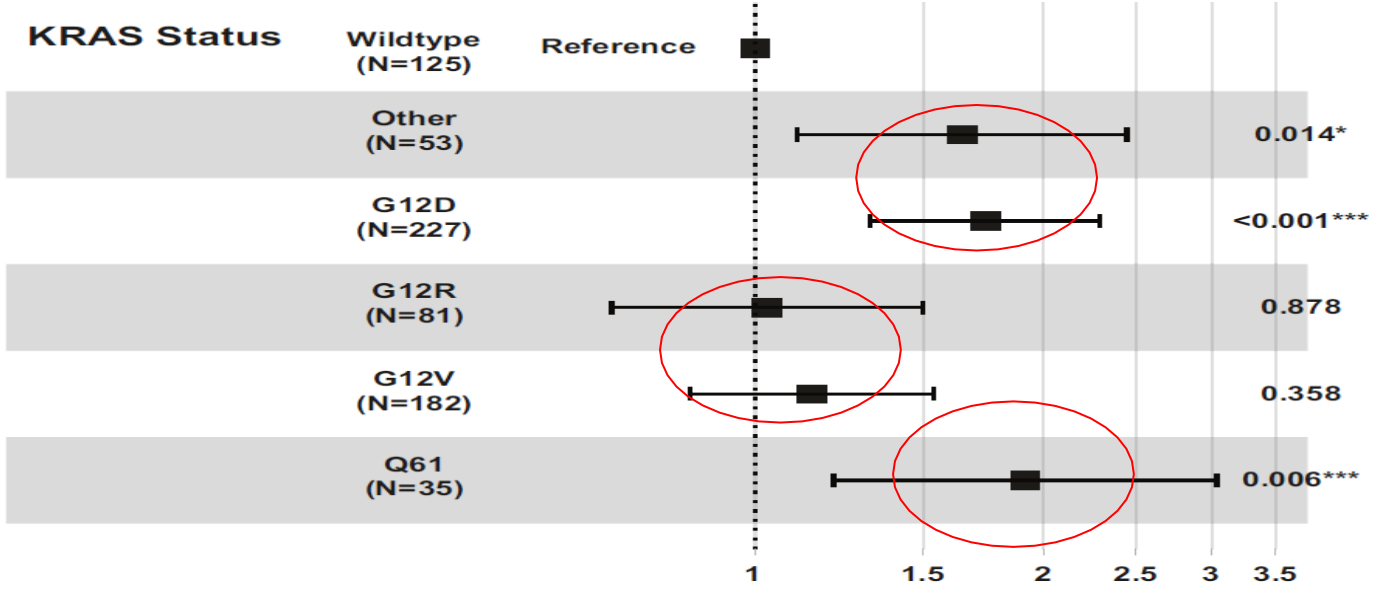


Golan. ASCO GI 2021. Abstr 378.

KRAS MUTATION AS PROGNOSTIC MARKER

- 803 patients
- retrospective





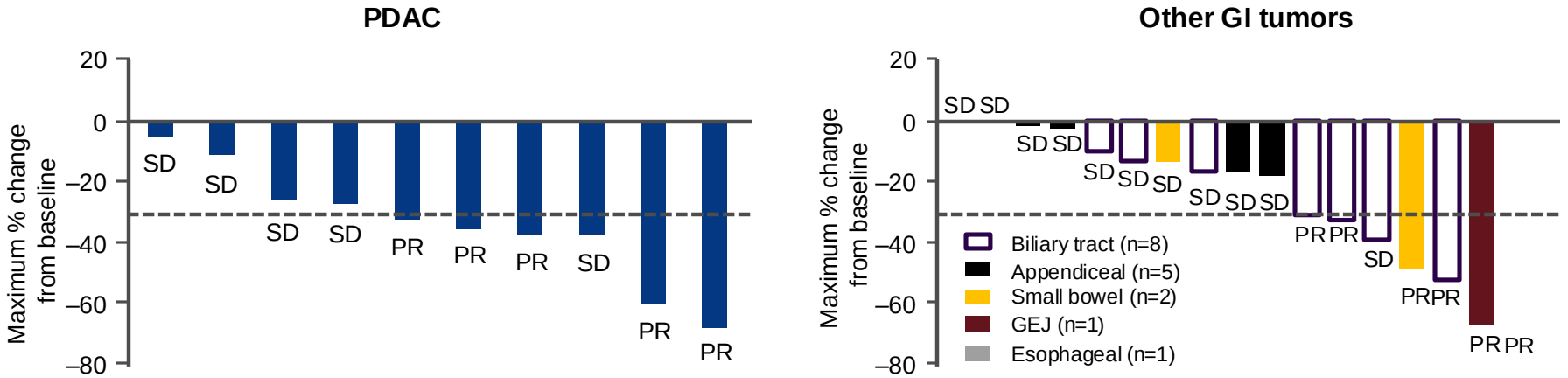
Yousef et al., npj, 2024

KRYSTAL-1: Adagrasib (MRTX849) unresectable or metastatic pancreatic cancer and other gastrointestinal tumors with KRASG12C mutation

63 pts treated. 21 PDA

ORR 35.1 %

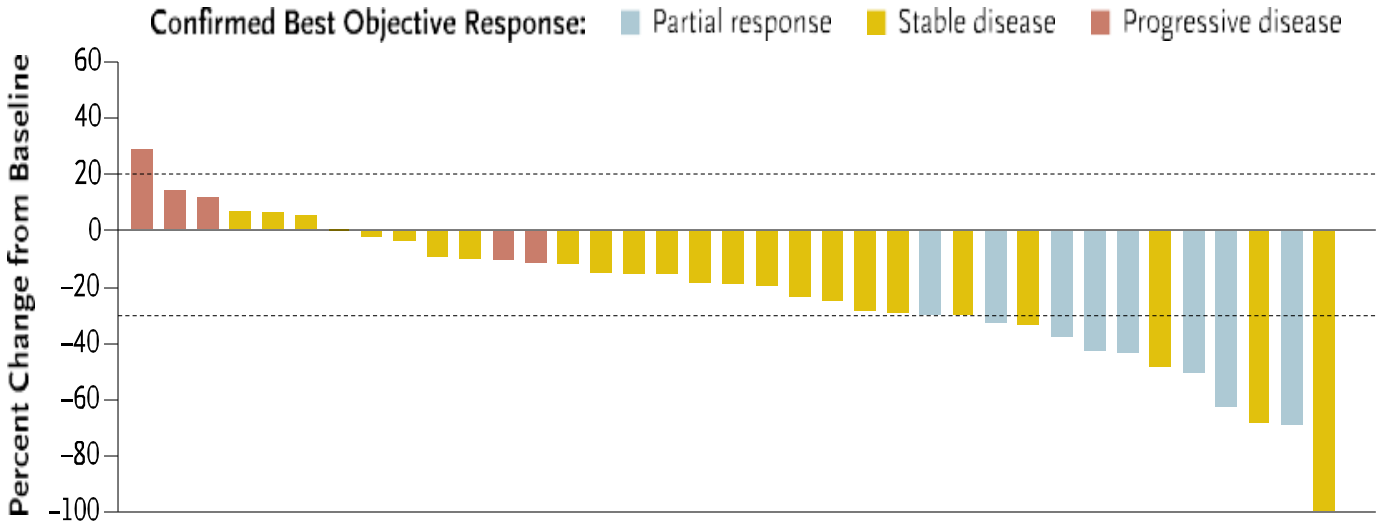
ORR PDA: 33%



Pant S, et al. JCO 2023, A 425082

Sotorasib, the phase 1-2 CodeBreaK 100 trial

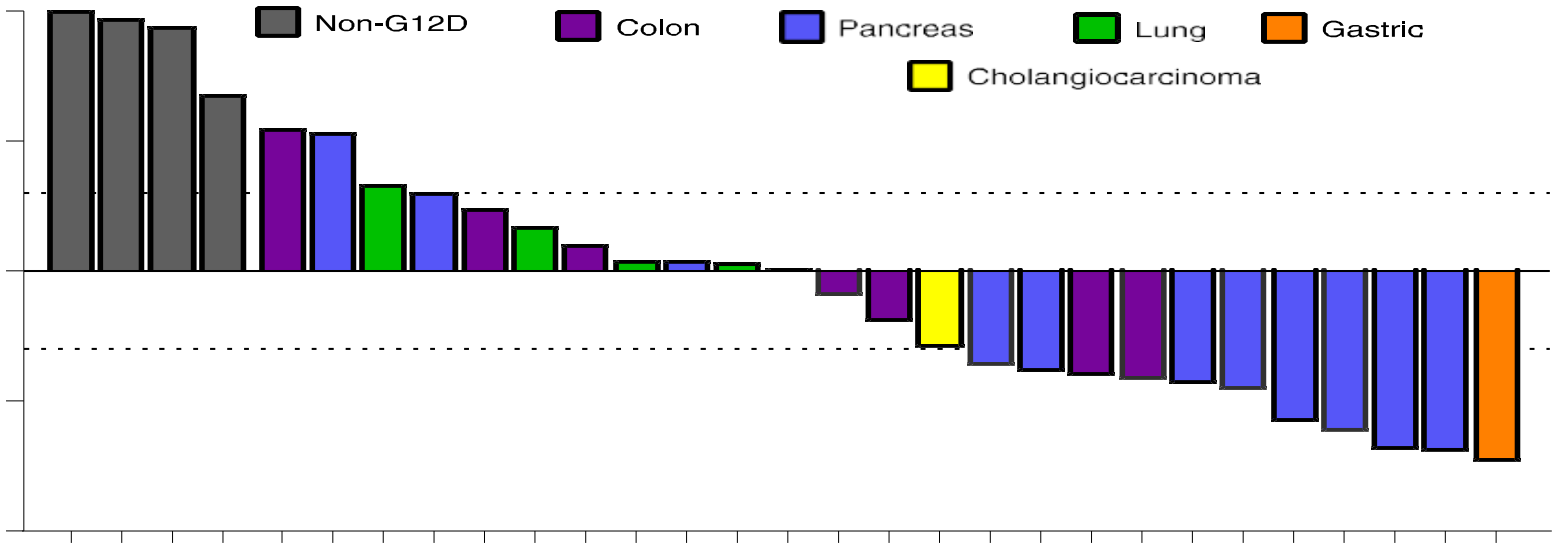
- 38 PDAC patients
  - ORR = 21 %
  - mPFS = 4 months
  - mOS= 6.9 months



Strickler JH, et al. NEJM 2023

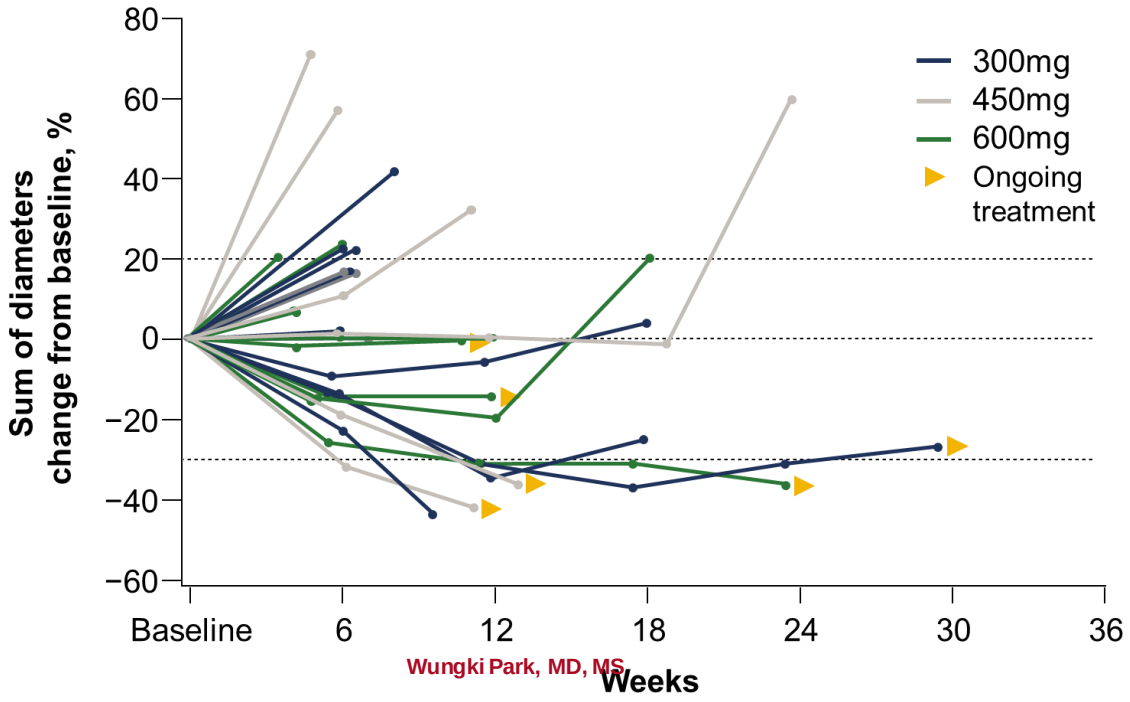
KRAS G12D

- MRTX 1133 shows promise in targeting and inhibiting KRAS G12D activation
- Preclinical data in human tumor xenographs



Wei J, et al. Clin Can Res 2023

Response to ASP3082 300–600mg over time in patients with PDAC Presented at ESMO 2024



- At data cutoff, 6 of 27 (22.2%) patients remained on treatment
- DOR and PFS endpoints were not mature at data cutoff
- For 5 patients with PR, median time to response[a] was 2.6 months (range: 1.4–3.0 months)

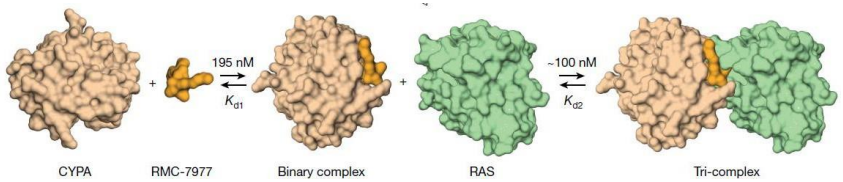
Wungki Park, MD, MS

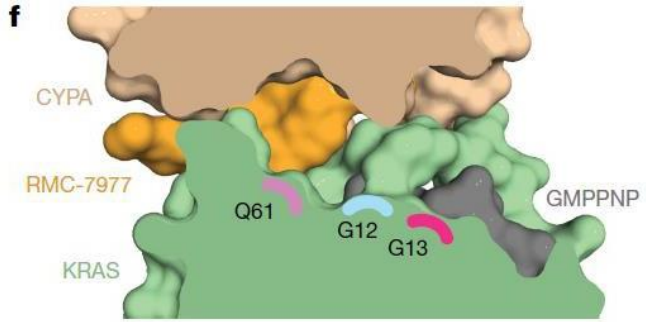
PAN-RAS INHIBITORS
Inhibition of both oncogenic and wild type RAS-GTP

RMC-7977:

- Reversible, tri-complex ***Ras(On)*** multiselective inhibitor
- Active for both mutant and wild-type KRAS, NRAS and HRAS variants
- May be active for KRAS G12C inhibitor Resistance

  Resistance mechanism: Myc copy number gain and YAP–TAZ pathway activation





Holderfield M, et al. Nature 2024
Wasko UN, et al. Nature 2024

RMC-6236: panRAS inhibitor Phase 1 trial ASCO GI 2025

KRAS non G12c patients 2L+,RMC-6236 ranging from 160 mg to 300 mg

NSCLC 40: ORR 38% and DCR 34%. Median TTR 1.4 m (1.2-2.7).
ESMO 2024 (*Arbour KC Ann Oncol*. 2023;34(suppl 2):S458)

Pancreas Ca:

	KRAS G12X	RAS mutant
Efficacy with 2L RMC-6236		
	(n=42)	**(n=57)**
ORR, % (95% CI) [confirmed + pending confirmation]	29 (16–45)	25 (14–38)
Median PFS, months (95% CI)	8.5 (5.3–11.7)	7.6 (5.9–11.1)
Median OS, months (95% CI)	14.5 (8.8–not evaluable)	14.5 (8.8–not evaluable)
ctDNA Response with 2L+ RMC-6236		
	(n=56)	**(n=68)**
>50% decrease from BL, n (%)	53 (95)	63 (93)
100% decrease from BL, n (%)	28 (50)	32 (47)

Garrido-Laguna I eta al et al JCO 43, 2025 https://doi.org/10.1200/JCO.2025.43.4_suppl.722

Zoldonrasib (RMC-9805) ASCO GI 2025 early results

- Among response-evaluable patients with *KRAS* G12D–mutated PDAC who received zoldonrasib at 1200 mg daily (once-daily dosing schedule ,n = 20; twice-daily dosing schedule, n = 20)
  - RR 30%
  - DCR 80%.
- **Safety Profile:** Manageable adverse events (nausea, diarrhea, vomiting), no treatment discontinuations due to toxicity.
- Combination strategies with chemotherapy and immune checkpoint inhibitors are under evaluation.

Spira A et al. J Clin Oncol. 2025;43(4):724. doi:10.1200/JCO.2025.43.4_suppl.724

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

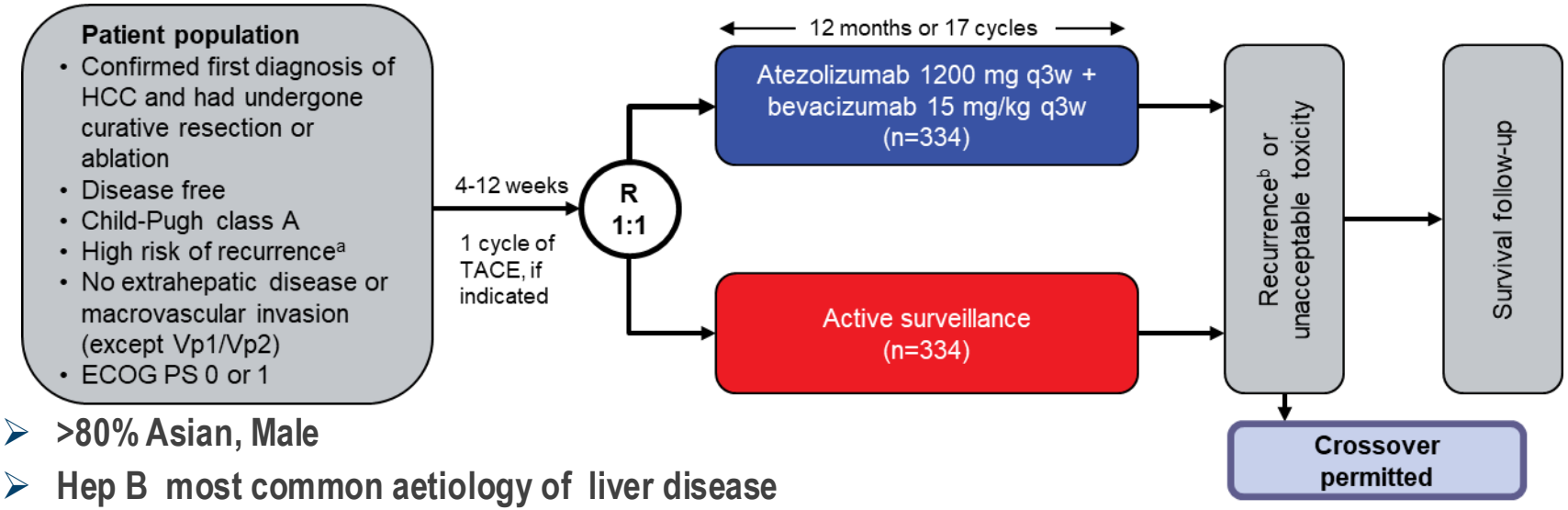
- Consider evaluational geriatric assessment (see NCCN Guidelines for Older Adult Oncology).

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	• FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • Gemcitabine + albumin-bound paclitaxel[6] (category 1) • NALIRIFOX[f,7] (category 1) Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • Gemcitabine + cisplatin[8,9]	• Gemcitabine (category 1) • Gemcitabine + erlotinib[g,11] (category 1) • Gemcitabine + capecitabine[10] • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] • Fluoropyrimidine + oxaliplatin ▸ CapeOx[12] (category 2B) ▸ OFF[13] (category 2B) • GTX[16] (category 2B)	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[21] • Pembrolizumab[j,22] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]

HCC

IMbrave050 – study population

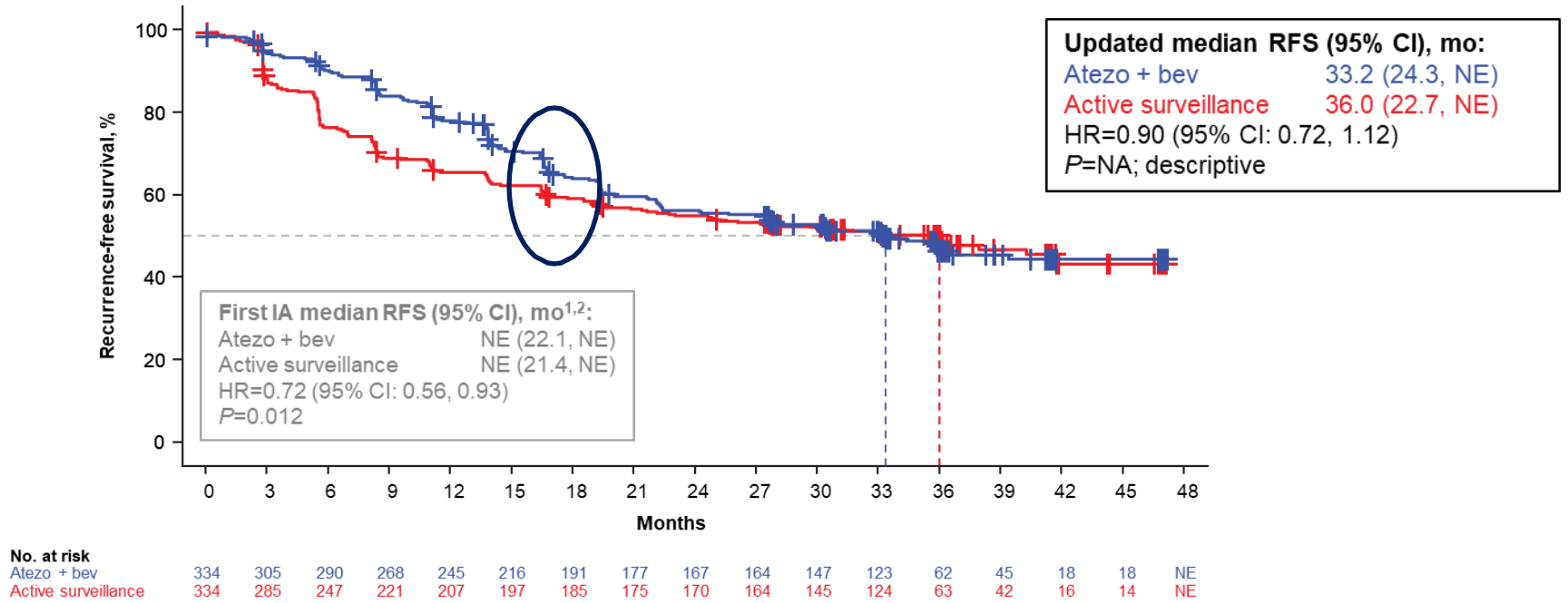
High risk HCC post resection or curative ablation



- >80% Asian, Male
- Hep B most common aetiology of liver disease
- BCLC stage A > 85%
- Tumour size > 5cm in 48.9%

Updated ESMO 2024

Updated RFS analysis @ 35 mo median follow up: negative

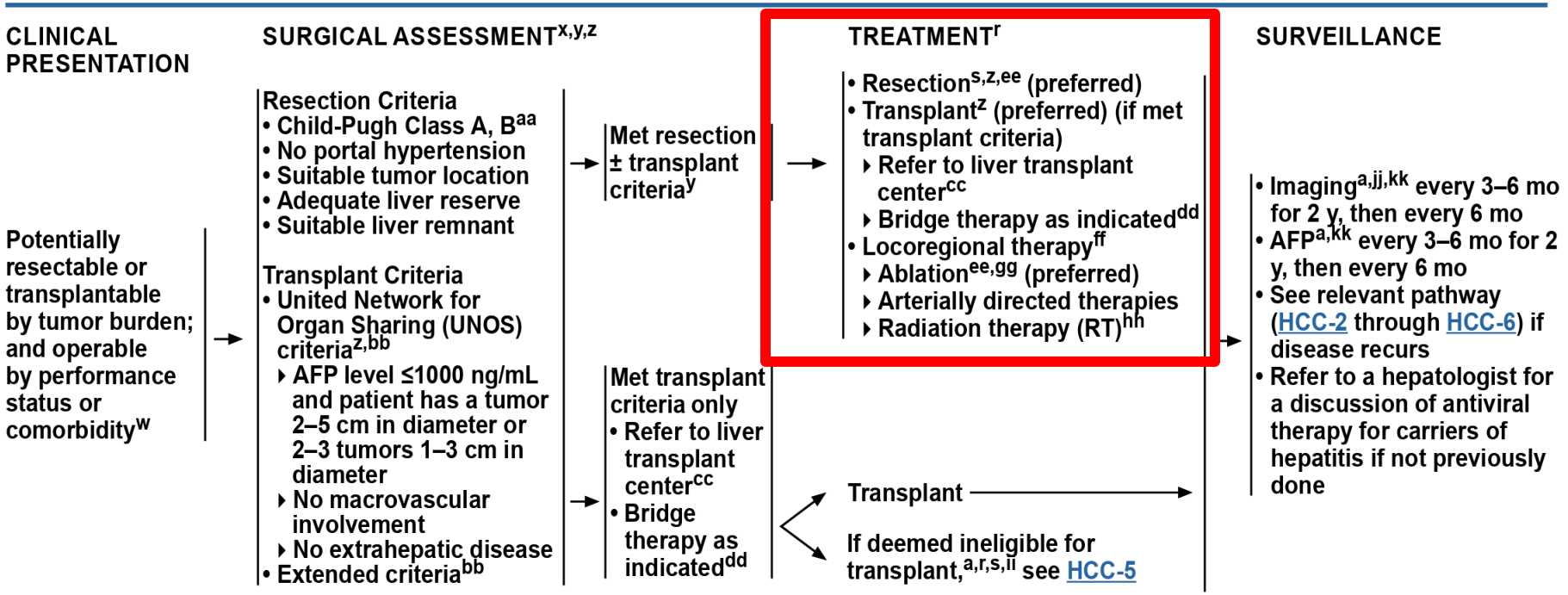


Updated ESMO 2024

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion



[a] Principles of Imaging (HCC-A).
[r] Principles of Mixed HCC-CCA (HCC-C).
[s] Principles of Pathology (HCC-D).
[w] Patients should be evaluated by a multidisciplinary team.
[x] Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.
[y] In patients being considered for surgery, patients with Child-Pugh Class A or highly selected patients with Child-Pugh Class B liver function, who fit UNOS criteria/extended criteria (www.unos.org) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.
[z] Principles of Resection and Transplant (HCC-F).
[aa] In highly selected patients with Child-Pugh Class B liver function with limited resection.
[bb] Extended criteria/downstaging protocols are available through UNOS. See https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09.
[cc] Mazzaferro V, et al. N Engl J Med 1996;334:693-700.
[dd] Many transplant centers consider bridge therapy for transplant candidates (See Discussion).

[ee] Adjuvant therapy with atezolizumab + bevacizumab may be considered in patients at high risk for recurrence (defined as size >5 cm, >3 tumors, macrovascular invasion or microvessel invasion on histology, or grade 3/4 histology based on the trial) on a case by case basis. Interim analysis of the phase III study of adjuvant therapy with atezolizumab + bevacizumab for 12 months in patients at high risk for recurrence after resection or ablation showed a higher rate of recurrence-free survival at 12 months compared to active surveillance, though overall survival benefit has not been established. Qin S, et al. Lancet 2023;402:1835-1847. Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for intravenous infusion. An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ff] Principles of Locoregional Therapy (HCC-G).
[gg] In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review.
[hh] Principles of Radiation Therapy (HCC-H).
[ii] Consider biopsy if imaging is not consistent or to confirm imaging diagnosis if it does not meet AASLD or LIRADS-5 criteria. See Principles of Core Needle Biopsy (HCC-B).
[jj] Multiphasic abdomen MRI or multiphase CT scans for liver assessment, CT chest, and CT/MRI pelvis.
[kk] Surveillance imaging and AFP should continue for at least 5 years; and thereafter screening is dependent on HCC risk factors.

Advanced or Metastatic HCC

CheckMate 9DW Trial: Phase III 668 pts: Nivo+Ipi to lenvatinib or sorafenib

- OS 23.7 x 20.6 months (HR 0.79; 95%, CI 0.65–0.96; p=0.0180).
- ORR 36% x 13%.

	Atezolizumab + Bevacizumab	Tremelimumab & Durvalumab	Nivolumab + Ipilimumab
Response rate	30%	20.1%	36%
Overall survival (median)	19.2 months	16.4 months	23.7 months
PFS (median)	6.8 months	3.78 months	9.1 months

Fin RS er al, N Engl J Med. 2020;382(20):1894–1905

Kudo M, et al ESMO Asia Congress 2024, Abstract 127O

Yau T, et al. ESMO Asia Congress 2024, Abstract 126O

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY[a,b,c]

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab[d] + bevacizumab (category 1)[e,f,g,1]
- Tremelimumab-actl + durvalumab (category 1)[f,2]

Other Recommended Regimens

- Durvalumab (category 1)[f,2]
- Lenvatinib (category 1)[3,4]
- Sorafenib (category 1)[5,6]
- Tislelizumab-jsgr (category 1)[f,7]
- Pembrolizumab (category 2B)[f,8]

Useful in Certain Circumstances

- For *NTRK* gene-fusion positive tumors:
  - Repotrectinib (category 2B)[9]

Subsequent-Line Systemic Therapy if Disease Progression[h,i,j]

Options

- Cabozantinib (category 1)[12]
- Regorafenib (category 1)[13]
- Lenvatinib
- Sorafenib

Other Recommended Regimens

- Nivolumab + ipilimumab[f,k,l,14-16]
- Pembrolizumab[f,m,n,o,17-19]

Useful in Certain Circumstances

- Ramucirumab (AFP ≥400 ng/mL) (category 1)[20]
- Nivolumab[f,m,n,p,21-24]
- For MSI-H/dMMR tumors
  - Dostarlimab-gxly (category 2B)[f,m,n,q,25]

Metastatic Biliary Cancers

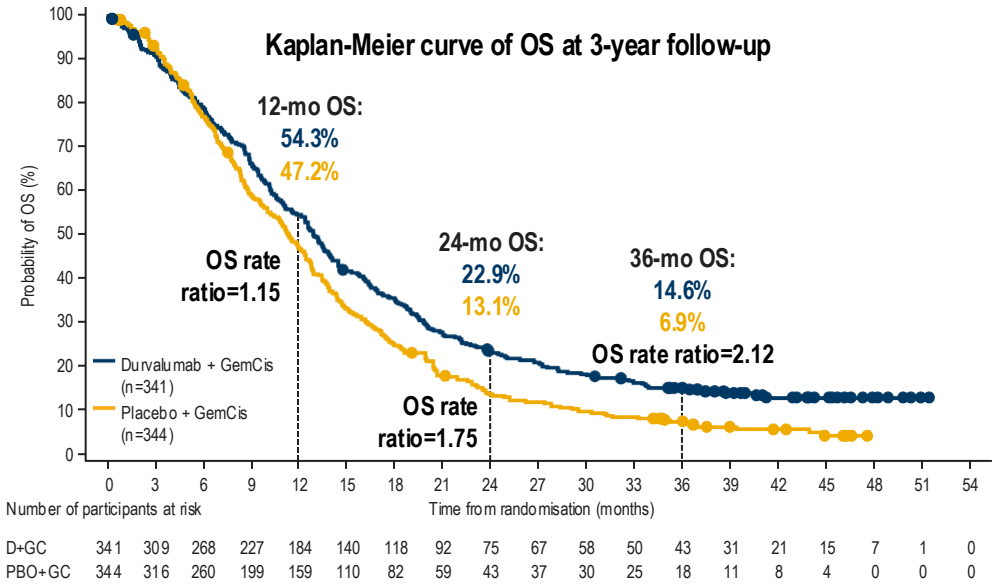
TOPAZ-1 VS KEYNOTE 966

	TOPAZ 1[1]	Keynote 966[2]
Median OS	12.9 vs 11.3 (HR 0.74 from 0.80 in FA)	12.7 vs 10.9 (HR 0.86 from 0.83 in FA)
ORR	26.7 vs 18.7 FA (55 % vs 40% in LTS)	28.7 vs 28.7 but DOR was 8.3 vs 6.9
N	685	1069
Median F/u	42.9 months	36.6 months

1. Do et al, ESMO 2024
2. Finn et al, ASCO 2024

3-YEAR OS UPDATE

OS benefit with durvalumab + GemCis continued at the updated data



	Primary analysis[1,*] DCO: Aug 11, 2021		3-year follow-up[†] DCO: Oct 23, 2023	
	D+GC (n=341)	PBO+GC (n=344)	D+GC (n=341)	PBO+GC (n=344)
Median OS[‡] (95% CI), months	12.8 (11.1–14.0)	11.5 (10.1–12.5)	12.9 (11.6–14.1)	11.3 (10.1–12.5)
OS HR[§] (95% CI)	0.80 (0.66–0.97)		0.74 (0.63–0.87)	

Usually driven by tail of curve

At 36-months, the survival rate in the durvalumab + GemCis arm was more than double the survival rate in the placebo + GemCis arm

Targets Biliary Tract Cancers

- IDH-1 mutations
- FGFR2 fusions
- BRAF
- Her-2 (ERBB2)
- Immunotherapy

FGFR2 inhibitors

Agent	Trial N size	RR (%)	PFS (m)	DOR (m)	OS (m)
Pemigatinib	107	37	7.0	9.1	17.5
Futibatinib	103	41.7	8.9	9.7	21.7
Derazantinib	103	21.4	7.8		
Erdafitinib	78	55%	8.5	6.9	18.1
Infigratinib	**108**	**23.1**	**7.3**		

First Line Trials with FGFR2 Inhibitors
Pemigatinib , Infigratinib, and Futibatinib

All are non selective FGFR inhibitors (FGFR 1-4)

Lancet Onc 2020
Lancet Gastro Hepato 2021
Goyal L, et al NEJM 2023
ESMO 2021

FGFR 2 Inhibitors toxicity

- Hyperphosphatemia (FGFR1)
- Eye disorders
- Stomatitis
- Fatigue
- Diarrhea (FGFR4)

Targeting HER-2

- **Pertuzumab and trastuzumab: phase 2a study (**Javle Lancet Oncol 2021**)**
  - 39 patients previously treated HER2 amplification, HER2 overexpression, or both
  - RR 23 %. Median DOR: 10.8 months. Median OS: 10.9 months
    - Higher activity in extrahepatic BTC RR: 40% (ampullary); 31% (GBC)

- **Neratinib, a pan-HER irreversible tyrosine kinase inhibitor** Harding ASCO 2022
  - 25 pts with activating somatic HER2 mutations (GB 40%, ICC24%, EHCC20%, AV 16%)
  - RR 16% and PFS 2.8 months. Median OS 5.4 months

ZANIDATAMAB Herizon- BTC-01 UPDATE

- Median f/u 21.9 mths
- ORR of 41.3% (investigator assessed)
- Median DOR was 14.9 months
- Median OS was 15.5 months

- FDA Accelerated Approval 11/20/24 previously treated, unresectable/metastatic HER2-positive (IHC 3+) BTC

Pant S, et al ASCO 2024

Targeting HER-2
Trastuzumab deruxtecan
FDA Approved (2024)

- 30 pts recurrent or unresectable:
- RR 36.4% and 12.5%. PFS 5.1 and 3.2 months in HER 2 + and HER 2 low
- DOR in Her 2 +: 7.4 months
- ILD: ≥ Grade 3: 12.5%

Ohba et al: A 4006, ASCO 2022

DESTINY Pan Tumor 02

- 41pts recurrent or unresectable:
- RR 22% (all 9 pts 3+)
- DOR 8.6 months
- PFS 4.6 - 7.4m (3+)
- OS 7.0 m -12.4m (3+)

Oh DY et al: Poster 4090, ASCO 2024

PRINCIPLES OF SYSTEMIC THERAPY[a]

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Durvalumab + gemcitabine + cisplatin (category 1)[e,f,g,4]
- Pembrolizumab + gemcitabine + cisplatin (category 1)[f,g,5]

Other Recommended Regimens

- Gemcitabine + cisplatin (category 1)[6]
- Capecitabine + oxaliplatin
- FOLFOX
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[h]

Preferred Regimens

- FOLFOX[7]

Other Recommended Regimens

- FOLFIRI[8]
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[9]
- Regorafenib (category 2B)[10]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)
- Nivolumab (category 2B)[f,g,11]

[a] Order does not indicate preference.
[e] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[f] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[h] Treatment selection depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.

References

Thanks For The Attention!