Role of Immunotherapy and Combination Approaches in Advanced Cholangiocarcinoma

Amit Mahipal MBBS, MPH

Professor

Director GI Oncology

UH Seidman Cancer center

Case Western Reserve University

February 8, 2025

University Hospitals
Seidman Cancer Center
Cleveland | Ohio

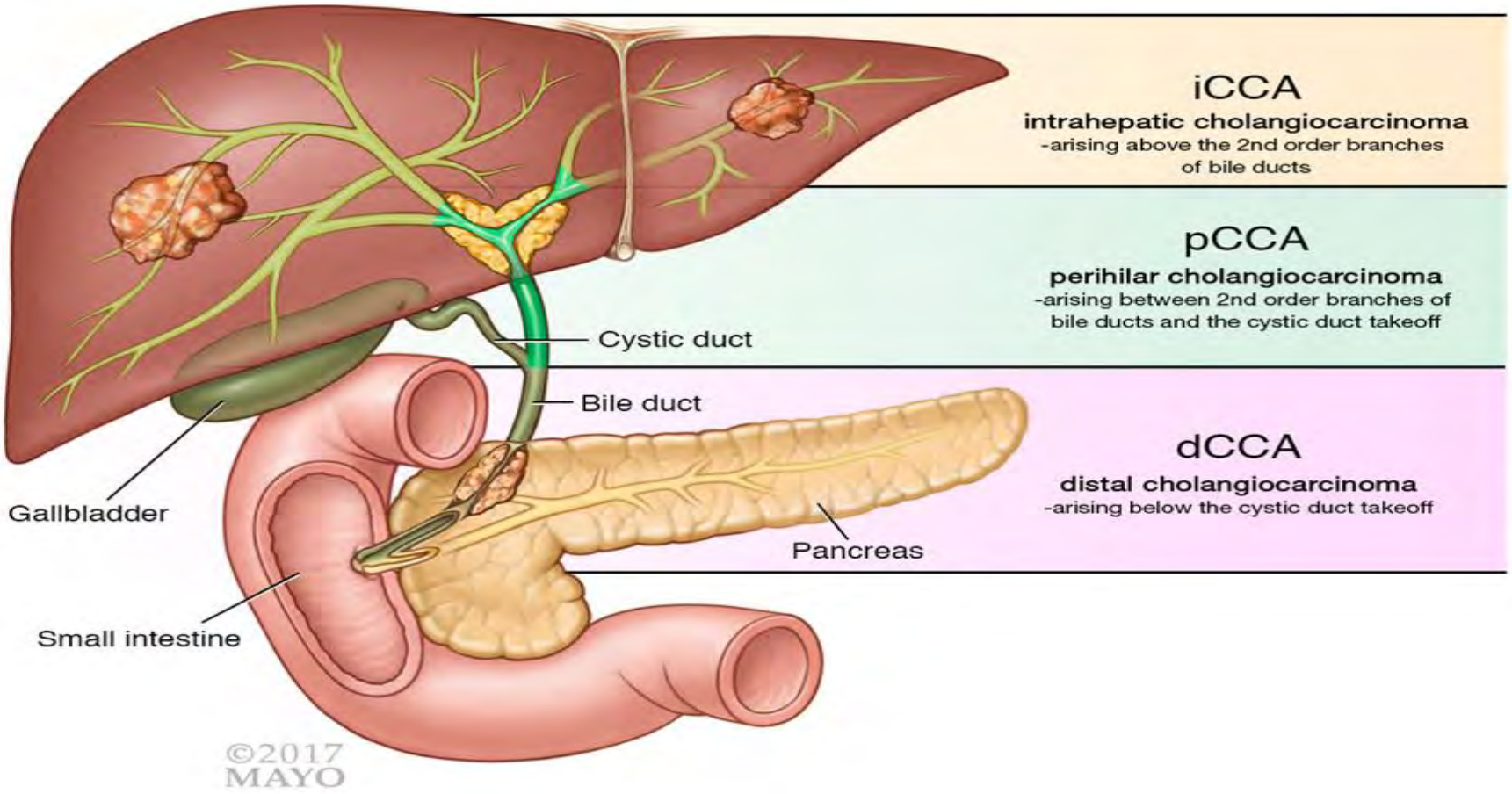
Case Western Reserve University
CASE COMPREHENSIVE CANCER CENTER

Part of a
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Background

- Annual incidence in US: 12,190
- Overall incidence has increased progressively worldwide over the past four decades.
- Aggressive disease with five year-overall survival rates for advanced stage disease <2%.
- Only 15-20% of the patients are candidates for surgical resection

Anatomical Classification



Mutation Profile

Intrahepatic	Prevalence
FGFR1-3 fusions, amplifications, and mutations	11-45%
IDGH1 or *IDH2* mutation	23-28%
TP53 mutation	2.5-44%
ARID1A mutation	15-36%
MCL-1 mutation	16-21%
EGFR expression	11-27%
CDKN2A or CDNK2B loss	6-30%
KRAS mutation	11-25%
MCL1 amplification	21%
SMAD4 mutation	4-17%
MLL3 mutation	15%
BAP1 mutation	13%
HER3 amplification	7%
CDK6 mutation	6%

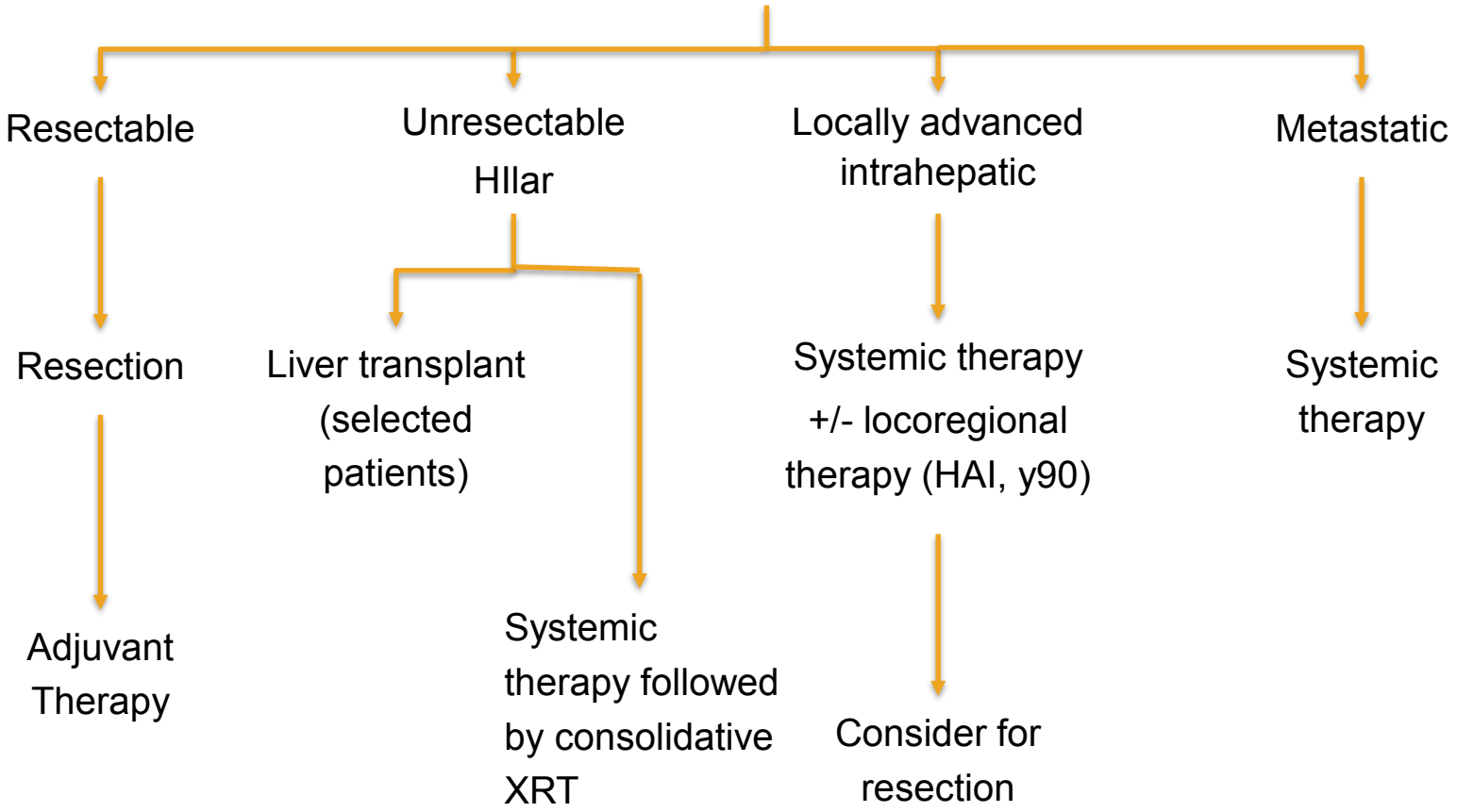
Gallbladder cancer	Prevalence
TP53 mutation	47-59%
HER2 amplification	10-19%
CDKN2A or CDKN2B loss	6-19%
ARID1A mutation	13%
PIK3CA mutation	6-12.5%
NRAS mutation	6%
BRAF mutation	6%
GNAS mutation	6%

Extrahepatic	Prevalence
TP53 mutation	40%
KRAS mutation	8-42%
SMAD4 mutation	21%
CDKN2A or CDKN2B loss	17%
HER2 amplification	11-17%
ARID1A mutation	12%
EGFR expression	5-9%
PIK3CA mutation	7%

FGFR fusion partner	Frequency
FGFR2-AHCYL	7/102 (7%)
FGFR2-BICC1	2/102 (2%)
	41/107 (38%)
	1/28 (4%)
FGFR2-PPHLN1	17/107 (16%)
FGFR2-MGEA5	1/6 (17%)
FGFR2-TACC3	1/6 (17%)
	1/28 (4%)
FGFR-KIAA1598	1/28 (4%)

Tella et al Lancet oncology 2020; Kayhaniyan et al. WJGO 2017

Bile Duct Cancer



Principles of Systemic Therapy

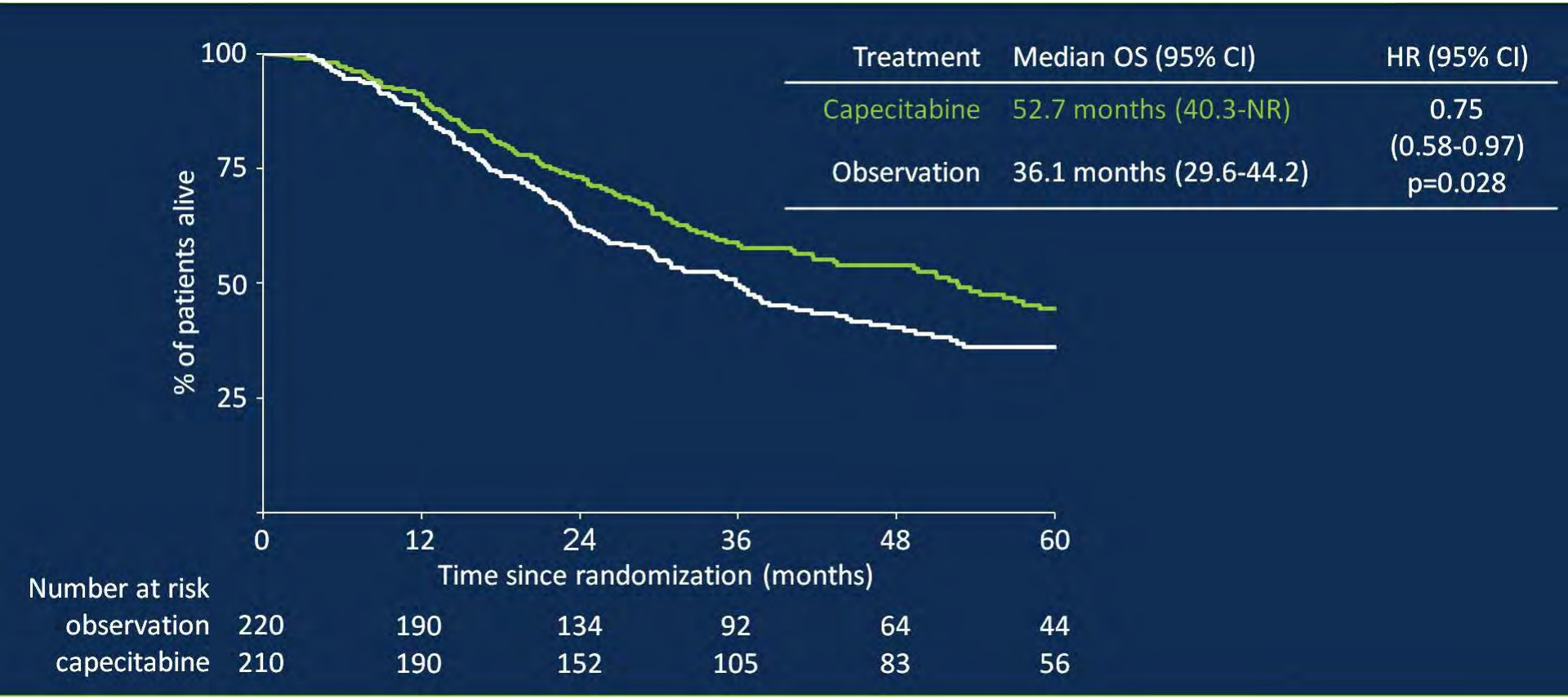
- Adjuvant treatment
  - Capecitabine (phase 3 trial)
  - Gemcitabine based
- Gemcitabine + cisplatin remained standard chemotherapy backbone for first line advanced BTC for more than a decade
- Addition of durvalumab/pembrolizumab to gemcitabine + cisplatin has additive effect with median OS ~13 months
- FOLFOX is second line chemotherapeutic option for patients who failed gemcitabine + cisplatin with median OS of 6-7 months.
- Targeted treatments in selected population

Adjuvant Therapy

Trial	Regimen	N	RFS (months)	OS (months)
PRODIGE12-ACCORD18	GEMOX Observation	98 98	30.4 18.5	75.8 50.8
BCAT	Gemcitabine Observation	117 108	36 39.9	62.3 63.8
KHBO1208	Gemcitabine S-1	70 70	1-year: 51.4% 1-year: 62.9%	1-year: 80% 1-year: 97.1%
BILCAP	Capecitabine Observation	223 224	25.9 17.4	51.1 (53) 36.4 (36)
JCOG1202/ASCOT	S-1 Observation	218 222	63.6 42	NR 6.1
ACCELERATE	GemOX/GemCis + CRT GemOx/GemCis	45 49	NS	NS
ACTICCA-1	Gemcitabine+cisplatin Capecitabine		NA	NA

Treatment arm in each of these trials did not achieve statistically significant difference with the exception of per-protocol analysis of BILCAP trial and JCOG1202 trial.

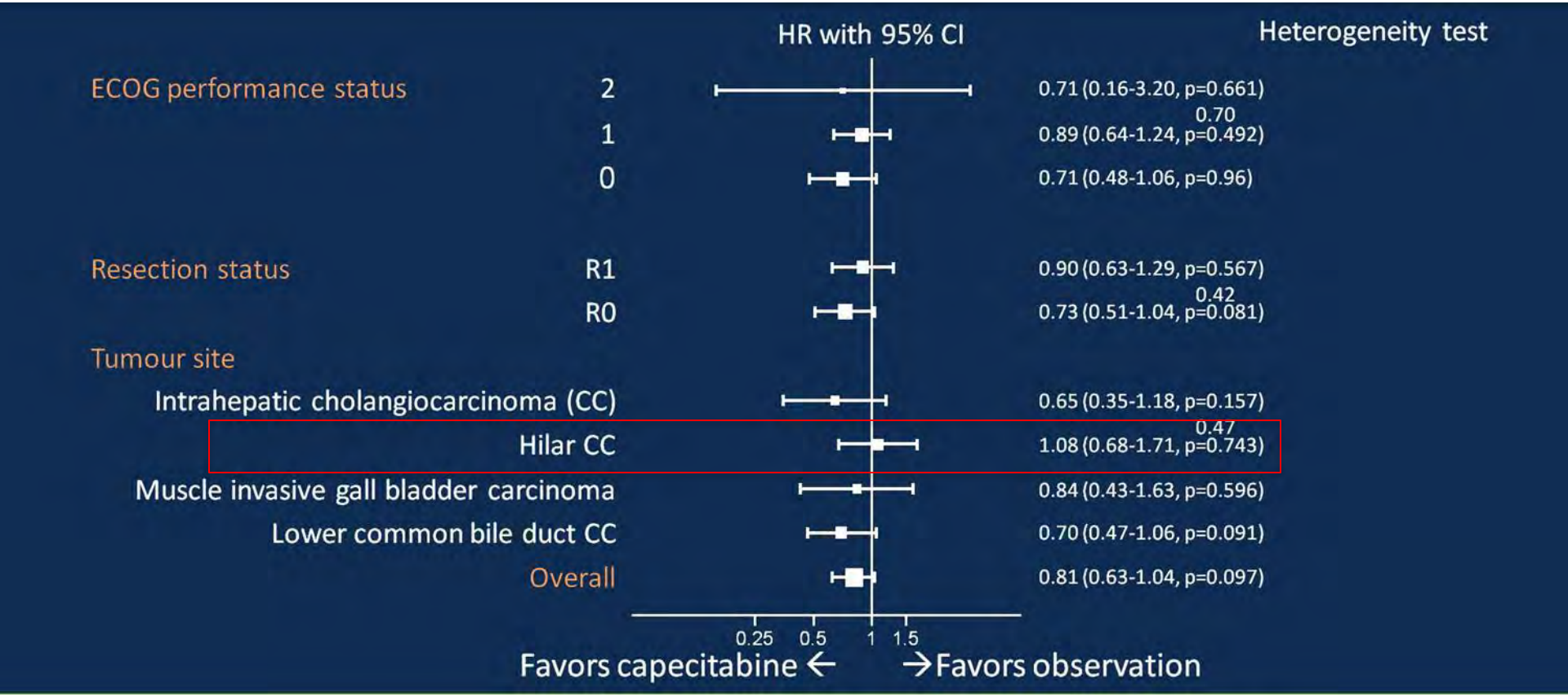
BILCAP study: Per Protocol Analysis



Treatment	Median OS (95% CI)	HR (95% CI)
Capecitabine	52.7 months (40.3-NR)	0.75 (0.58-0.97) p=0.028
Observation	36.1 months (29.6-44.2)	

Primrose et al. ASCO annual meeting, 2017

BILCAP study



SWOG 0809 Trial

- Single arm Phase 2 trial
- 79 patients
  - Extra hepatic cholangiocarcinoma
  - Gallbladder cancer
- Treatment
  - 4 cycles of gemcitabine + capecitabine
  - Concurrent chemoradiation therapy with capecitabine
- Median OS: 35 months
- 2-year OS: 65%

Joseph et al JCO 2015

Adjuvant Treatment

- Capecitabine is standard of care
  - BILCAP was largest trial
  - Statistically significant difference based on per-protocol analysis
- Future trial results with S-1 and gemcitabine + cisplatin may change management
- Neoadjuvant therapy remains experimental
- Role of radiation therapy remains unclear
  - R1 resection
  - Extrahepatic cholangiocarcinoma
  - Gallbladder cancer
  - Lymph node positive

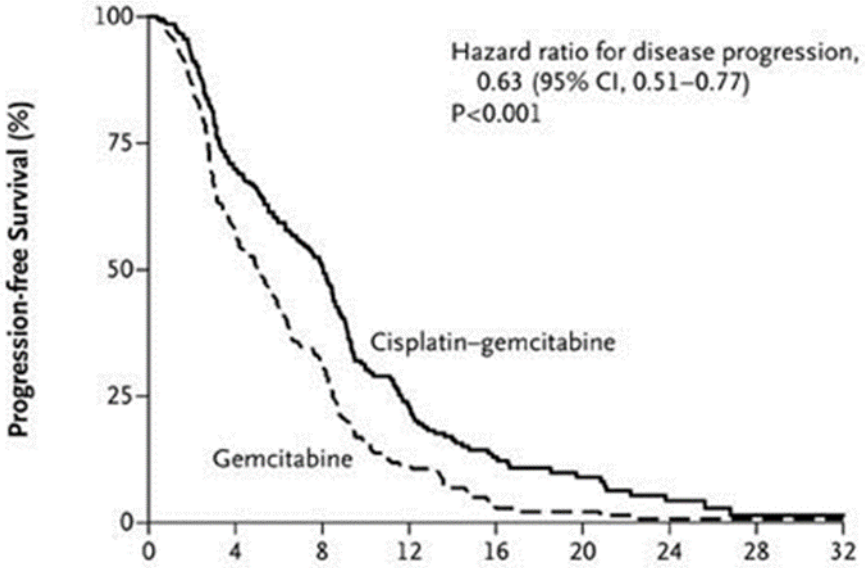
First line chemotherapy

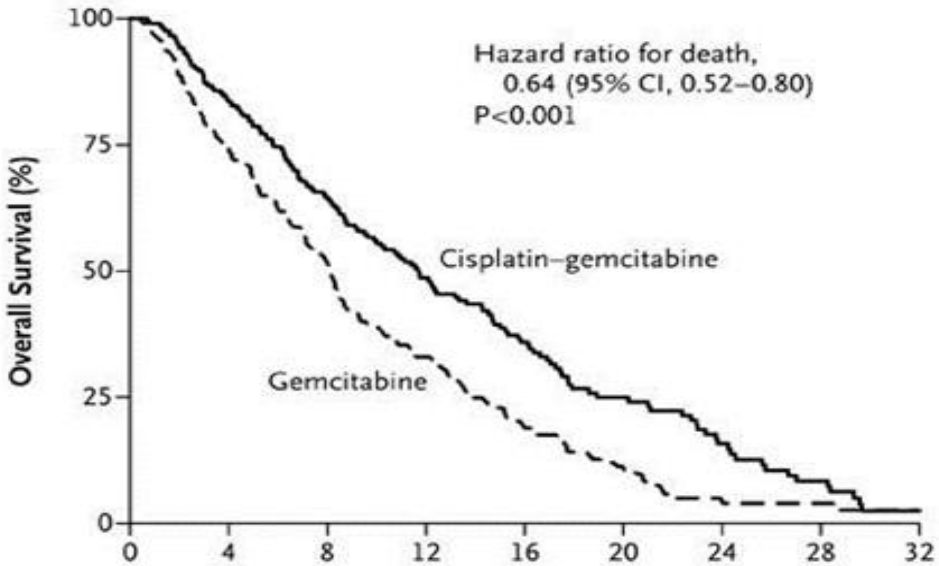
Trial	Regimen	N	RR	PFS (months)	OS (months)
Glimelius et al	5-FU + etoposide Observation	47 43			6.5 2.5
ABC-02	Gem-Cis Gemcitabine	204 206	26.1% 15.5%	8 5	11.7 8.1
BT-22	Gem-Cis Gemcitabine	42 42	19.5% 11.9%	5.8 3.7	11.2 7.7
PRODIGE-38	FOLFIRINOX Gem-Cis	92 93	NA	6.2 7.4	11.7 13.8
S1815	Gem-Cis-Abraxane Gem-Cis	294 147	29% 21%	8.2 6.4	14.0 12.7
TOPAZ-1	Gem-Cis Gem-Cis-Durvalumab	341 344	15.5% 26.1%	5.7 7.2	11.5 12.8
KEYNOTE-966	Gem-Cis Gem-Cis-Pemrolizumab	536 533	29% 29%	5.6 6.6	10.9 12.7

ABC-02 Trial

Median PFS: 8 vs 5 months

Median OS: 11.7 vs 8.1 months



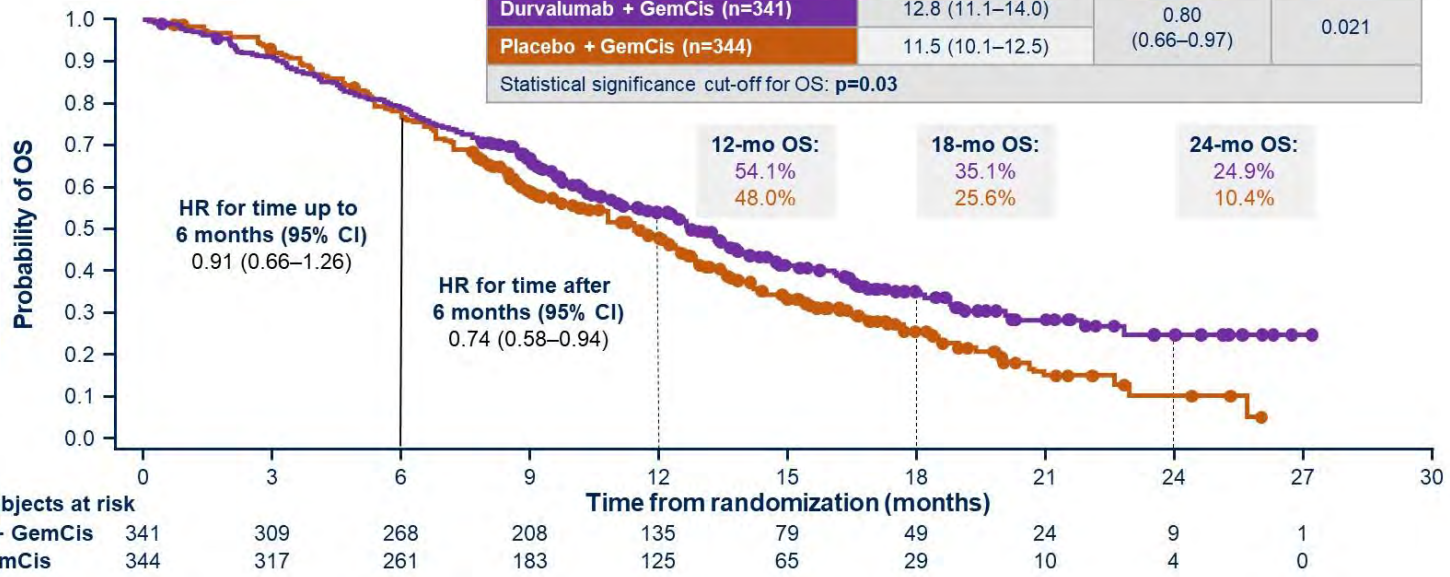


Valle J et al. N Engl J Med 2010;362:1273-1281.

TOPAZ-1 Trial

Primary endpoint: OS

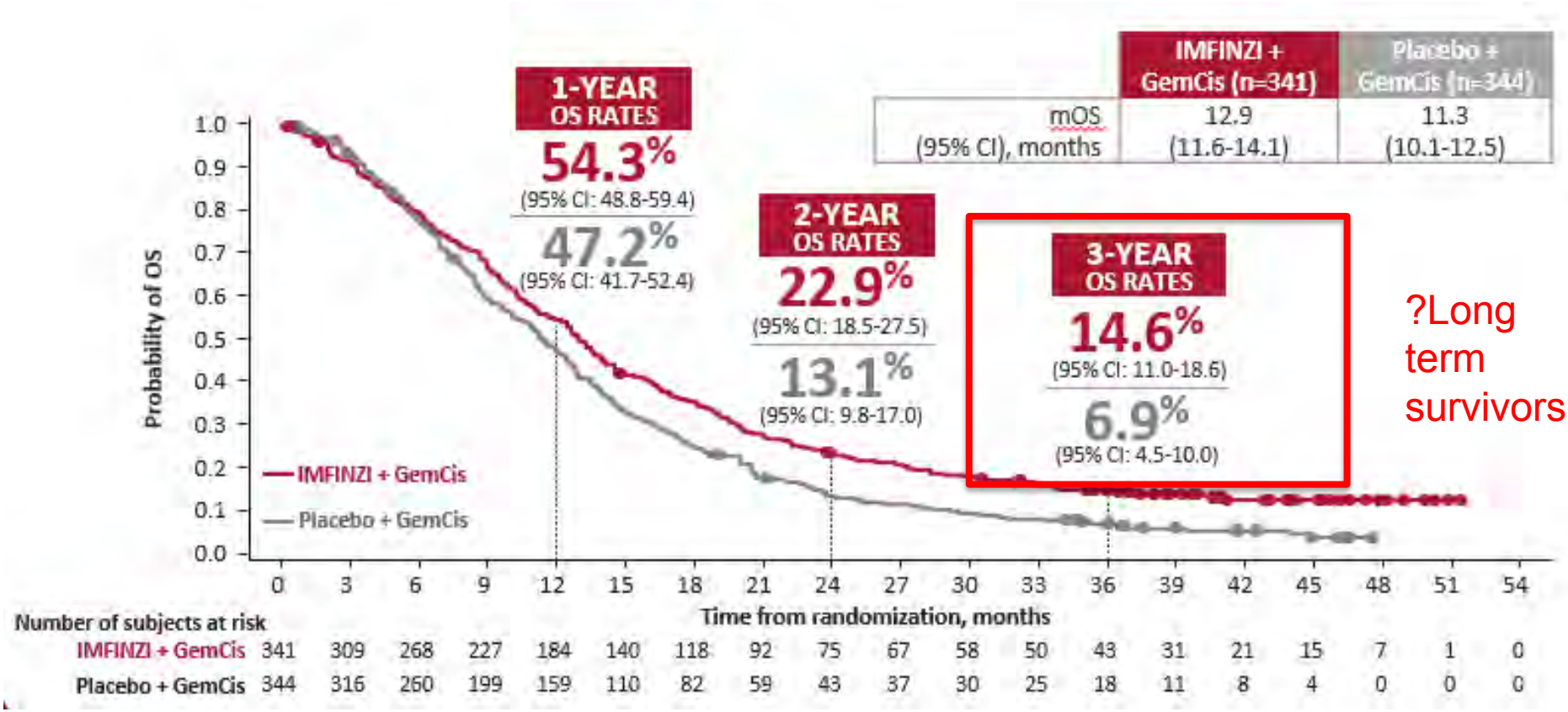
	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



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.

TOPAZ-1 Trial: Updated OS

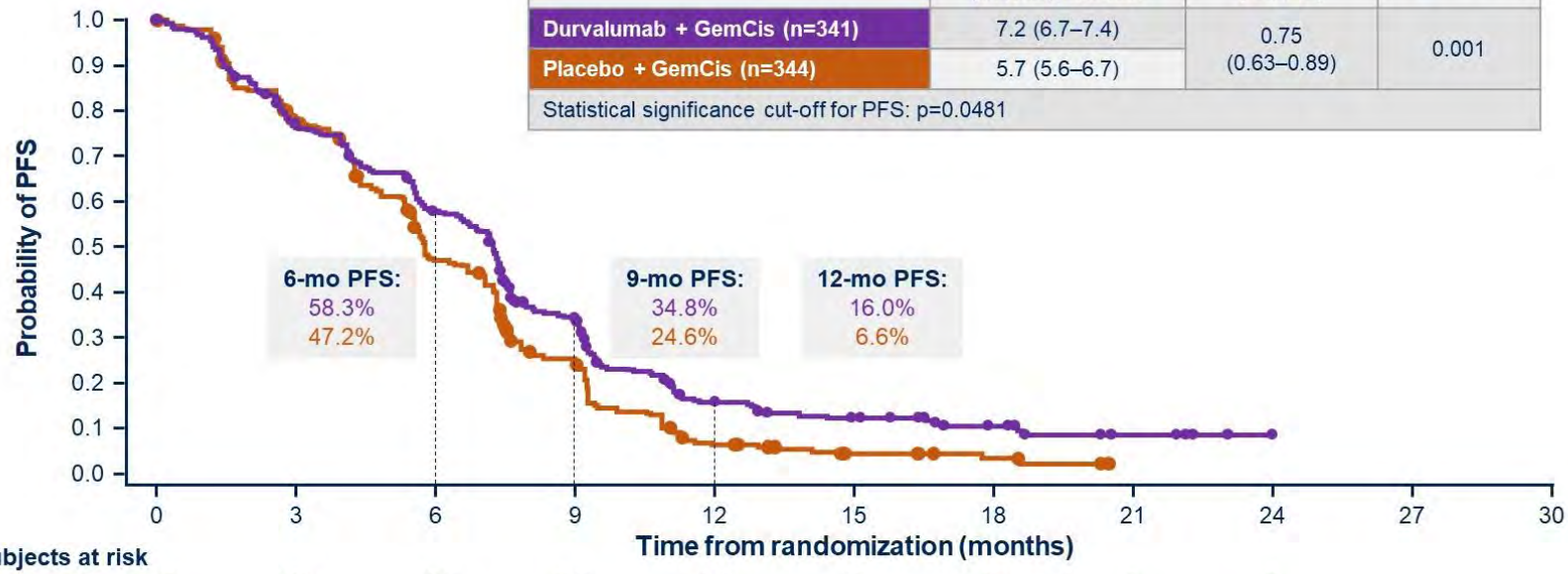


?Long term survivors

TOPAZ-1 Trial

Secondary endpoint: PFS

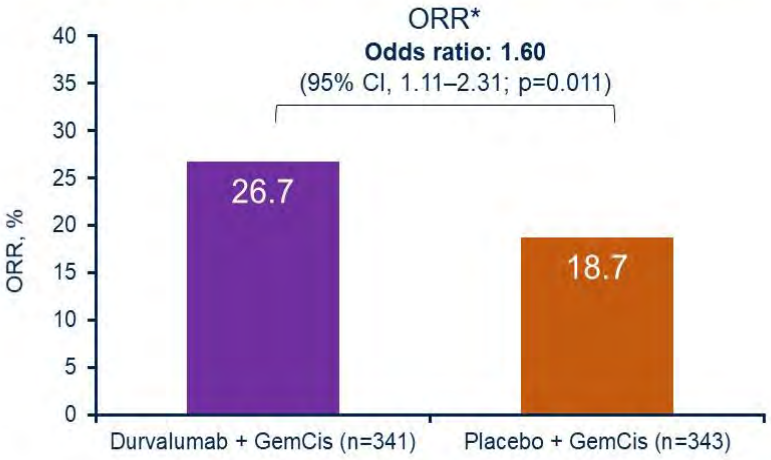
	Median PFS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + GemCis (n=344)	5.7 (5.6–6.7)		
Statistical significance cut-off for PFS: p=0.0481			



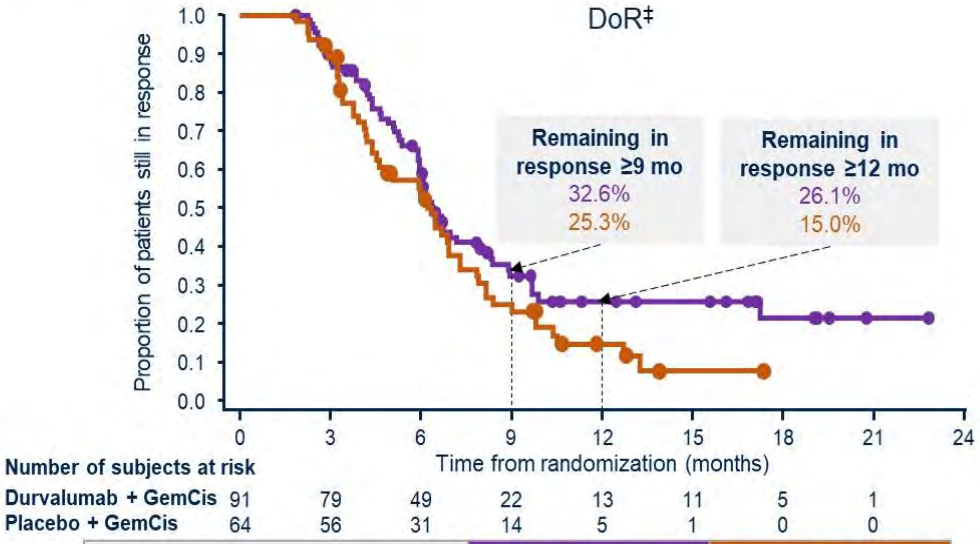
Number of subjects at risk									
Durvalumab + GemCis	341	258	189	100	38	25	15	5	0
Placebo + GemCis	344	255	149	71	17	7	4	0	0

TOPAZ-1 Trial

Secondary endpoint: Tumor response



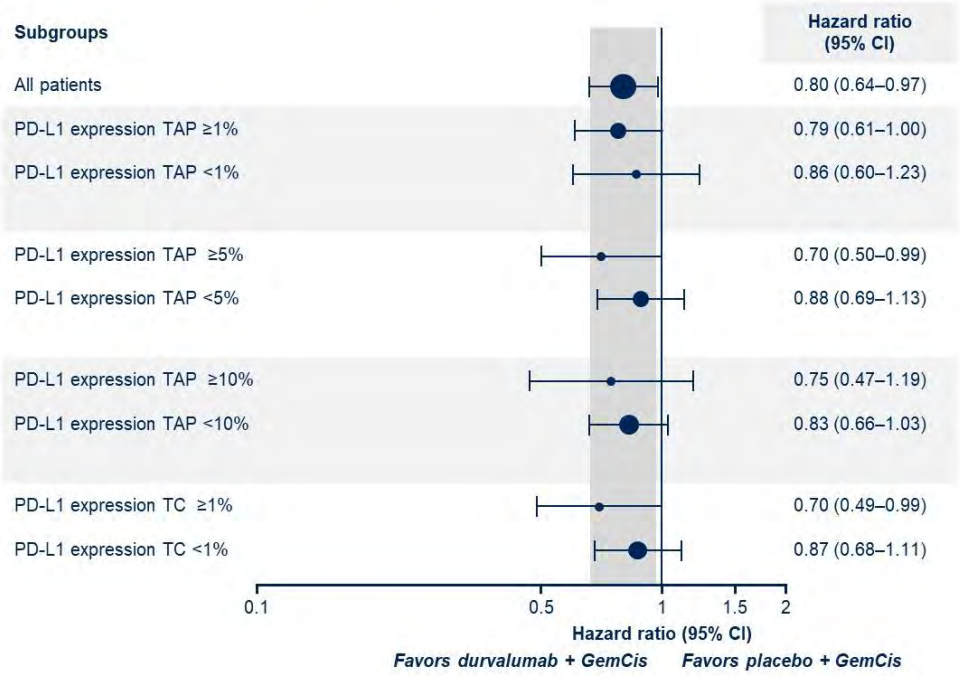
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)

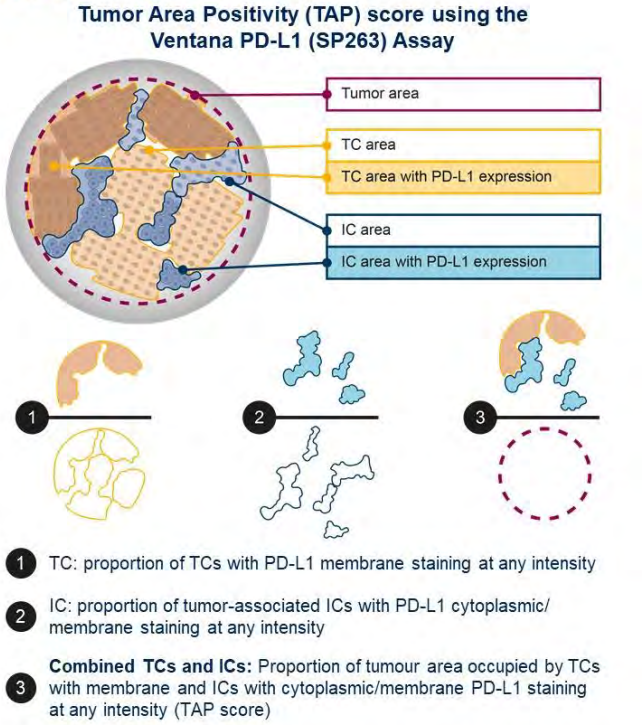


	Durvalumab + GemCis (n=91)	Placebo + GemCis (n=64)
Median DoR (quartile 1–3), months	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Median time to response (quartile 1–3), months	1.6 (1.3–3.0)	2.7 (1.4–4.1)

TOPAZ-1: PDL-1 is not a good biomarker

OS in subgroups by PD-L1 expression



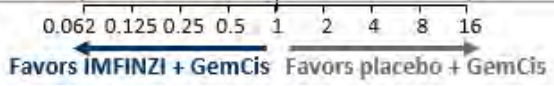


CI, confidence interval; IC, immune cell; OS, overall survival; PD-L1, programmed cell death ligand-1; TC, tumor cell; TAP, tumor area positivity

TOPAZ-1: Genetic alterations

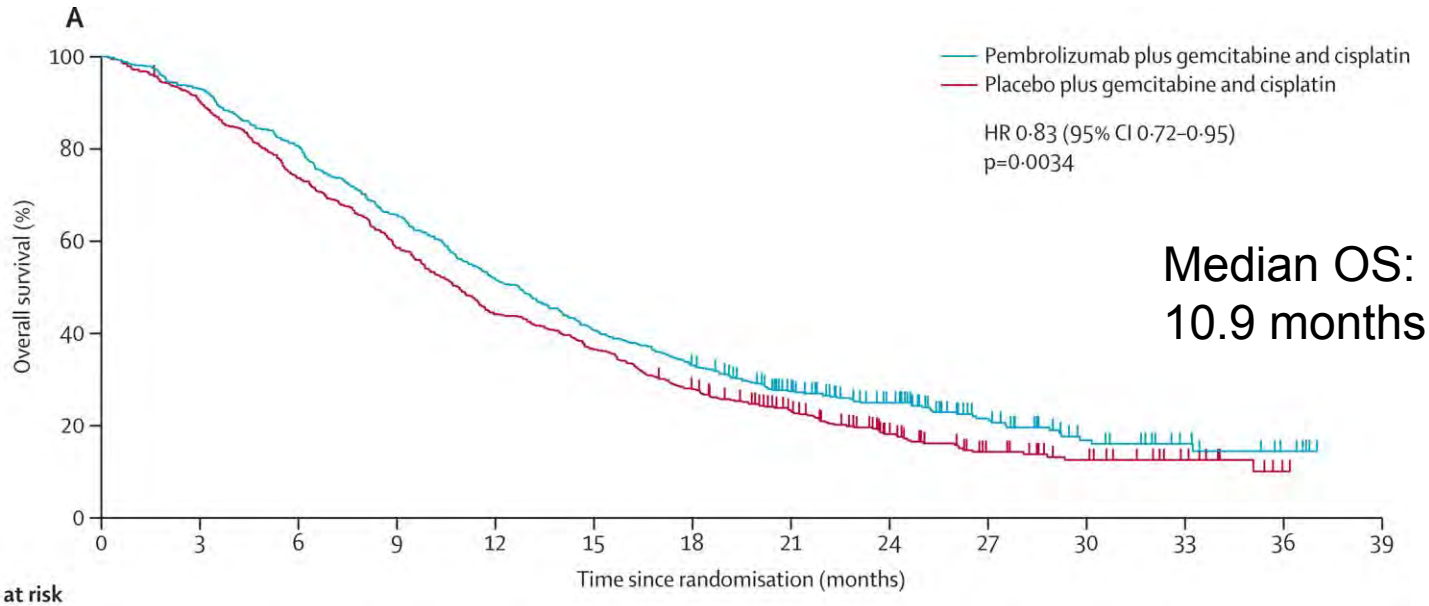
Exploratory OS Subgroup Analysis by Genomic Alteration Status[1]

		IMFINZI + GemCis n/N (%)	Placebo + GemCis n/N (%)	HR (95% CI)
Biomarker evaluable patients		**151/214 (70.6)**	**181/227 (79.7)**	**0.76 (0.61-0.94)**
TP53	Wild-type	74/111 (66.7)	85/115 (73.9)	0.78 (0.57-1.07)
	Alteration	77/103 (74.8)	96/112 (85.7)	0.74 (0.55-1.00)
CDKN2A/2B/MTAP loss	Wild-type	112/164 (68.3)	131/166 (78.9)	0.71 (0.55-0.91)
	Alteration	39/50 (78.0)	50/61 (82.0)	0.95 (0.62-1.45)
KRAS	Wild-type	110/158 (69.6)	139/177 (78.5)	0.81 (0.63-1.04)
	Alteration	41/56 (73.2)	42/50 (84.0)	0.55 (0.35-0.86)
ARID1A	Wild-type	120/174 (69.0)	145/175 (82.9)	0.66 (0.52-0.85)
	Alteration	31/40 (77.5)	36/52 (69.2)	1.22 (0.75-1.99)
IDH1	Wild-type	139/192 (72.4)	172/210 (81.9)	0.77 (0.61-0.96)
	Alteration	12/22 (54.5)	9/17 (52.9)	0.76 (0.31-1.89)
ERBB2 (HER2) amplification[2,a]	Wild-type	138/199 (69.3)	165/207 (79.7)	0.72 (0.57-0.90)
	Alteration	13/15 (86.7)	16/20 (80.0)	1.71 (0.82-3.56)
BRCA1/2	Wild-type	147/203 (72.4)	175/219 (79.9)	0.78 (0.62-0.97)
	Alteration	4/11 (36.4)	6/8 (75.0)	NC[b]
FGFR2 rearrangement	Wild-type	149/210 (71.0)	173/216 (80.1)	0.76 (0.61-0.95)
	Alteration	2/4 (50.0)	8/11 (72.7)	NC[b]
BRAF	Wild-type	144/206 (69.9)	173/219 (79.0)	0.76 (0.61-0.95)
	Alteration	7/8 (87.5)	8/8 (100.0)	NC[b]



● Clinically actionable alterations ● Most common alterations in the TOPAZ-1 trial

KEYNOTE-966



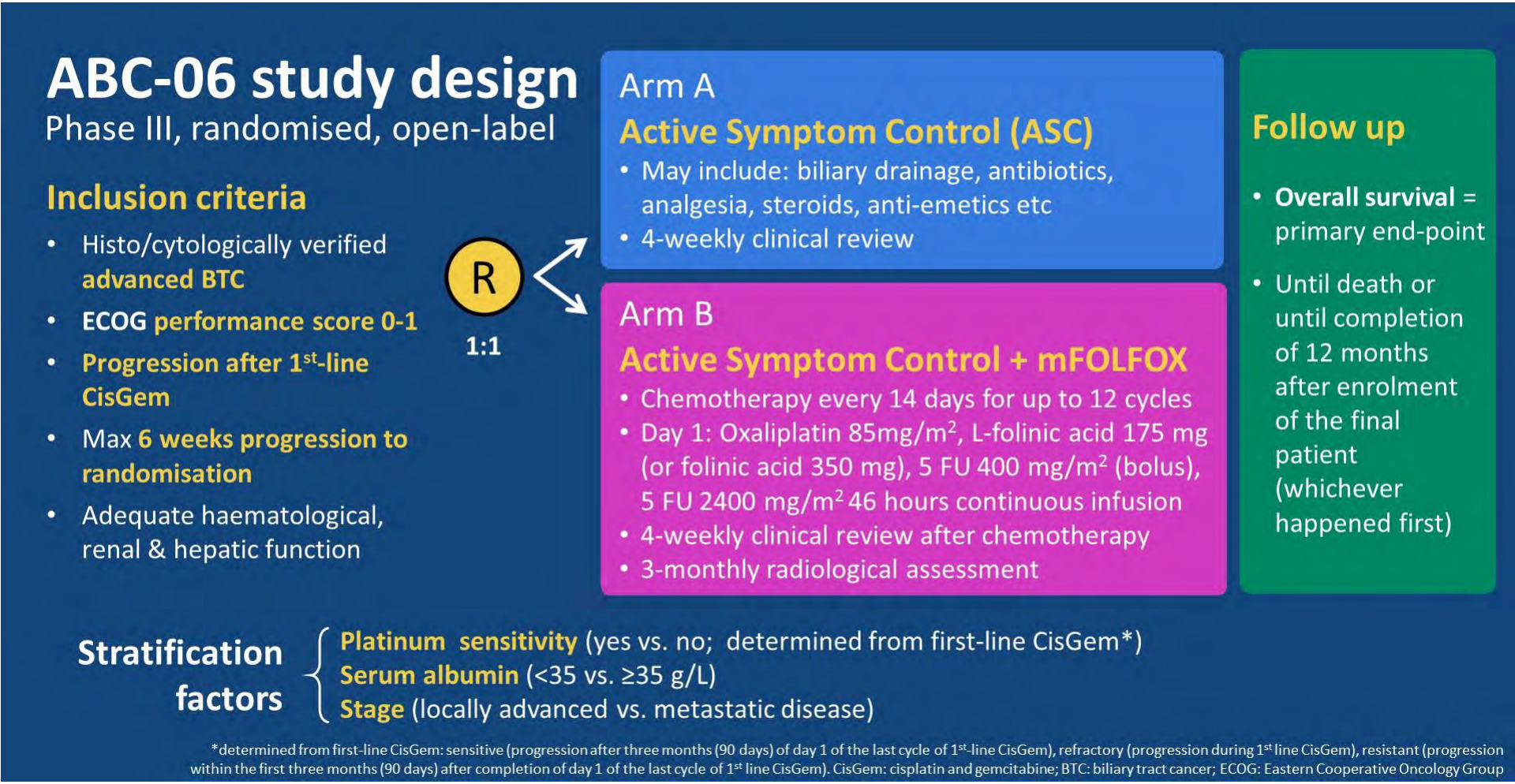
Number at risk (number censored)														
Pembrolizumab plus gemcitabine and cisplatin	533 (0)	496 (0)	430 (0)	350 (0)	275 (0)	217 (0)	175 (1)	122 (26)	88 (50)	46 (83)	21 (100)	11 (109)	5 (114)	0 (119)
Placebo plus gemcitabine and cisplatin	536 (0)	483 (1)	394 (1)	313 (1)	236 (1)	195 (1)	148 (3)	97 (30)	59 (49)	32 (65)	20 (74)	10 (84)	1 (92)	0 (93)

Median OS: 12.7 vs 10.9 months

Second Line Treatment

- No FDA approved chemotherapeutic regimen
- FOLFOX is most commonly used
- Other chemotherapeutic regimens mostly based on small phase 2 trials/retrospective studies
  - 5-Fluorouracil + nal-irinotecan
  - FOLFIRI/XELIRI
  - Single agent fluoropyrimidine
  - Docetaxel

ABC-06

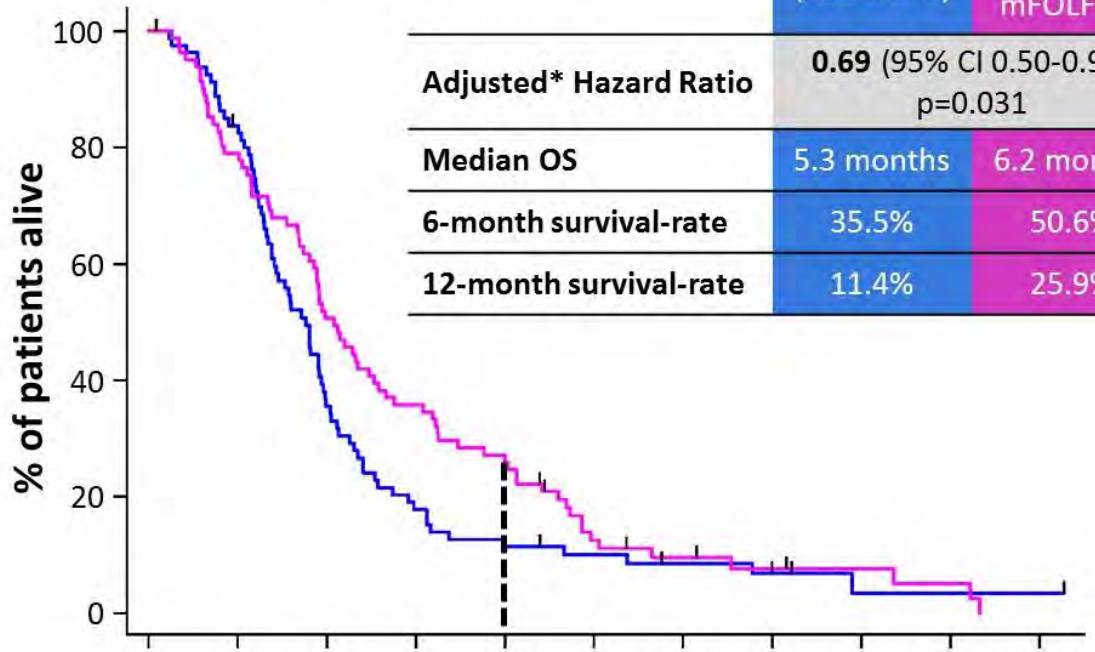


Lamarca et al, 2019 ASCO Annual meeting

ABC-06

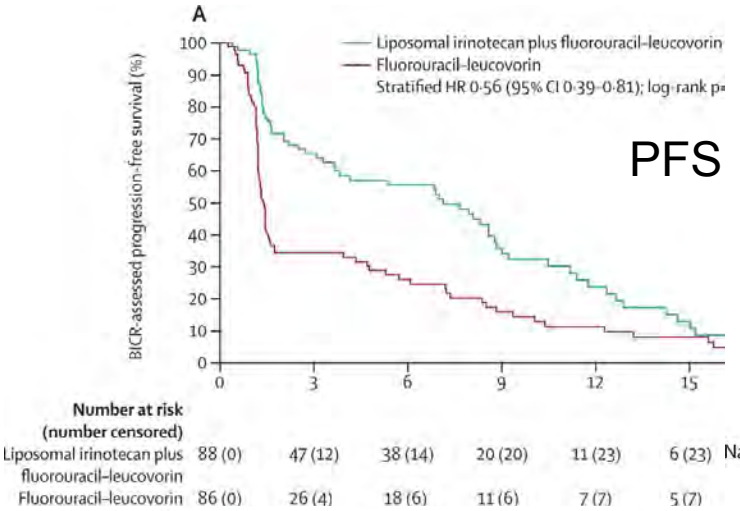
Overall survival by trial arm

	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

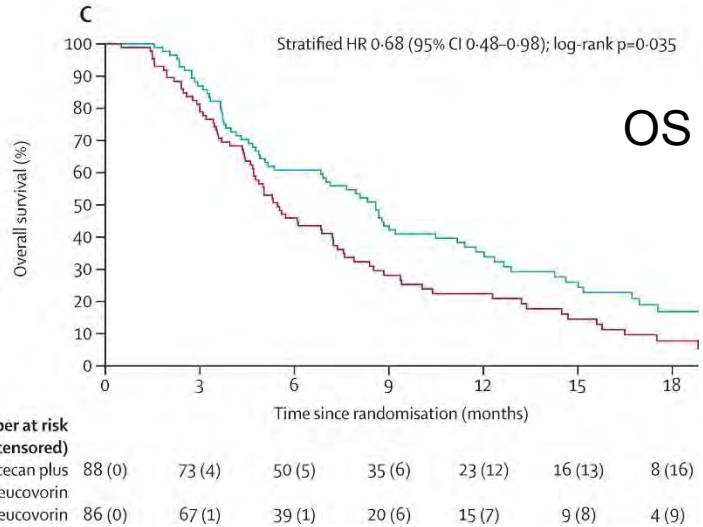


Number at risk											
ASC alone	81	66	28	14	9	7	5	3	1	1	1
ASC + mFOLFOX	81	64	41	29	21	9	6	4	3	2	0

NIFTY Trial

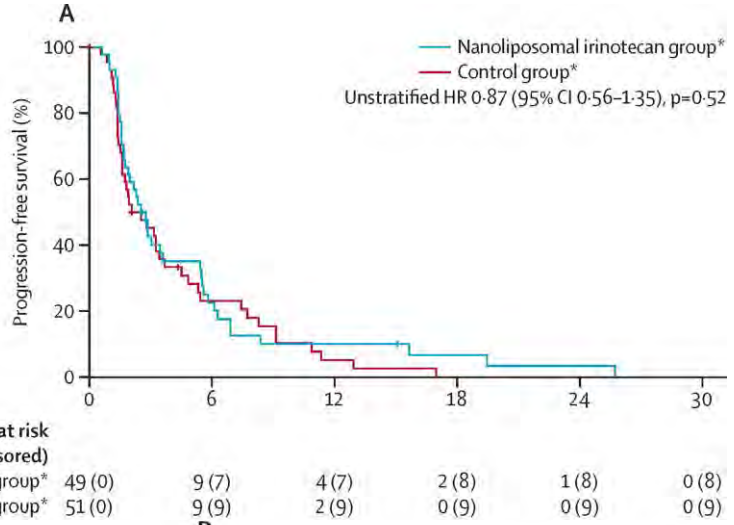


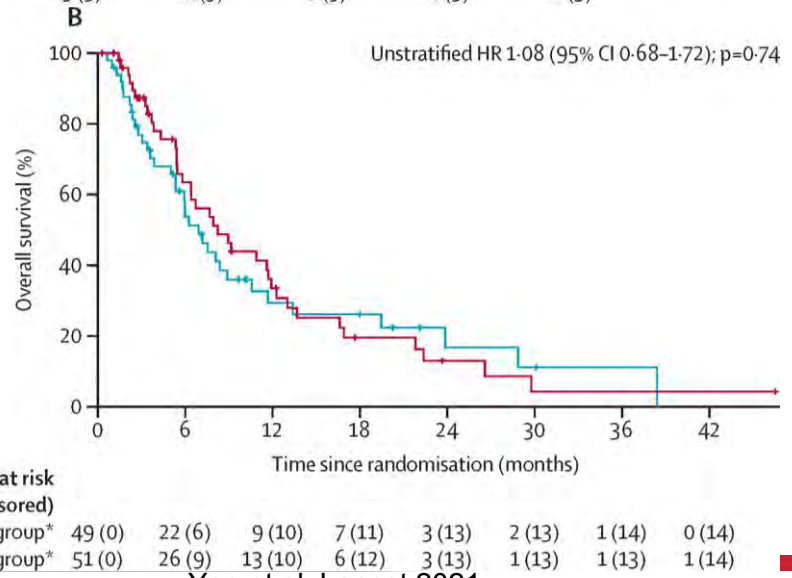
PFS



OS

AIO NALIRICC



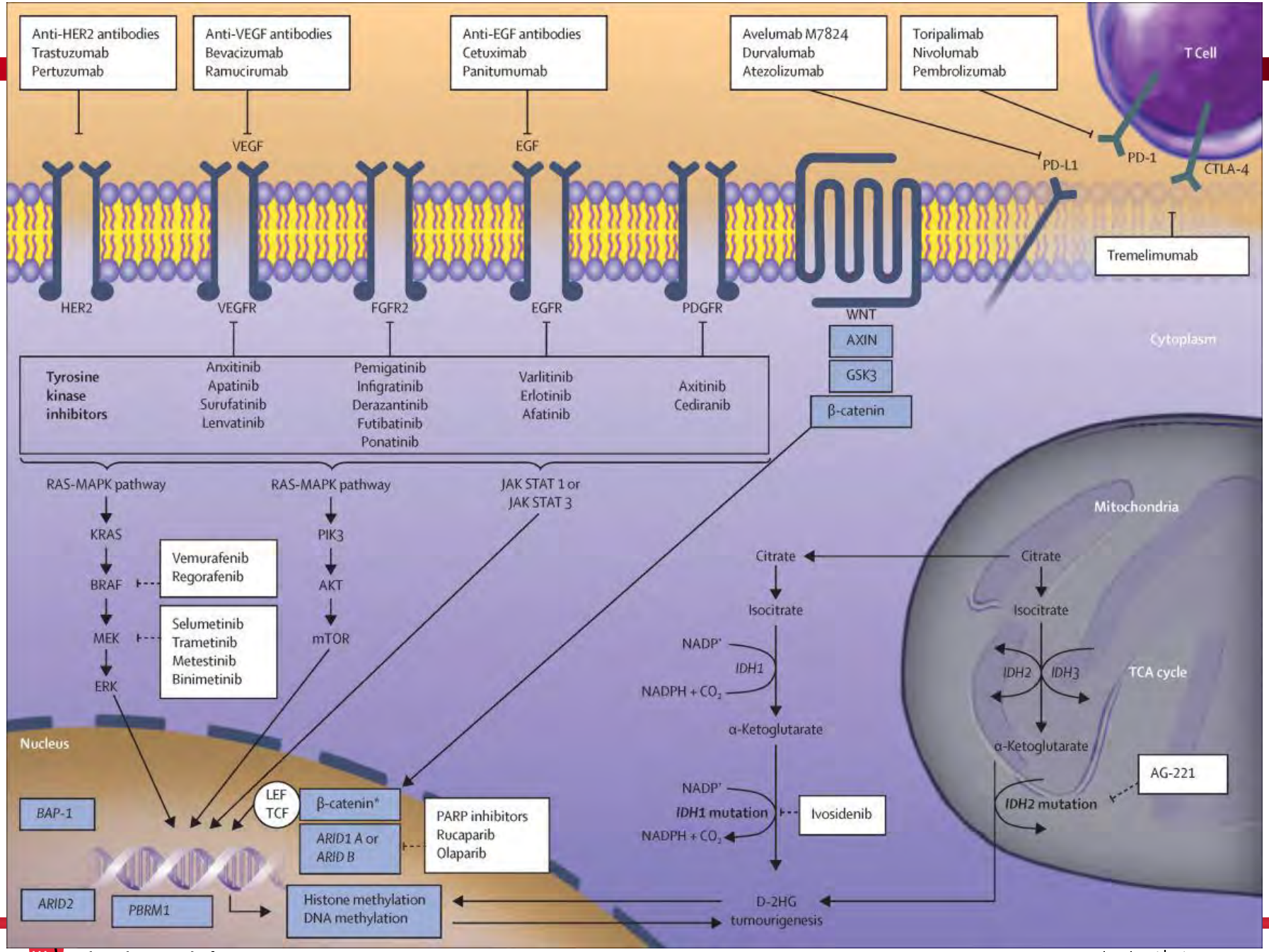


Yoo et al. Lancet 2021

Prognostic factors for second line chemotherapy

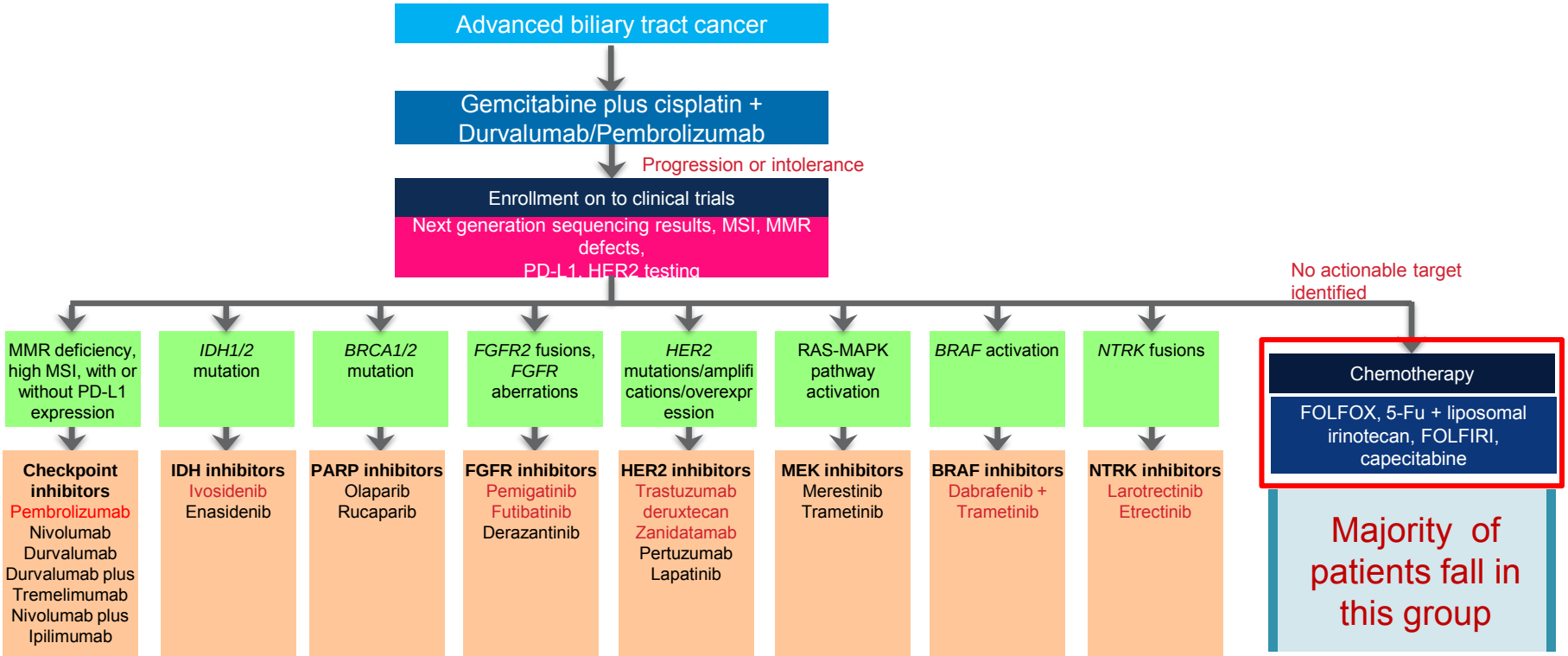
- Excellent performance status (ECOG: 0)
- PFS on first line chemotherapy > 6 months
- Prior surgery on primary tumor
- Low CA 19-9
- Can mutations predict?
  - KRAS and TP53 mutations: worse outcomes
  - FGFR2 fusion: better outcomes

Brieau et al. Cancer 2015

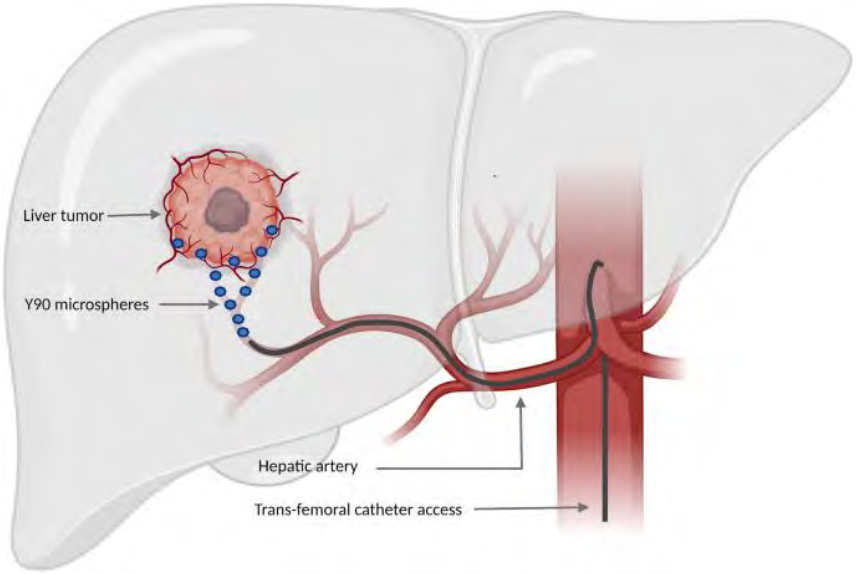


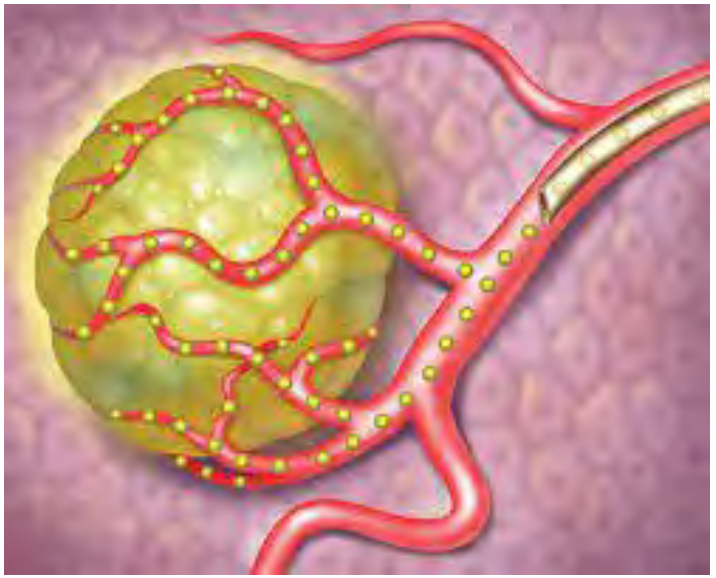
Tella, Mahipal et al. Lancet Oncology 2020

Treatment Algorithm

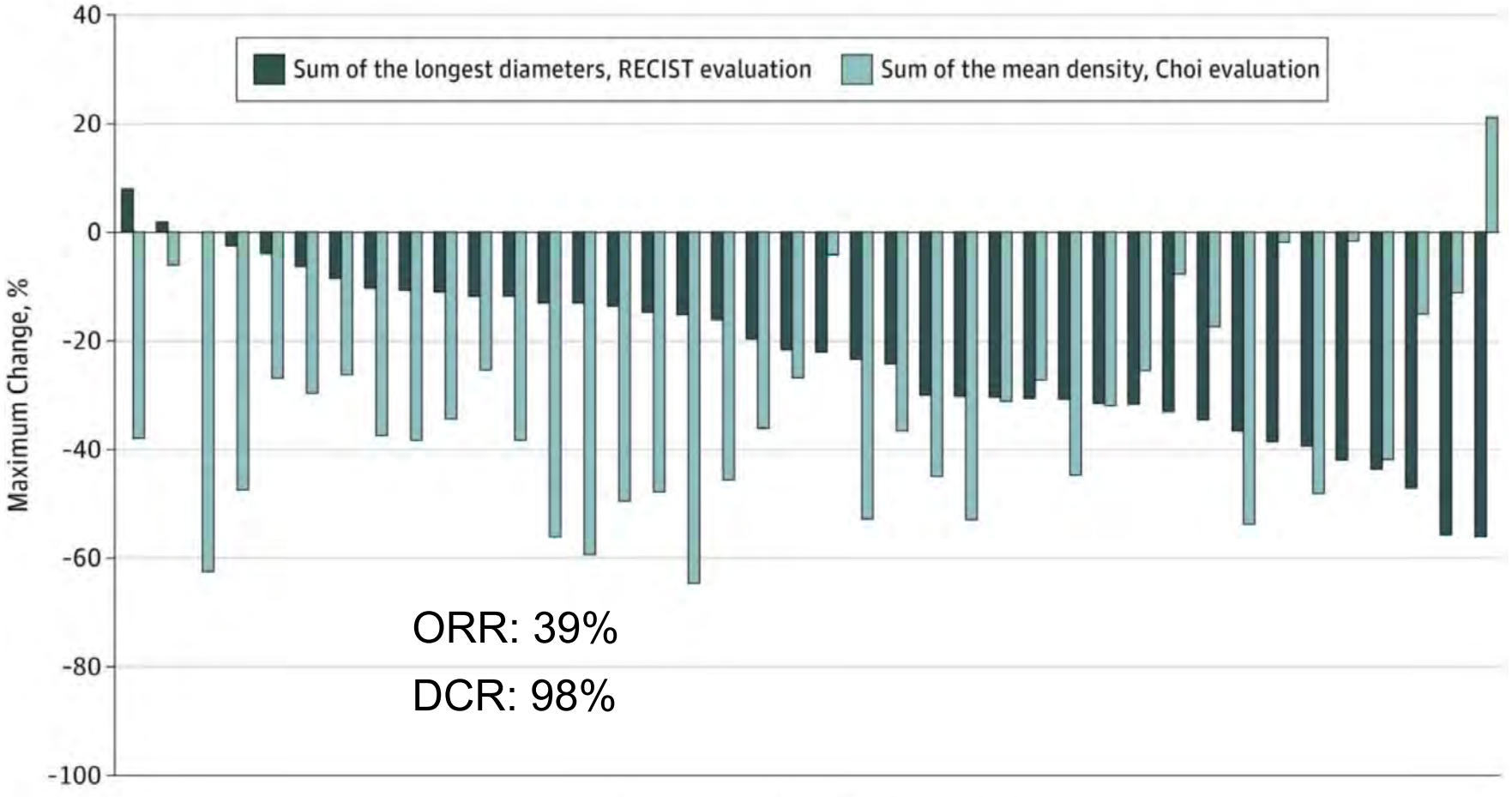


Locoregional Therapies: Y90

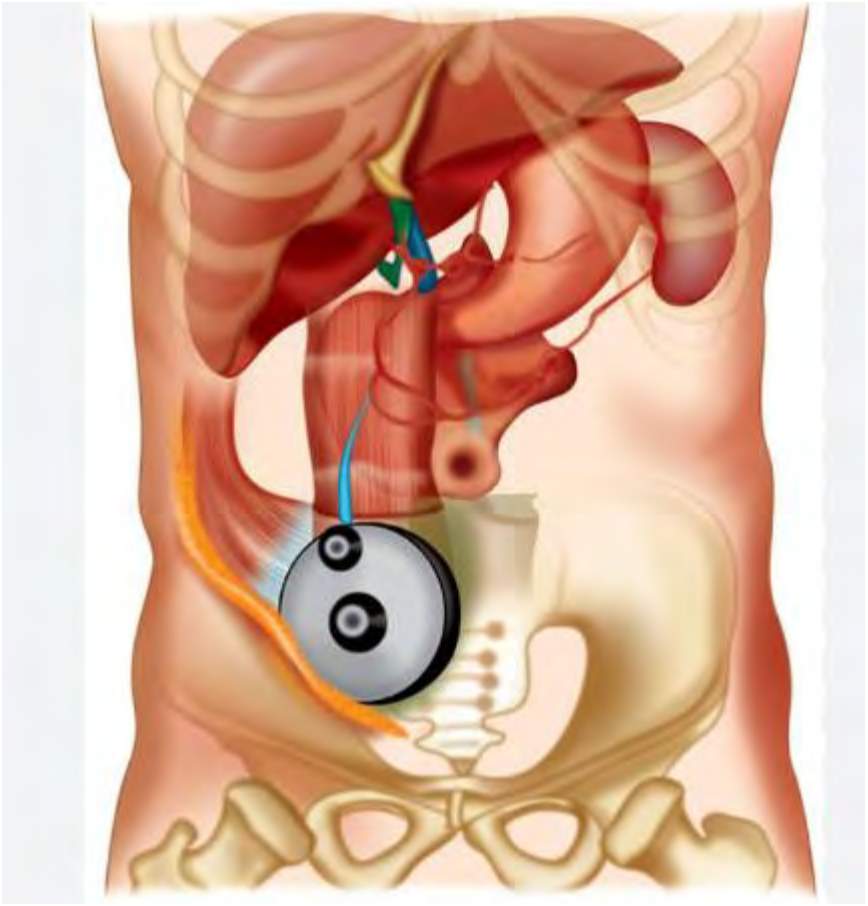




Y90 Radioembolization: MISPHEC trial

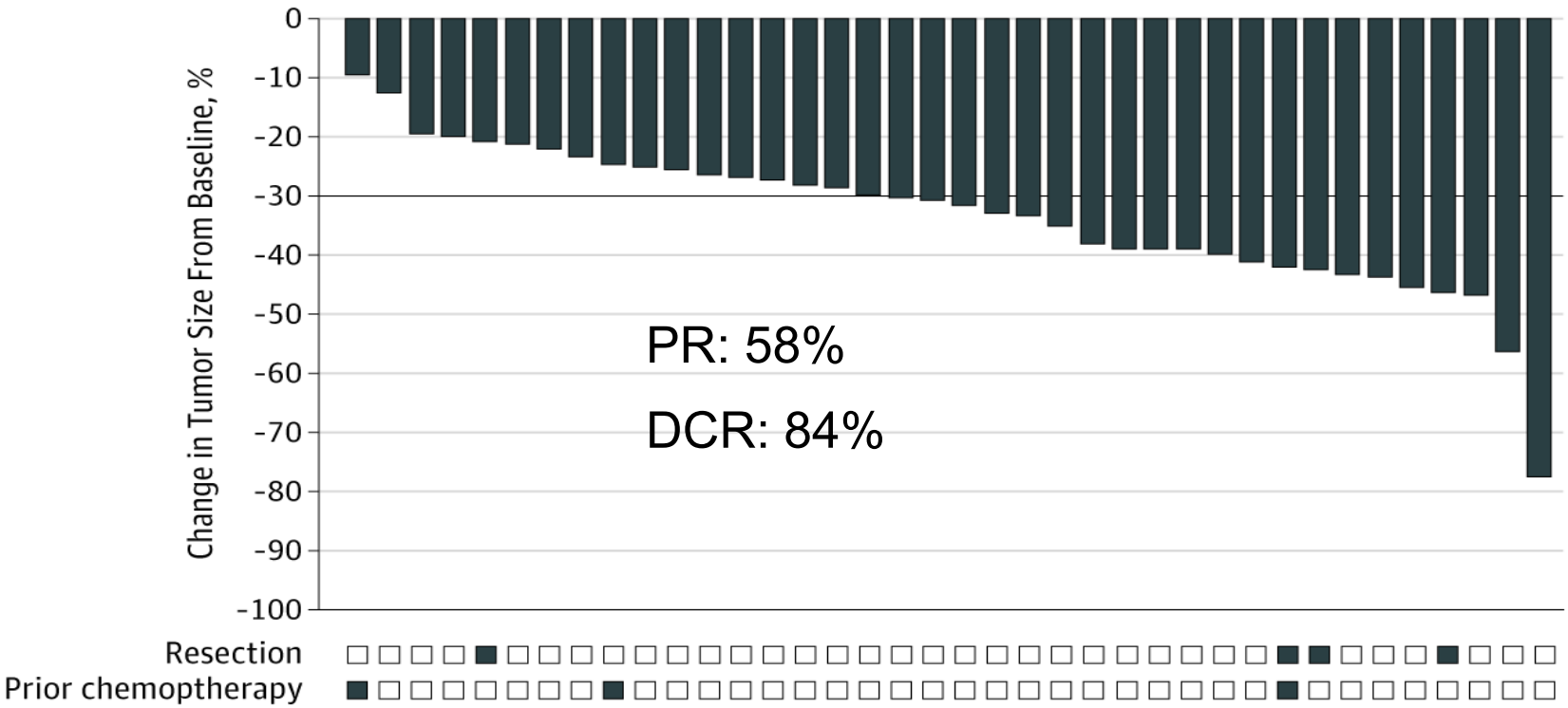


Locoreginal Therapy: Hepatic Artery Infusion Pump



Hepatic artery Infusion: Phase 2 trial

Percent change in tumor size from baseline



Implications

- Current systemic therapies are associated with limited survival
- Urgent need to develop novel therapies to improve outcomes
- All advanced patients should undergo:
  - NGS
  - Her-2 testing
  - MSI testing
- Selected patients can be considered for
  - Liver transplant
  - Y90 radioembolization
  - HAI
- Targeted therapies hold promise for selected patients population including FGFR2 fusion, IDH mutations, MSI-high, her-2 amplifications but still limited to minority of population
- Targeting RAS, CDKN2A, p53. loss of MTAP may dramatically alter the natural history of disease

Questions