August 25, 2023

ASCO Updates 2023

- **Esophageal/Gastric Adenocarcinoma**
  Pancreatic Adenocarcinoma
  Cholangiocarcinoma

Naomi Fei, MD MS

Outline

- **Pancreatic Adenocarcinoma**
  - NORPACT-1
  - NAPOLI-3
- **Esophageal / Gastric Adenocarcinoma**
  - SPOTLIGHT
  - INTEGRATE IIA
  - NEO-AEGIS
- **Cholangiocarcinoma**
  - IMBRAVE-151
  - SWOG 1815

NORPACT-1: Short-course neoadjuvant FOLFIRINOX vs. upfront surgery for resectable pancreatic head cancer.

Knut Jørgen Labori, Svein Olav Bratlie, Christina Biörserud, Bergthor Björnsson, Erling Bringeland, Nils Elander, Jon Erik Grønbech, Oskar Hemmingsson, Linn Nymo, Per Pfeiffer, Ville Sallinen, Ernesto Sparrelid, Kjetil Søreide, Bobby Tingstedt, Caroline Verbeke, Leif Klint, Svein Dueland, Kristoffer Lassen, Johan Haux

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

NORPACT-1: Background & Aim

- In resectable pancreatic cancer, upfront surgery followed by adjuvant chemotherapy is standard of care.
- In fit patients, FOLFIRINOX is the preferred adjuvant regimen.

- **Aim**: Compare the efficacy of neoadjuvant FOLFIRINOX to upfront surgery in patients with resectable pancreatic head cancer.

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

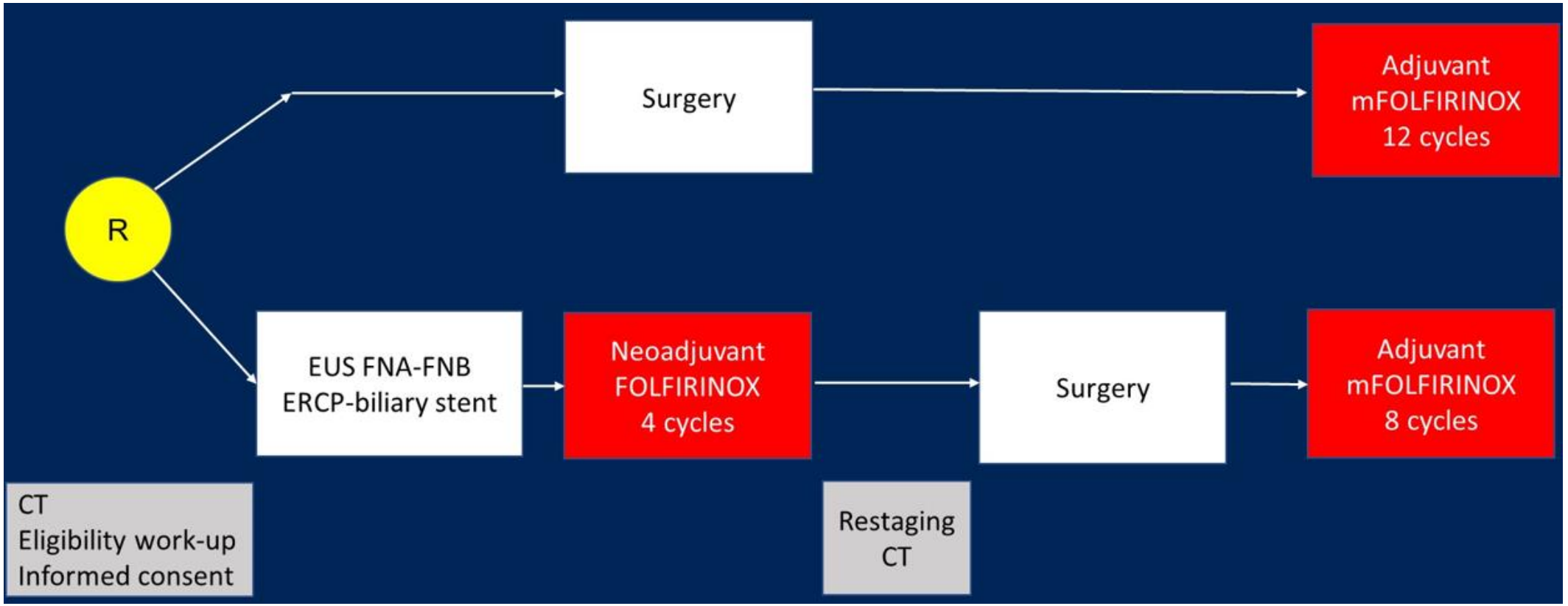
NORPACT-1: Eligibility

- Radiologically (CT) resectable pancreatic head cancer (NCCN criteria)
  - No arterial involvement
  - <180* interface with portal/superior mesenteric vein, no contour irregularity
  - No distant metastases
- Age >18 yr and considered fit for major surgery
- ECOG 0 or 1
- Adequate bone marrow, hepatic and renal function

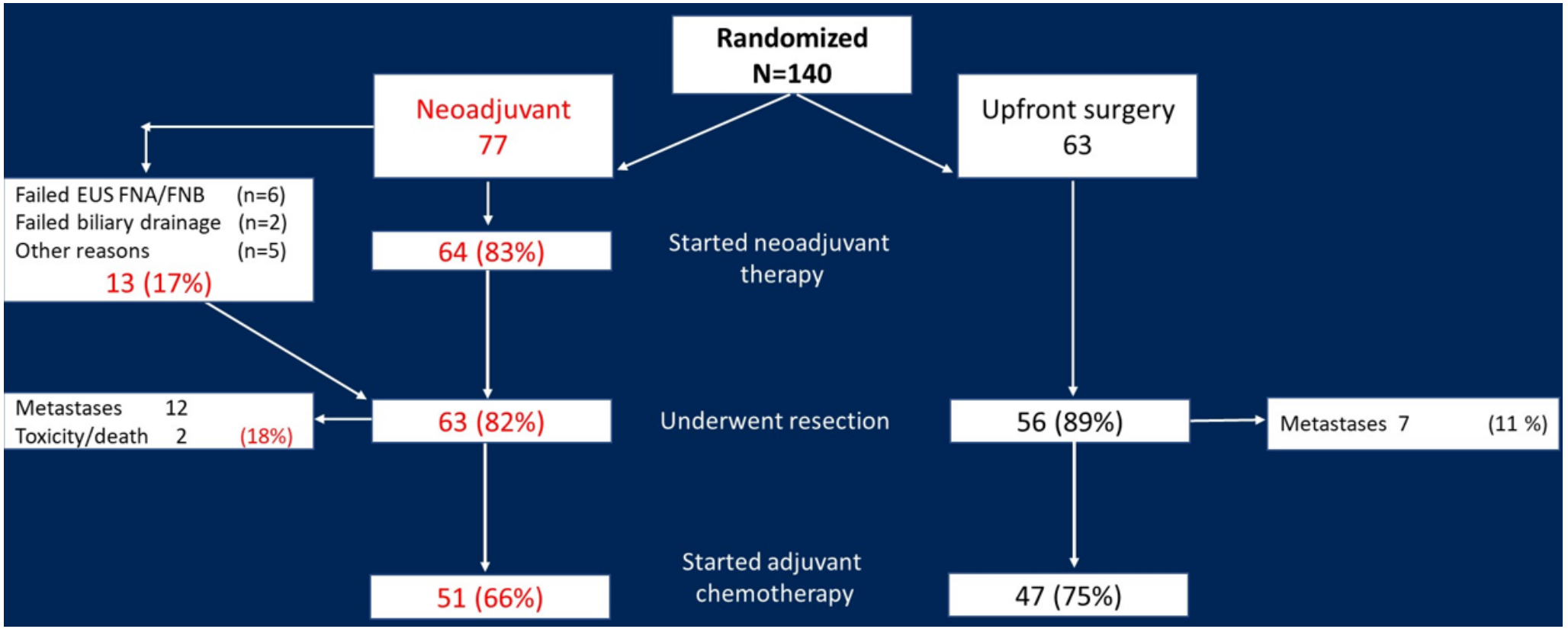
J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

NORPACT-1: Trial Design

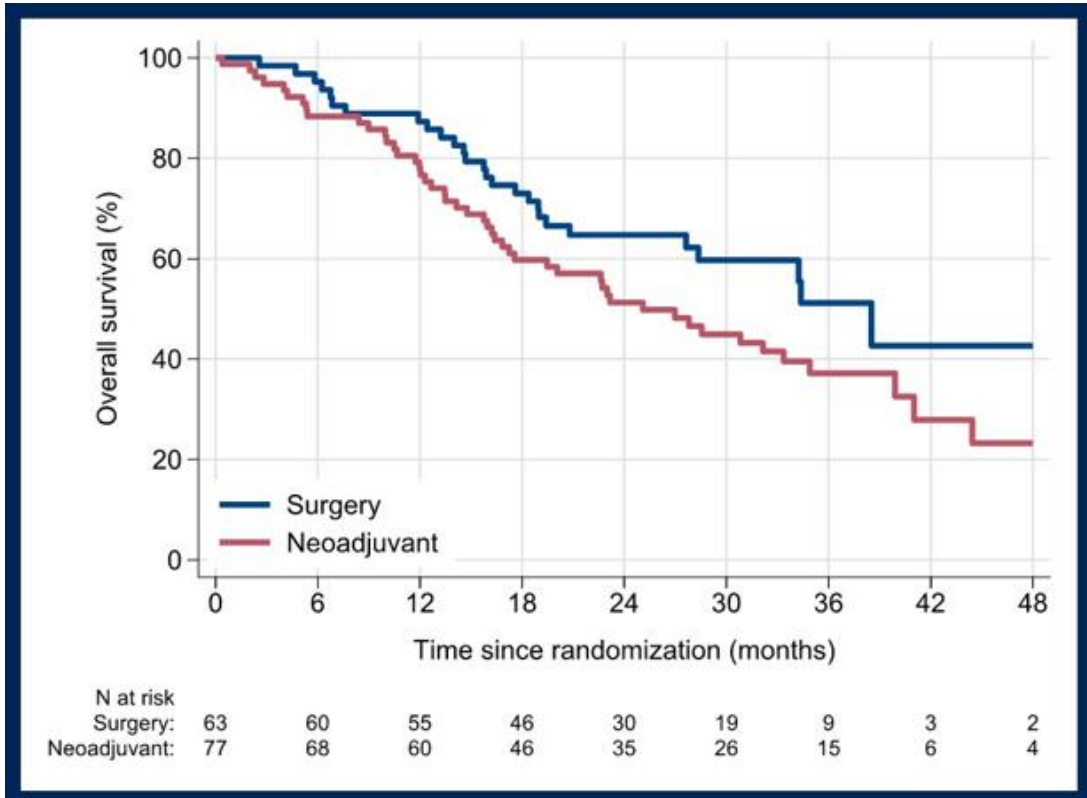
- Randomized, unblinded, phase-2 trial. Sample size 140.
- Primary Endpoint: OS



NORPACT-1: Flow Chart



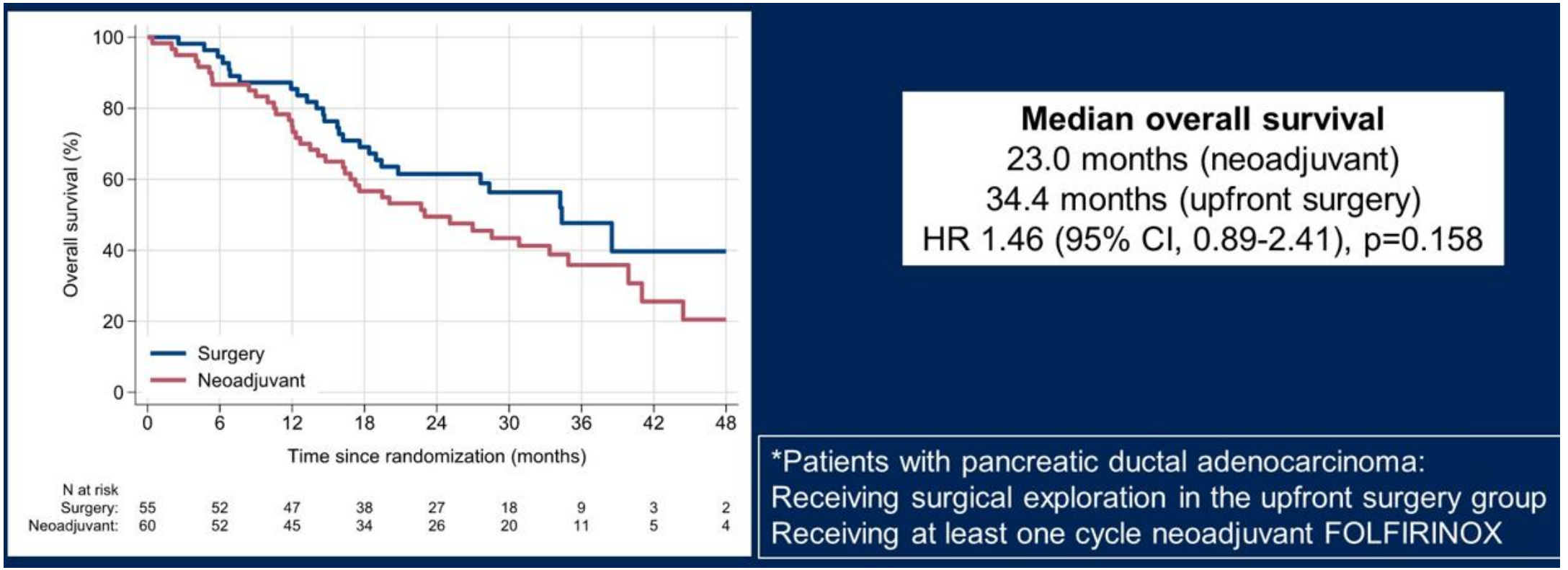
NORPACT-1: OS Intention to Treat



Median overall survival
25.1 months (neoadjuvant)
38.5 months (upfront surgery)
HR 1.52 (95% CI, 0.94-2.46), p=0.096

Proportion alive at 18 months
60% vs 73%, p=0.1

NORPACT-1: OS Per Protocol Analysis



Median overall survival
23.0 months (neoadjuvant)
34.4 months (upfront surgery)
HR 1.46 (95% CI, 0.89-2.41), p=0.158

*Patients with pancreatic ductal adenocarcinoma:
Receiving surgical exploration in the upfront surgery group
Receiving at least one cycle neoadjuvant FOLFIRINOX

NORPACT-1: Histopathologic Results

- The Neoadjuvant group had improved R0 and N0 rates in both intent to treat and per protocol analysis

	Neoadjuvant group (n=63)	Upfront surgery (n=56)	p-value
Intention-to-treat			
R0	56%	39%	0.076
N0	29%	14%	0.060
Per-protocol	(n=46)	(n=49)	
R0	59%	33%	0.011
N0	37%	10%	0.002

NORPACT-1: Conclusions

- Neoadjuvant FOLFIRINOX did not improve OS compared to upfront surgery
- Neoadjuvant FOLFIRINOX resulted in improvement in R0 and N0 rates – additional follow-up may determine long term effects
- Considerations:
  - Neoadjuvant chemo group required biliary drainage and tissue biopsy, did this lead to delay in initiation of therapy?
  - Population limited to 12 Nordic centers (Norway, Sweden, Denmark, Finland)
  - Eagerly await results of ALLIANCE

NAPOLI-3: NALIRIFOX vs. Gemcitabine/Nab-paclitaxel in 1L mPDAC

Eileen Mary O'Reilly, Davide Melisi, Teresa Macarulla, Roberto A. Pazo Cid, Sreenivasa R Chandana, Christelle De La Fouchardiere, Andrew Peter Dean, Igor Kiss, Woo Jin Lee, Thorsten Oliver Goetze, Eric Van Cutsem, Scott Paulson, Tanios S. Bekaii-Saab, Shubham Pant, Richard Hubner, Zhimin Xiao, Huanyu Chen, Fawzi Benzaghou, Zev A. Wainberg

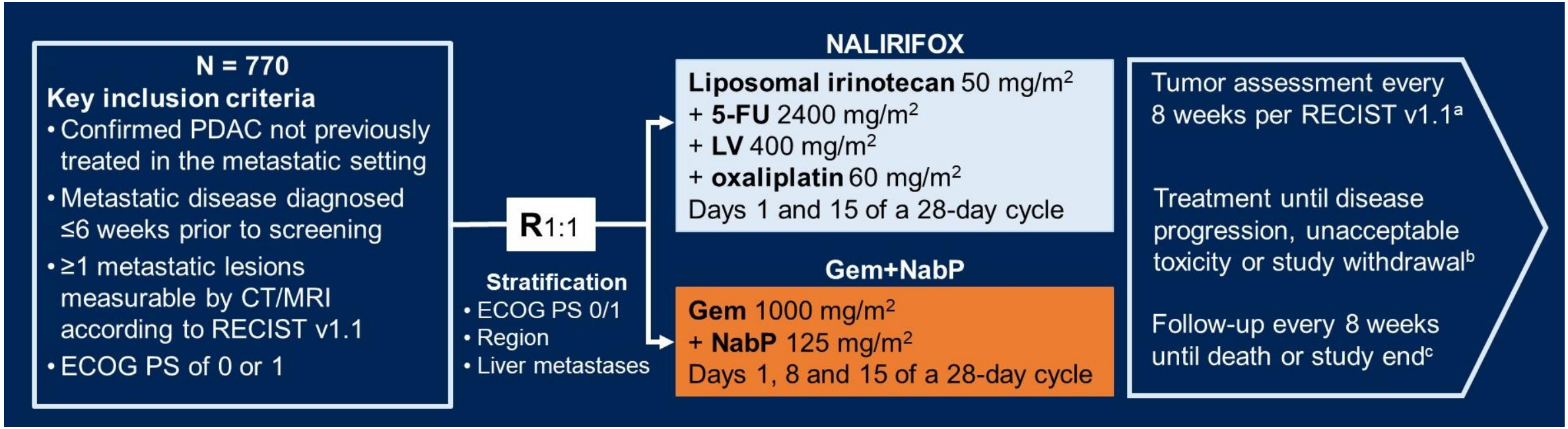
J Clin Oncol 41, 2023 (suppl 16; abstr 4006)

NAPOLI-3: Background & Aim

- NAPOLI-1: Lipsomal irinotecan + 5FU/LV in mPDAC following progression with gemcitabine based therapy.
- NCT02441991: Phase 1/2 study demonstrated efficacy of liposomal irinotecan 50mg/m2 + 5FU 2400mg/m2 + LV 400mg/m2 + oxaliplatin 60mg/m2 (NALIRIFOX) in 1L mPDAC

- **Aim**: Efficacy & safety of NALIRIFOX vs. Gem/Abraxane in 1L mPDAC

NAPOLI-3: Study Design



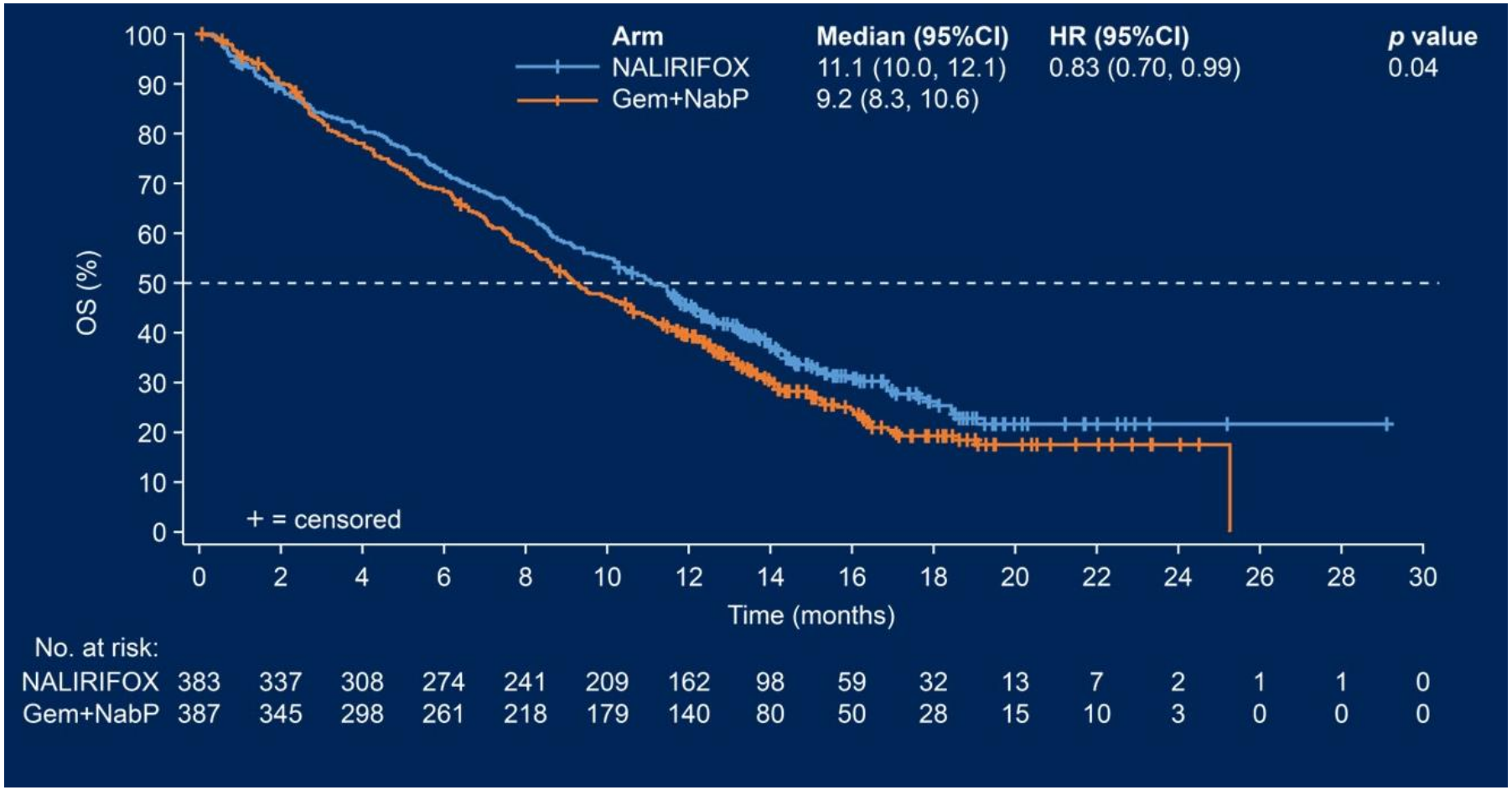
- Primary Endpoint: OS
- Secondary Endpoint: PFS and ORR
- Overall median follow-up: 16 months

As presented by Dr. Zev A Wainberg, ASCO 2023

NAPOLI-3: Baseline Characteristics

Characteristic	NALIRIFOX (N = 383)	Gem+NabP (N = 387)
Median (range) age, years	64.0 (20.0–85.0)	65.0 (36.0–82.0)
Men, %	53.3	59.4
White, %	82.2	83.7
ECOG performance status score, %		
0	41.8	43.4
1[a]	58.0	56.6
Number of metastatic sites, %		
1 / 2 / ≥3	29.8 / 31.3 / 38.9	35.7 / 27.9 / 36.4
Liver metastases, %	80.2	80.4
Geographic region, %		
North America	31.3	31.5
East Asia	2.9	2.8
Rest of the world	65.8	65.6
Main pancreatic tumor location		
Head	38.4	40.3
Other[b]	61.6	59.7
Baseline CA 19-9, %[c]		
<37 U/mL	15.7	18.3
≥37 U/mL	83.8	81.7
Median (range) time from metastatic diagnosis at study entry until randomization, weeks	3.00 (0.6–9.1)	3.57 (0.4–10.9)

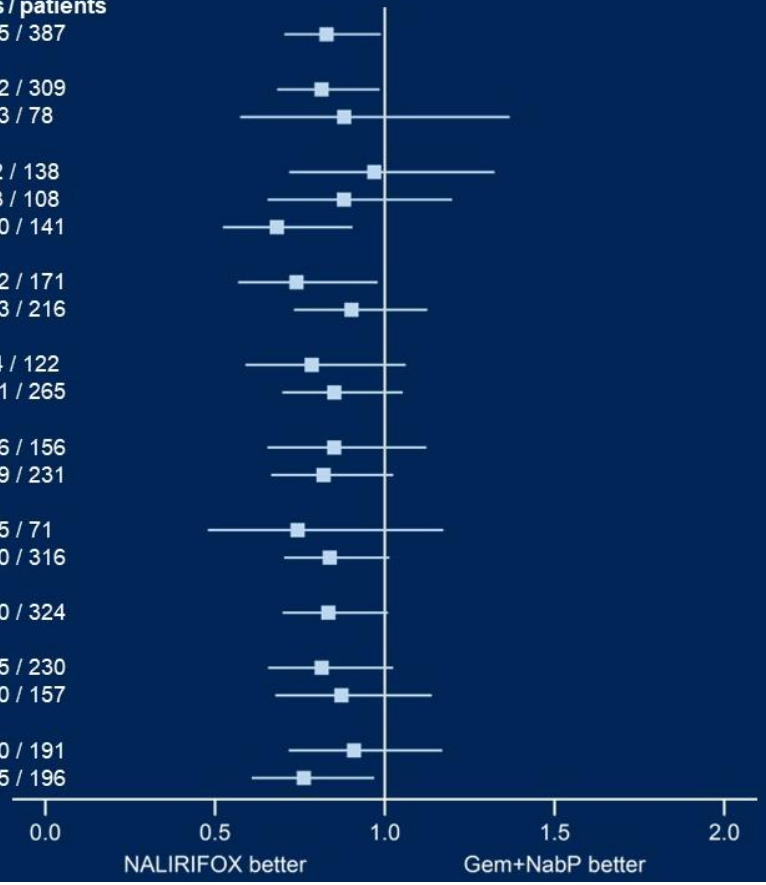
NAPOLI-3: mOS (ITT population)



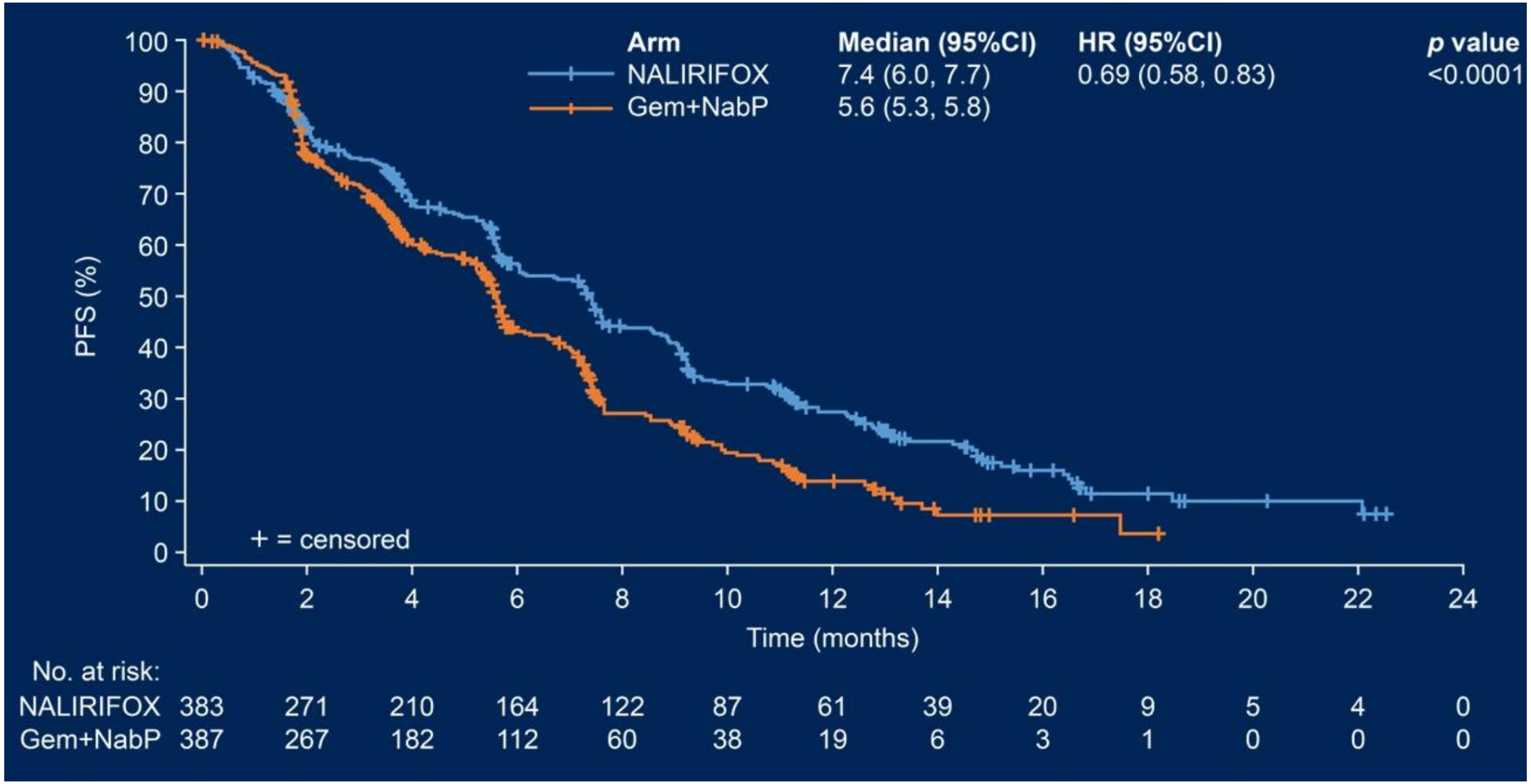
As presented by Dr. Zev A Wainberg, ASCO 2023

NAPOLI-3: OS subgroup analyses (ITT population)

Subgroup	NALIRIFOX, events / patients	Gem+NabP, events / patients	HR (95% CI)
Overall	259 / 383	285 / 387	0.83 (0.70, 0.99)
Presence of liver metastases at baseline			
Yes	220 / 309	242 / 309	0.82 (0.68, 0.98)
No	39 / 74	43 / 78	0.89 (0.57, 1.37)
Number of metastatic sites			
1	75 / 114	92 / 138	0.98 (0.72, 1.32)
★ 2	87 / 120	83 / 108	0.89 (0.65, 1.20)
≥3	97 / 149	110 / 141	0.69 (0.52, 0.90)
Baseline ECOG performance status			
0	97 / 168	112 / 171	0.75 (0.57, 0.98)
1	162 / 215	173 / 216	0.91 (0.73, 1.13)
Region			
North America	85 / 120	94 / 122	0.79 (0.59, 1.06)
Rest of the world	174 / 263	191 / 265	0.86 (0.70, 1.05)
Main pancreatic tumor location			
Head	97 / 147	116 / 156	0.86 (0.65, 1.12)
Other	162 / 236	169 / 231	0.83 (0.67, 1.02)
Baseline CA 19-9			
<37 U/mL	34 / 60	45 / 71	0.75 (0.48, 1.17)
≥37 U/mL	223 / 321	240 / 316	0.84 (0.70, 1.01)
Race			
White	218 / 315	240 / 324	0.84 (0.70, 1.01)
Sex			
Male	139 / 204	175 / 230	0.82 (0.66, 1.02)
Female	120 / 179	110 / 157	0.88 (0.68, 1.14)
Age			
<65 years	127 / 193	130 / 191	0.92 (0.72, 1.17)
★ ≥65 years	132 / 190	155 / 196	0.77 (0.61, 0.97)



NAPOLI-3: mPFS (ITT population)



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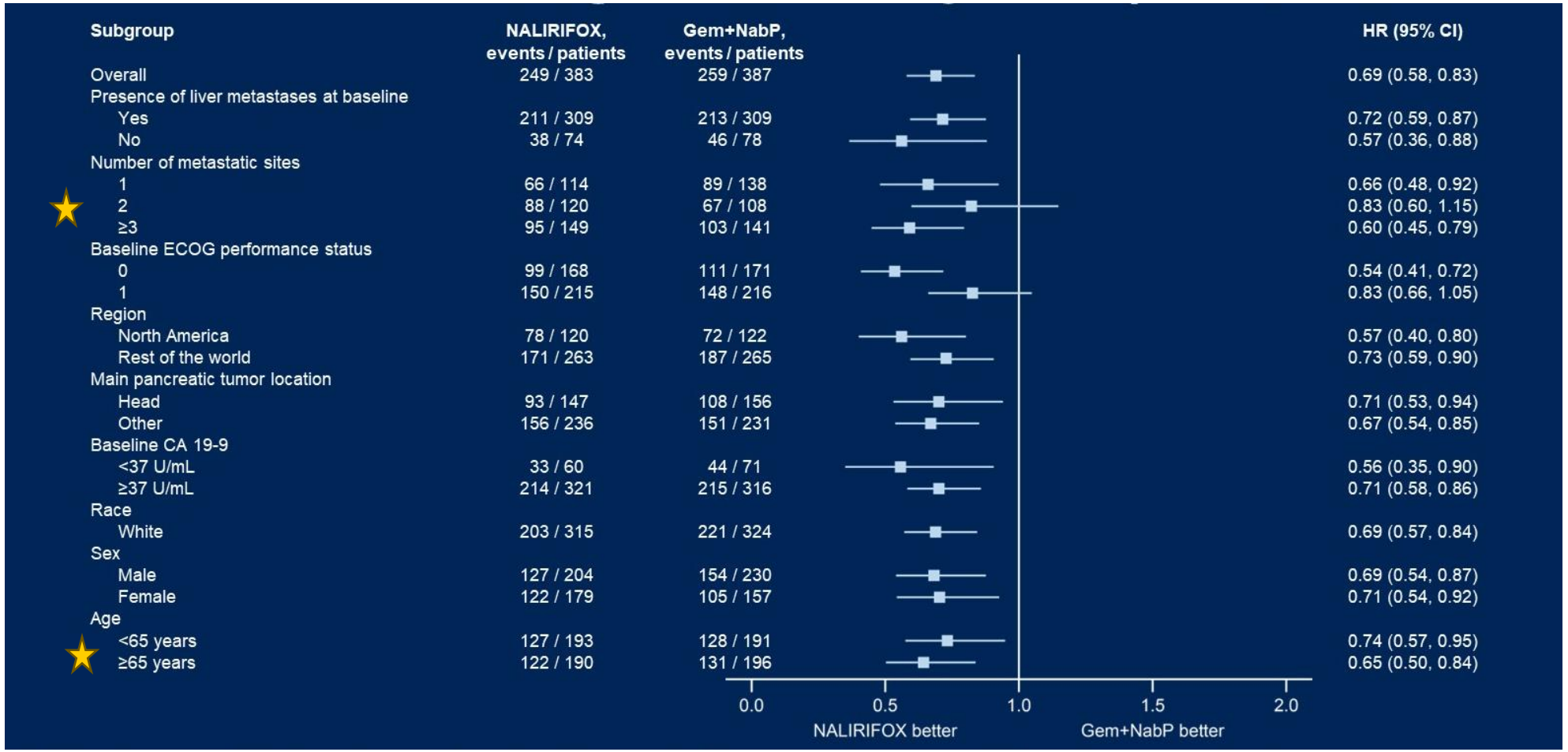
NAPOLI-3: mPFS subgroup analyses (ITT population)



NAPOLI-3: Treatment Associated Adverse Events

	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

NAPOLI-3: Conclusions

- NALIRIFOX demonstrated significant improvement in OS and PFS compared with Gem/NabP in 1L mPDAC
- This contrasts with SWOG S1505 data suggesting mFOLFIRINOX vs. Gem/NabP in the resectable setting had similar outcomes
- High rates of toxicity were seen in both arms of NAPOLI3.

Esophageal / GEJ / Gastric Adenocarcinoma

SPOTLIGHT: Zolbetuximab + mFOLFOX6 in CLDN18.2+, HER2-, untreated, locally advanced unresectable/metastatic Gastric / GEJ Adenocarcinoma.

Kohei Shitara, Florian Lordick, Yung-Jue Bang, Peter C. Enzinger, David H. Ilson, Manish A. Shah, Eric Van Cutsem, Rui-hua Xu, Giuseppe Aprile, Jianming Xu, Joseph Chao, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Diarmuid Martin Moran, Pranob P. Bhattacharya, Ahsan Arozullah, Jung Wook Park, Jaffer A. Ajani

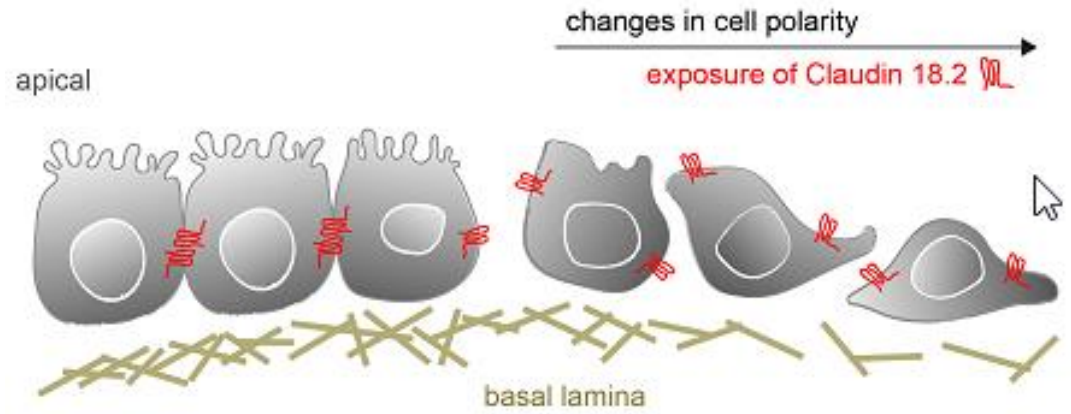
SPOTLIGHT: Introduction

- For Advanced Unresectable / Metastatic Gastric/GEJ, chemotherapy is the standard with mOS ~1yr[1-4].
- The addition of targeted therapy to Chemotherapy has improved survival in select patient populations[5-9].
  - HER2 positive: Trastuzumab
  - PD-L1 CPS>5: Nivolumab
- Claudin 18.2 offers a new target

1. Van Cutsem et al. *Lancet.* 2016; 388(10060):2654-2664; 2. Lordick F et al. *Ann Oncol.* 2022; 33(10):1005-1020; 3. Obermannová R et al. *Ann Oncol.* 2022; 33(10):992-1004; 4. JGCA. Gastric Cancer 2021; 24(1):1-21; 5. Kelly RJ et al. *NEJM.* 2021; 384(13):1191-1203; 6. NHCPRC. *Chin J Cancer Res.* 2022; 34(3):207-237; 7. Bang Y-J et al. *Lancet.* 2010; 376(9742):687-97; 8. Janjigian YY et al. *Lancet.* 2021; 398(10294):27-40; 9. Shitara K et al. *Nature.* 2022; 603(7903):942-948.

SPOTLIGHT: Claudin 18.2

- Claudins are major components of tight junctions.
- In normal tissues, Claudin-18.2 is expressed in differentiated gastric epithelial cells
- In malignancy, Claudin-18.2 is overexpressed in primary gastric cancers and their metastases.
  - The expression rate of claudin-18.2 in gastric cancer varies from 53.0–87.0%.
- Malignant transformation results in CLDN18.2 expression on the surface of gastric and GEJ adenocarcinoma cells, which might render CLDN18.2 more accessible to antibodies.

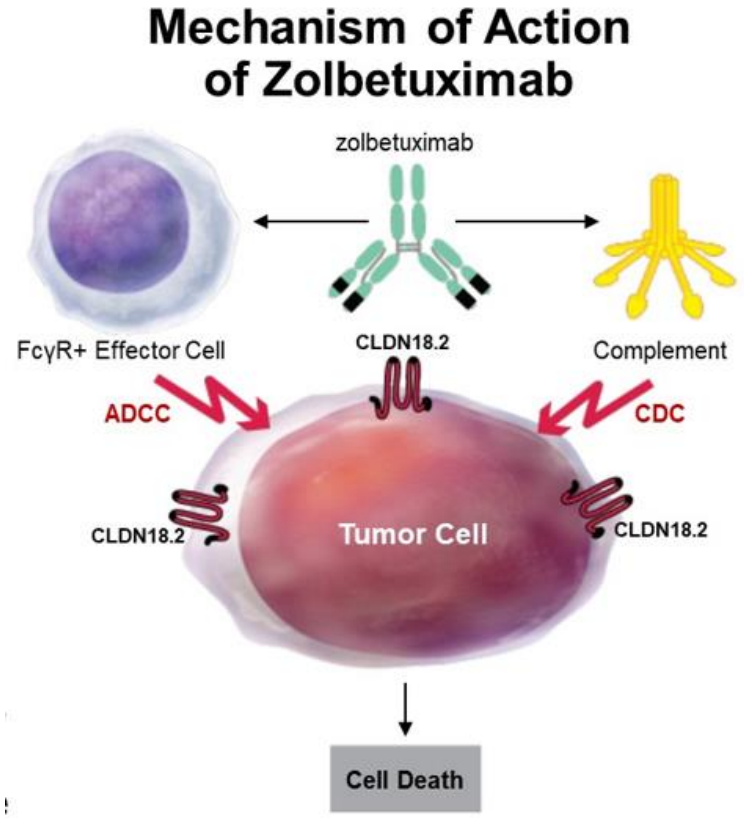


IOWA

Hong JY, An JY, Lee J, Park SH, Park JO, Park YS, Lim HY, Kim KM, Kang WK, Kim ST. Claudin 18.2 expression in various tumor types and its role as a potential target in advanced gastric cancer. Transl Cancer Res. 2020 May;9(5):3367-3374. doi: 10.21037/tcr-19-1876. PMID: 35117702; PMCID: PMC8797704.

SPOTLIGHT: Zolbetuximab

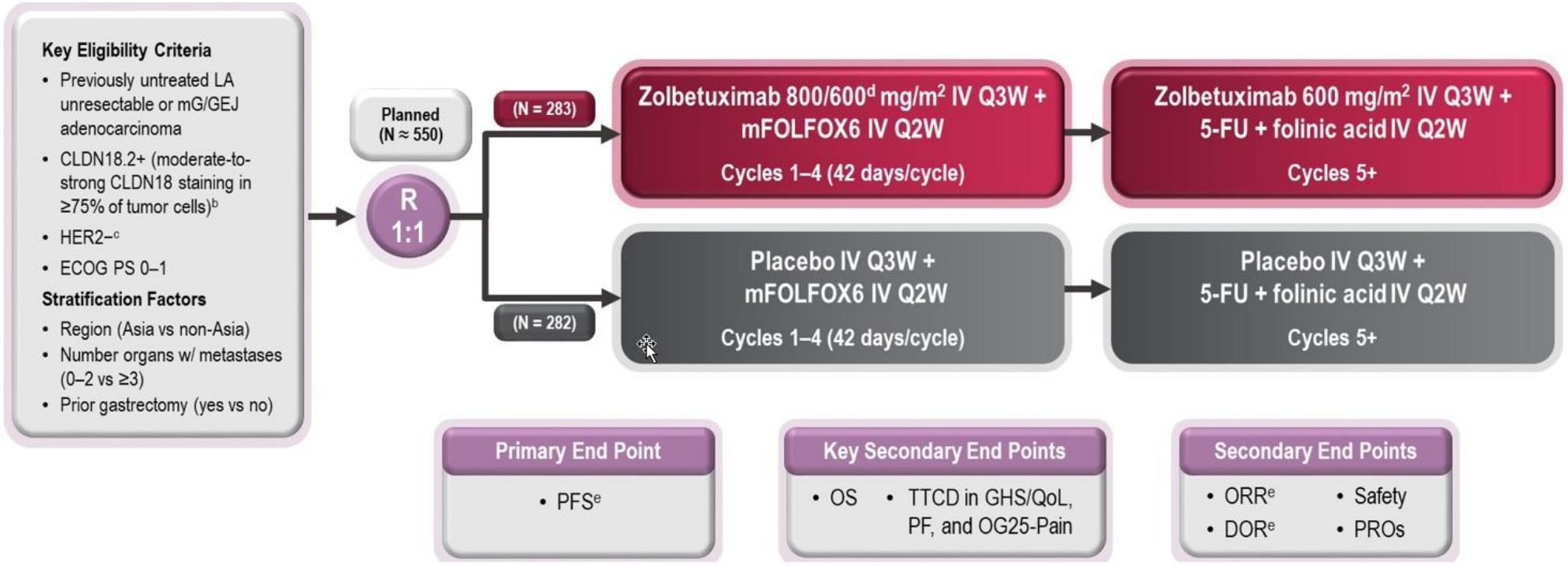
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2
- Zolbetuximab may induce tumor cell death via complement and cytotoxic immune effector cells.
- In Phase IIb FAST study, EOX +/- Zolbetuximab resulted in improved OS for patients with higher expression of CLDN 18.2
  - Mos 16.5 vs 8.9 months for Zolbetuximab + EOX vs. EOX alone



Sahin U, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Ann Oncol. 2021 May;32(5):609-619. doi: 10.1016/j.annonc.2021.02.005. Epub 2021 Feb 19. PMID: 33610734.

SPOTLIGHT: Study Design

- Global, randomized, double-blinded, placebo-controlled Phase 3



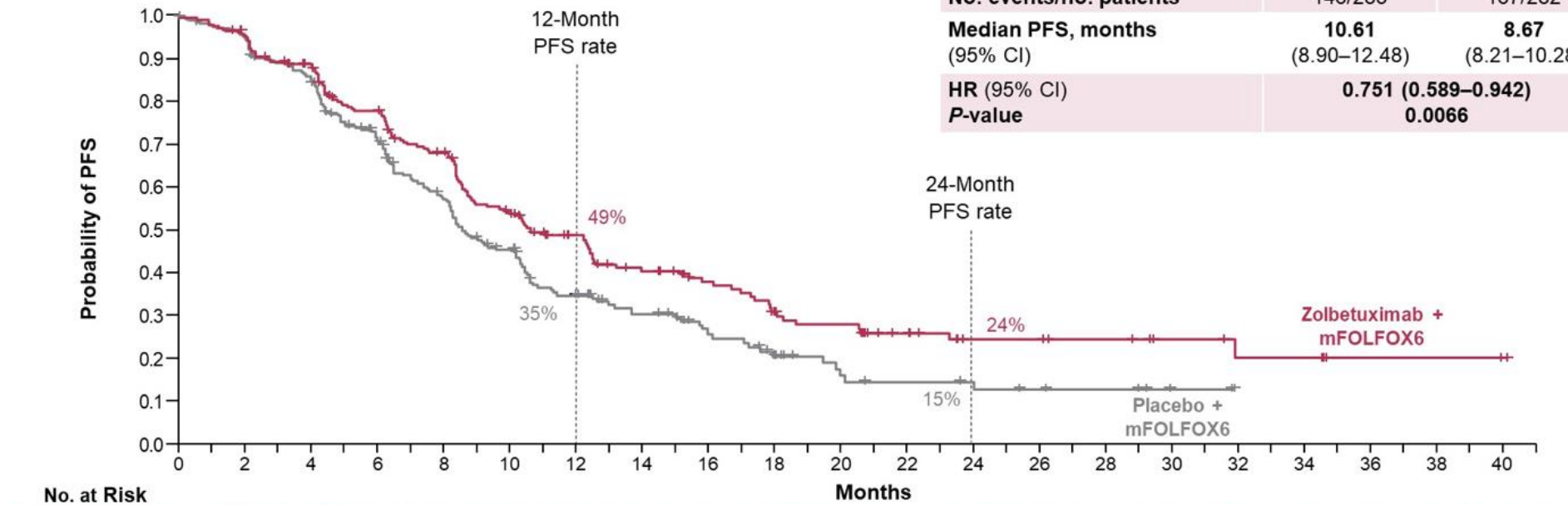
SPOTLIGHT: Baseline Characteristics

		Zolbetuximab + mFOLFOX6 (N = 283)	Placebo + mFOLFOX6 (N = 282)
Age, years (range)	Median	62.0 (27–83)	60.0 (20–86)
Sex, n (%)	Male	176 (62.2)	175 (62.1)
Region, n (%)	Asia	88 (31.1)	89 (31.6)
	Non-Asia	195 (68.9)	193 (68.4)
Organs with metastases, n (%)	0–2	219 (77.4)	219 (77.7)
	≥3	64 (22.6)	63 (22.3)
★ **Prior gastrectomy, n (%)**	Yes	84 (29.7)	82 (29.1)
	No	199 (70.3)	200 (70.9)
★ **Primary site, n (%)**	Stomach	219 (77.4)	210 (74.5)
	GEJ	64 (22.6)	72 (25.5)
Lauren classification, n (%)	Diffuse	82 (29.1)	117 (42.1)
	Intestinal	70 (24.8)	66 (23.7)
	Mixed/others[a]	130 (45.9)	95 (33.7)
ECOG PS[b,c], n (%)	0	125 (44.8)	115 (41.4)
	1	153 (54.8)	163 (58.6)

- As an ad hoc analysis, 41/311 (13.2%) of assessable patients had tumors with PD-L1 CPS ≥5[d]
- Subsequent anticancer therapies were administered to 48% of patients in the zolbetuximab arm and 53% in the placebo arm

SPOTLIGHT: PFS

	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**	

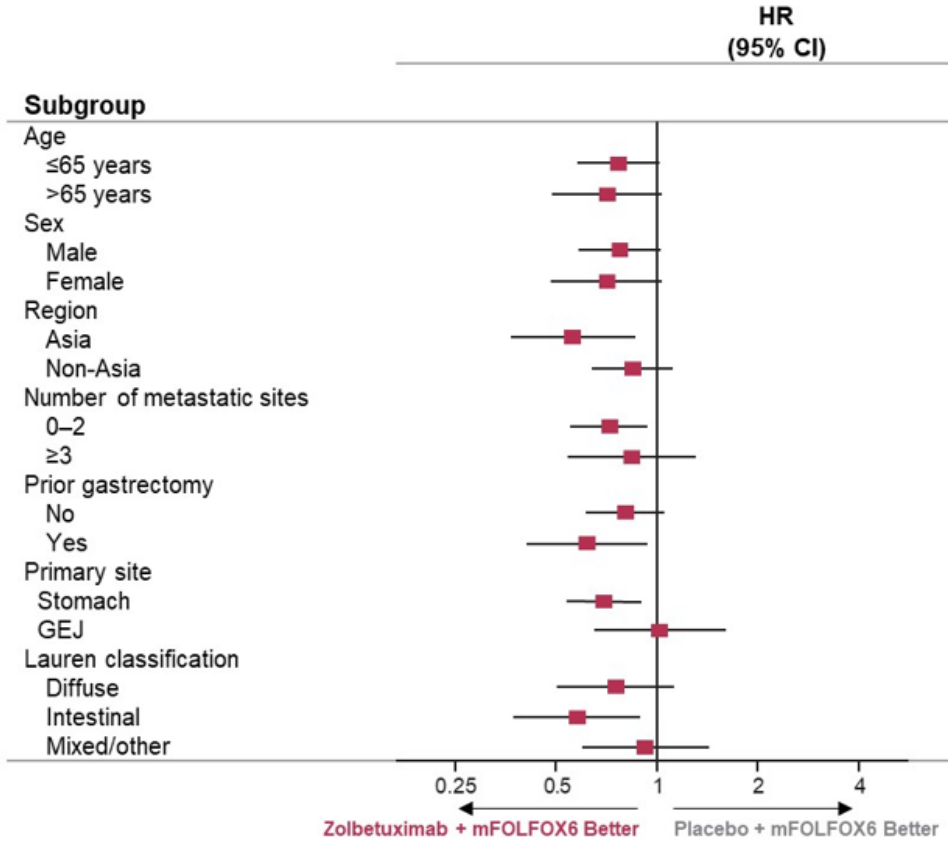


- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

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.

SPOTLIGHT: PFS Subgroup Analysis

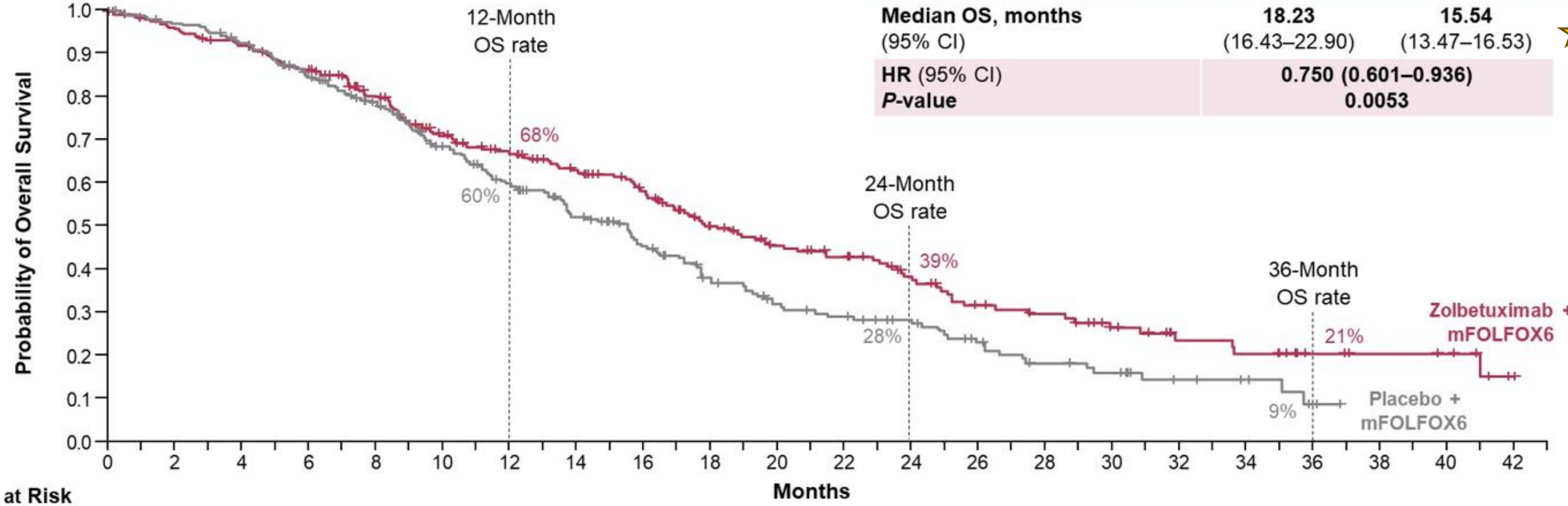


Subgroup	HR (95% CI)	Zolbetuximab + mFOLFOX6 no. events/ no. patients	Placebo + mFOLFOX6 no. events/ no. patients
Age			
≤65 years	0.771 (0.583–1.019)	94/181	106/181
>65 years	0.714 (0.492–1.038)	52/102	61/101
Sex			
Male	0.776 (0.587–1.024)	95/176	106/175
Female	0.711 (0.488–1.034)	51/107	61/107
Region			
Asia	0.563 (0.372–0.852)	45/88	47/89
Non-Asia	0.848 (0.650–1.106)	101/195	120/193
Number of metastatic sites			
0–2	0.726 (0.559–0.943)	107/219	123/219
≥3	0.844 (0.548–1.301)	39/64	44/63
Prior gastrectomy			
No	0.808 (0.620–1.053)	106/199	117/200
Yes	0.622 (0.410–0.943)	40/84	50/82
Primary site			
Stomach	0.688 (0.531–0.890)	109/219	126/210
GEJ	1.015 (0.649–1.586)	37/64	41/72
Lauren classification			
Diffuse	0.756 (0.506–1.129)	40/82	64/117
Intestinal	0.582 (0.379–0.894)	41/70	46/66
Mixed/other	0.929 (0.601–1.434)	49/81	35/55

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

SPOTLIGHT: OS

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI) *P*-value	**0.750 (0.601–0.936)** **0.0053**	

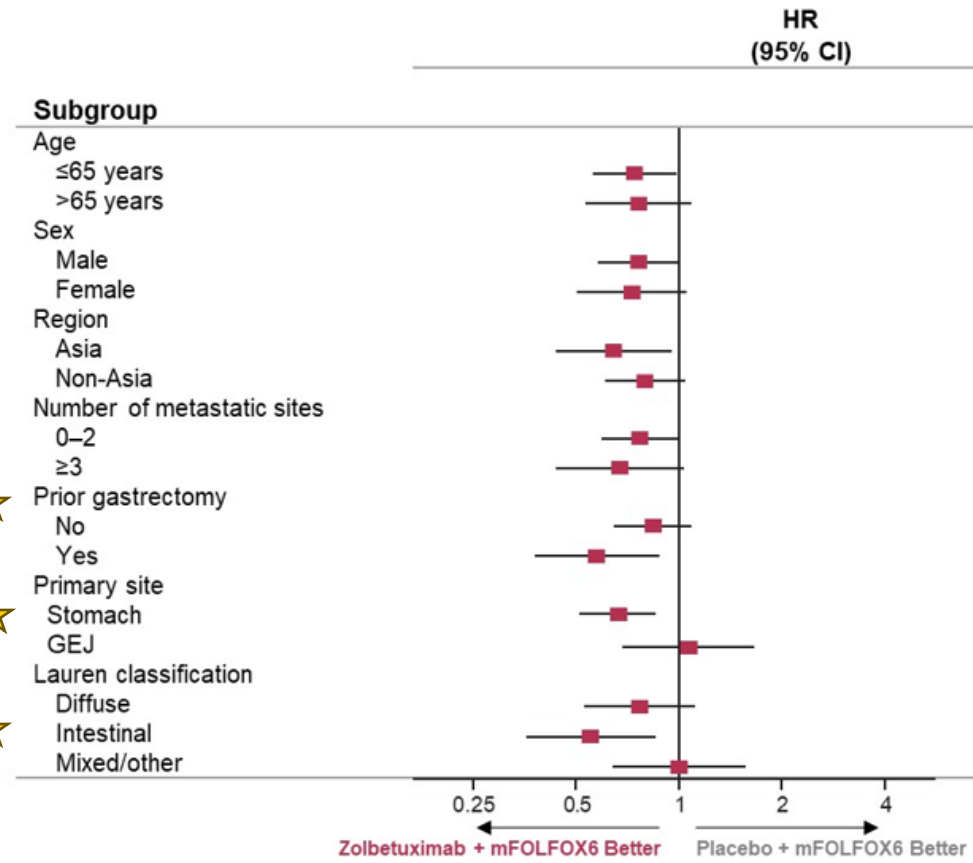


No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

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

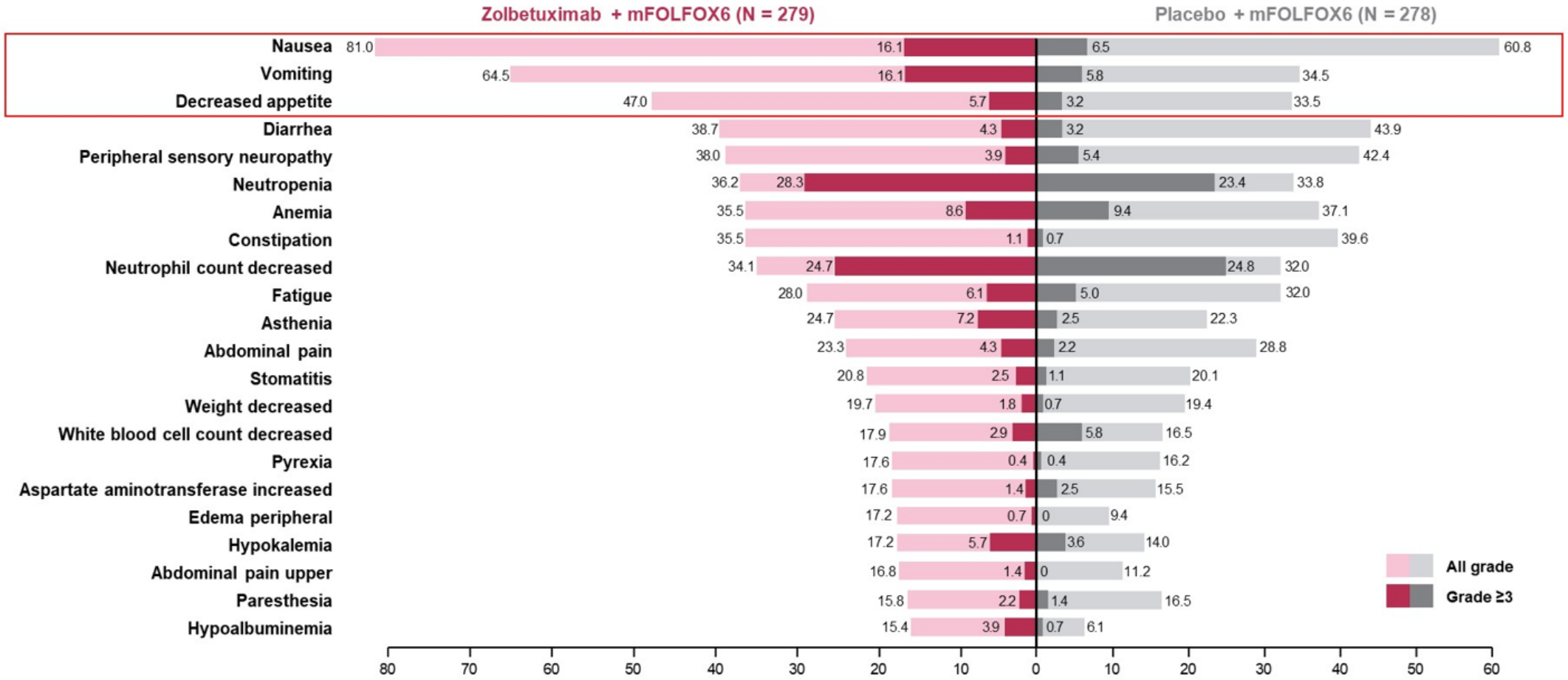
SPOTLIGHT: OS Subgroup Analysis



Subgroup	HR (95% CI)	Zolbetuximab + mFOLFOX6 no. events/ no. patients	Placebo + mFOLFOX6 no. events/ no. patients
Age			
≤65 years	0.741 (0.561–0.980)	89/181	112/181
>65 years	0.761 (0.533–1.086)	60/102	65/101
Sex			
Male	0.760 (0.579–0.999)	98/176	113/175
Female	0.726 (0.502–1.049)	51/107	64/107
Region			
Asia	0.643 (0.437–0.947)	47/88	59/89
Non-Asia	0.796 (0.610–1.039)	102/195	118/193
Number of metastatic sites			
0–2	0.767 (0.594–0.990)	110/219	129/219
≥3	0.670 (0.436–1.030)	39/64	48/63
★ Prior gastrectomy			
No	0.839 (0.648–1.086)	109/199	125/200
Yes	0.575 (0.380–0.869)	40/84	52/82
Primary site			
★ Stomach	0.666 (0.517–0.858)	111/219	135/210
GEJ	1.072 (0.690–1.666)	38/64	42/72
Lauren classification			
Diffuse	0.766 (0.530–1.108)	46/82	75/117
★ Intestinal	0.552 (0.358–0.851)	38/70	48/66
Mixed/other	0.992 (0.638–1.543)	48/81	34/55

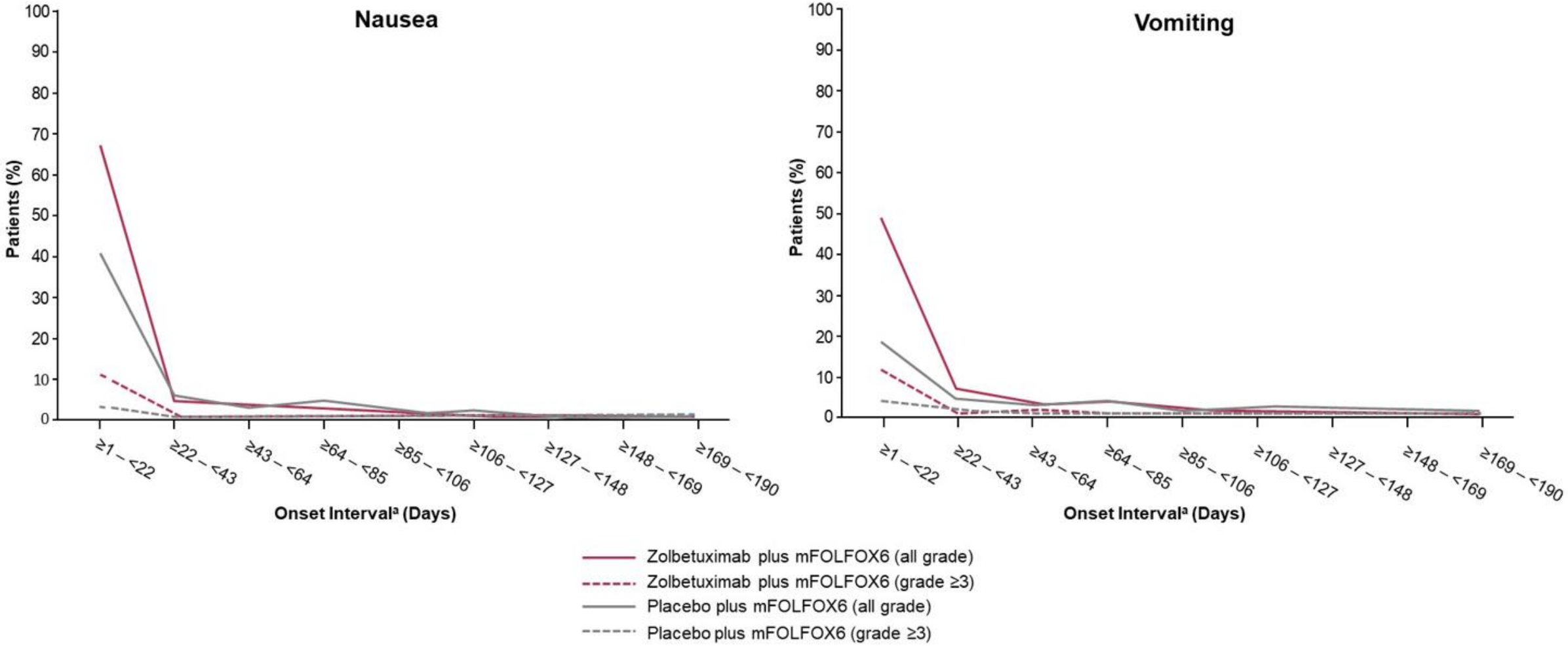
- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

TEAEs[a] Occurring in ≥15% of All Treated Patients



- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

First Occurrence of Nausea and Vomiting



SPOTLIGHT: Conclusions

- Zolbetuximab + mFOLFOX6 showed significant improvement in PFS and OS
- Zolbetuximab + mFOLFOX6 demonstrated a manageable safety profile
- Of Note: The control arm performed well (mOS 15m vs. 12m)
  - Potentially claudin 18 positivity characterizes a better prognostic subset of diffuse GC?
  - 3/4 patients had limited metastases
  - 1/3 patients had prior gastrectomy – potentially diagnosed earlier under surveillance

SPOTLIGHT: Next Steps

- Standardization of CLDN 18.2 IHC
- Nivolumab vs. Zolbetuximab with chemotherapy in 1L?
- Current studies underway investigating combination of Zolbetuximab with Immunotherapy

INTEGRATE IIa: A randomized, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-esophageal cancer

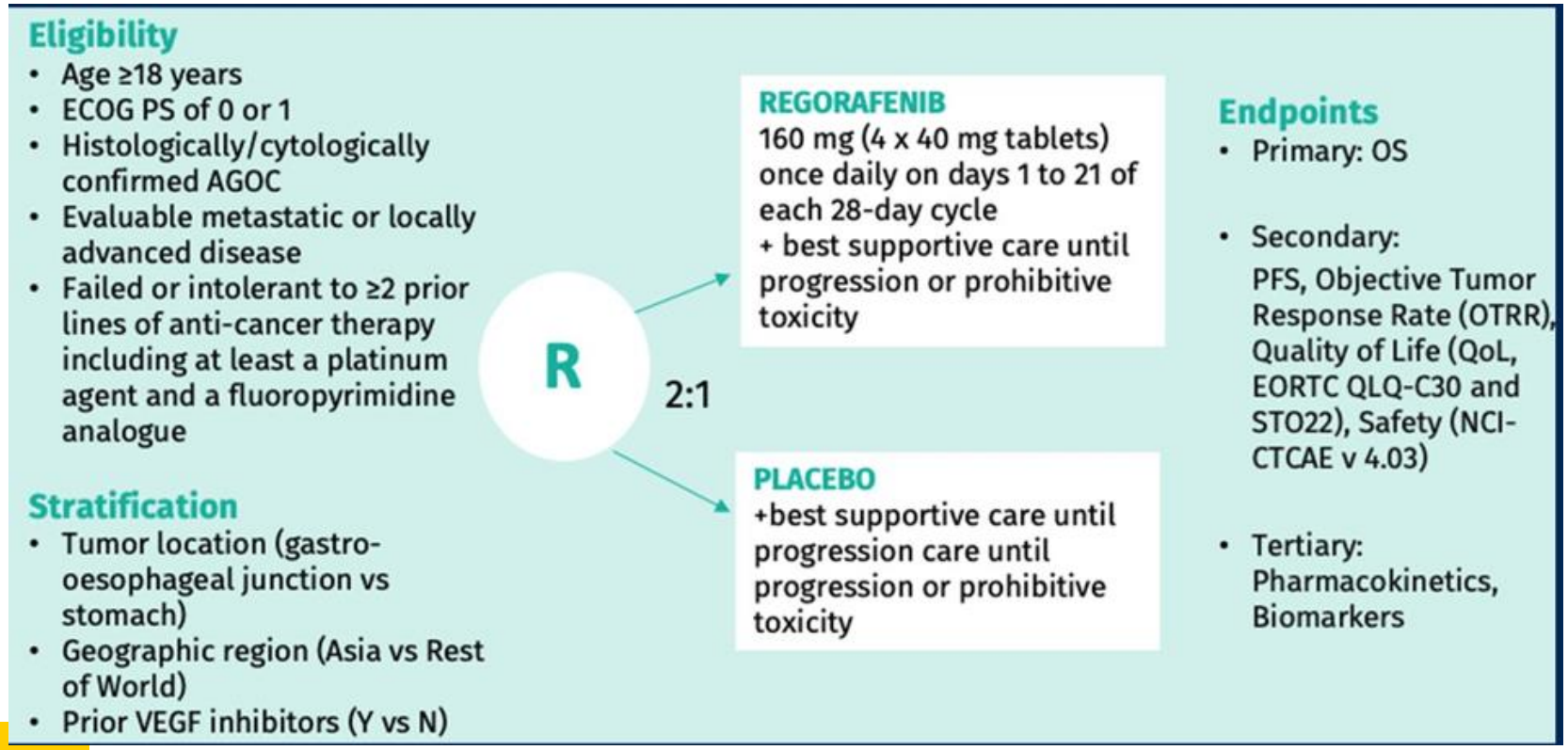
Nick Pavlakis, Kohei Shitara, Katrin Marie Sjoquist, Andrew James Martin, Anthony Jaworski, Sonia Yip, Yung-Jue Bang, Thierry Alcindor, Christopher J. O'Callaghan, Niall C. Tebbutt, Andrew Strickland, Sun Young Rha, Keun-Wook Lee, John Raymond Zalcberg, Timothy Jay Price, John Simes, David Goldstein

Integrate IIa: Background & Introduction

- Integrate: Phase II: Regorafenib vs. placebo in advanced gastric adenocarcinoma improved PFS (2.6m vs. 0.9m). A survival trend was noted 5.8m vs. 4.5m.
- Integrate II: Phase III trial to examine if regorafenib improves overall survival after failure of at least 2 lines of treatment.

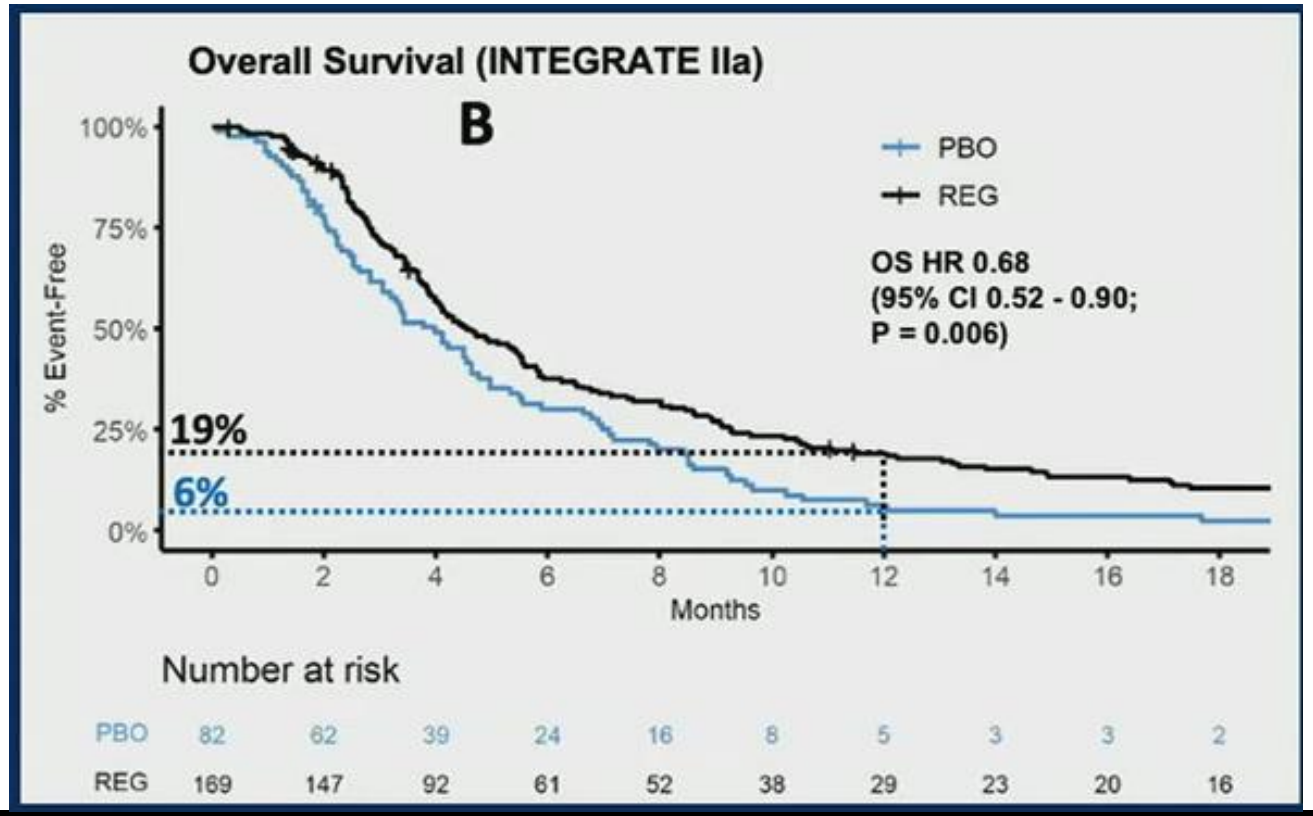
INTEGRATE IIa: Study design

- Phase III International, multi-center, randomized controlled clinical trial: Regorafenib vs. Placebo



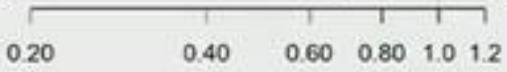
INTEGRATE IIA: OS

- Regorafenib improves OS: At 12 months, regorafenib improved survival over placebo (19% vs 6%)



INTEGRATE IIA: Subgroup Analyses

Subgroup	Level	PBO n/N	REG n/N	HR (CI)	P int.	FDR P int.
Primary disease site	Stomach	57/60	112/122	0.74 (0.53 to 1.02)		
	Gastro-oesophageal junction	22/22	47/47	0.62 (0.37 to 1.03)	0.57	0.71
Region	Rest of world	31/31	63/63	0.50 (0.32 to 0.79)		
	Asia	48/51	96/106	0.83 (0.58 to 1.18)	0.03	0.17
Prior use of VEGF inhibitors	Yes	33/35	65/70	0.64 (0.42 to 0.99)		
	No	46/47	94/99	0.75 (0.52 to 1.06)	0.85	0.85
Ethnicity	Not NE Asian	29/29	61/61	0.53 (0.34 to 0.84)		
	NE Asia	50/53	98/108	0.78 (0.56 to 1.11)	0.11	0.29
Prior Immunotherapy	Yes	22/22	40/44	0.58 (0.33 to 1.00)		
	No	57/60	119/125	0.78 (0.57 to 1.07)	0.38	0.64
Primary Analysis Model	All Patients	79/82	159/169	0.68 (0.52 to 0.90)		



INTEGRATE IIA: QoL

- Regorafenib delays deterioration in global QoL compared to placebo (p=0.0043)

INTEGRATE IIA: Toxicities

- Regorafenib toxicity profile was similar to that seen in previous reports

	Regorafenib (N= 166)				Placebo (N= 79)			
	Gr 1-2	Gr 3	Gr 4	Gr 5	Gr 1-2	Gr 3	Gr 4	Gr 5
Any adverse event	52 (31)	92 (55)	12 (7)	3 (2)#	37 (47)	29 (37)	3 (4)	0
Fatigue	40 (24)	15 (9)	0	0	18 (23)	5 (6)	0	0
★ Palmar-plantar erythrodysesthesia syndrome*	52 (31)	15 (9)	0	0	4 (5)	0	0	0
Abdominal pain	30 (18)	6 (4)	0	0	14 (18)	4 (5)	0	0
Anorexia	30 (18)	7 (4)	0	0	16 (20)	0	0	0
★ Oral mucositis*	34 (20)	1 (1)	0	0	0	0	0	0
Nausea	24 (14)	2 (1)	0	0	17 (22)	3 (4)	0	0
Vomiting	15 (9)	3 (2)	0	0	8 (10)	3 (4)	0	0
Diarrhea*	30 (18)	6 (4)	0	0	4 (5)	1 (1)	0	0
Constipation*	20 (12)	1 (1)	0	0	4 (5)	1 (1)	0	0
ALT increase*	20 (12)	9 (5)	0	0	3 (4)	1 (1)	0	0
AST increase*	23 (16)	7 (4)	2 (1)	0	3 (4)	2 (3)	0	0
Anemia	6 (4)	9 (5)	0	0	4 (5)	6 (8)	0	0
Hypertension*	23 (16)	13 (8)	0	0	2 (3)	0	0	0

* Toxicities more common with regorafenib; #One death was due to hepatic failure, and two were due to sepsis.

INTEGRATE IIA: Conclusions

- Regorafenib significantly improves survival in patients with refractory advanced gastric/esophageal cancer compared to placebo.
- Regorafenib delays deterioration in global QoL compared to placebo
- Toxicity profile similar to prior studies
- Integrate Iib is ongoing international Phase III RCT in pre-treated patients with advanced gastric/esophageal cancer comparing Regorafenib + Nivolumab to standard chemotherapy.

NEOAEGIS: Neoadjuvant Trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study

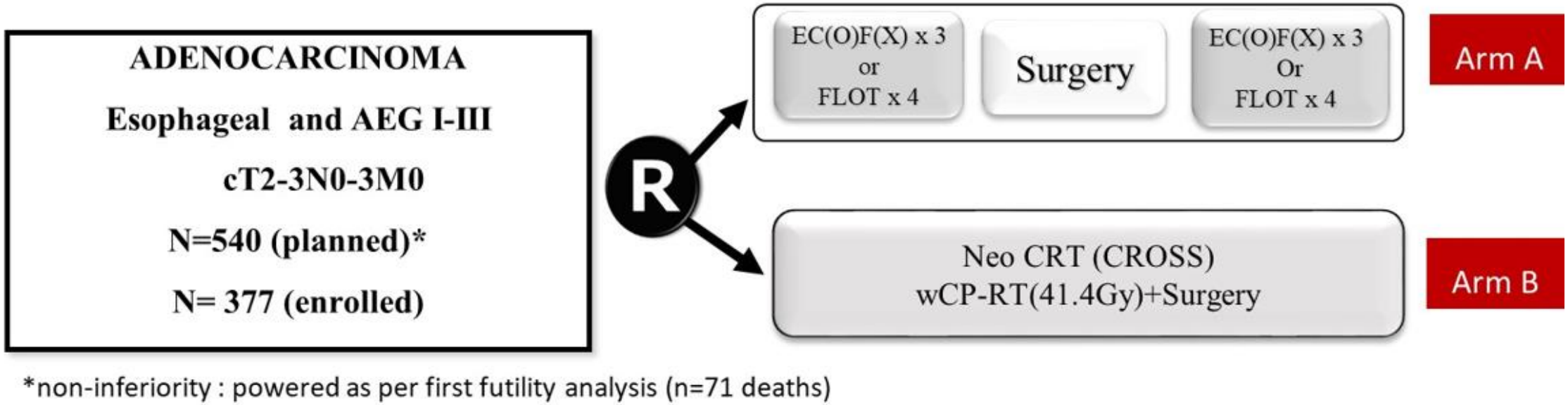
Final primary outcome analysis

Reynolds JV, Preston SR, O'Neill B, et al: Neo-AEGIS (neoadjuvant trial in adenocarcinoma of the esophagus and esophago-gastric junction international study): Final primary outcome analysis. 2023 ASCO GI Cancers Symposium. Abstract 295. Presented January 19, 2023.

NEOAEGIS: Background

- What is the optimal curative approach in locally advanced Esophageal & Gastroesophageal Junction Adenocarcinoma?
  - Preoperative Chemoradiotherapy:
    - CROSS: carboplatin or paclitaxel plus 41.4 Gy of radiation therapy
  - Perioperative Chemotherapy:
    - MAGIC: epirubicin, cisplatin or oxaliplatin, and fluorouracil or capecitabine.
    - FLOT: fluorouracil, leucovorin, oxaliplatin, and docetaxel.
- Locally Advanced: $cT_{2\text{-}3}N_{0\text{-}3}M_0$ - stage 2 or 3 disease, tumors up to 8 cm, and any nodal involvement

NEOAEGIS: Study Design



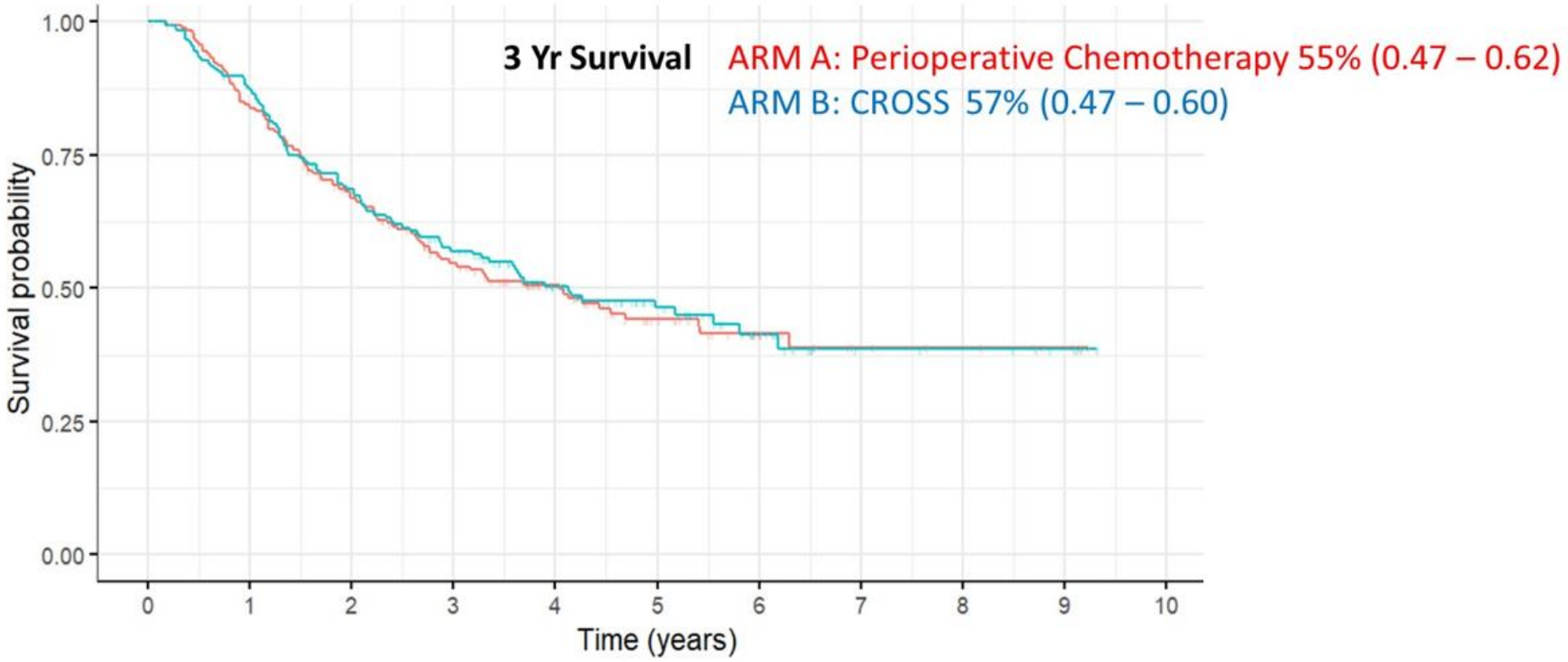
*non-inferiority : powered as per first futility analysis (n=71 deaths)

- Primary Endpoint: Overall Survival
- Secondary Endpoints: Disease free Survival, time to treatment failure, Toxicity, Tumor regression grade, R0 resection, Post-op complications, Quality of Life

NEOAEGIS: Patient Characteristics

	ARM A (Chemo) N = 184	ARM B (CROSS) N = 178
Median (range) age	64 (35-83)	64 (45-81)
Male	91.8%	88.8%
MAGIC/FLOT	157 (85%)/27 (15%)	-
cT3	84%	84%
cN 1-3	60.3%	56 %
Radical en bloc Transthoracic Esophagectomy	75%	80 %
Transhiatal	1.2%	4.3%

NEOAEGIS: Overall Survival



HR (95% CI) 1.03 (0.77- 1.38)

Median follow-up of 34.2 (0.43-111.8) mo

NEOAEGIS: Pathological Response

TABLE 1: Oncologic Outcomes for Two Approaches to Treating Locally Advanced Esophageal or Gastroesophageal Junction Cancer

Endpoint	Neo-AEGIS Regimen (Perioperative Chemotherapy/Surgery)	CROSS Regimen (Chemoradiation/Surgery)	*P* Value
3-Year overall survival rate	55%	57%	HR = 1.03 (95% CI = 0.77–1.38)
Nodal downstaging to ypNO rate	44%	60%	.004
R0 resection	82%	95%	< .001
Pathologic complete response rate	5%	17%	.001
Major pathologic response rate	12%	42%	< .001

CI = confidence interval; HR = hazard ratio.

As Per AscoPost.com, 2/25/23

NEOAEGIS: Toxicity

	ARM A (Chemo)	ARM B (CROSS)	p	P value
Toxic deaths	1.6%	3%		0.497
★ Neutropenia	14.1%	2.8%		< 0.001
★ Diarrhea	10.9%	0%		< 0.001
Neutropenic Sepsis	2.2%	0.6%		0.215
★ Vomiting	7.6%	2.8%		0.035
Pulmonary embolism	5.4%	5.1%		0.872

NEOAEGIS: Operative Complications

	ARM A (Chemo) N = 162	ARM B (CROSS) N = 167
In hospital mortality	1.6%	2.8% p =0.723
Anastomotic Leaks	11.1%	11.4%
Pneumonia	19.8%	15.6%
ARDS	0.6%	4.2%
Respiratory Failure	7.6%	8%
Venous Thromboembolism	3.8%	3%
Atrial Fibrillation	11.1%	11.4%
Clavien-Dindo ≥3<V severity	23.5%	22.8%

NEOAEGIS: Summary

- Perioperative chemotherapy is non-inferior to multimodal therapy in the primary outcome of 3 yr overall survival (55% and 57% respectively)
- Markers of local tumor response (pCR, R0, Nodal downstaging) are significantly better in the CROSS arm.
- Toxicity and grade 3 or 4 adverse events occurred more often with the Neo-AEGIS regimen (primarily neutropenia, diarrhea, and vomiting).
- No significant difference in severity of complications or postoperative mortality - hence, no negative effect of radiotherapy.

NEOAEGIS: Considerations

- Pattern of recurrence data may inform how markers of local disease response in the CROSS arm did not translate into a survival advantage
- Peri-operative Chemotherapy arm:
  - Only 15% of patients in NEOAEGIS received FLOT
  - Only 40% of patients completed adjuvant therapy
- Preoperative chemoRT arm:
  - Checkmate 577 data: adjuvant Nivolumab after CROSS for yp T/N positive
- In the setting of clinical equipoise, how do you choose which way to go?
  - Consider the nodal burden, signet ring / diffuse subtype, Siewert Type I/III

Cholangiocarcinoma

SWOG 1815: A phase III randomized trial of Gemcitabine, cisplatin and nab-paclitaxel vs. Gemcitabine and cisplatin in 1L advanced biliary tract cancers

Rachna T. Shroff, Katherine A Guthrie, Aaron James Scott, Mitesh J. Borad, Laura Williams Goff, Khalid Matin, Amit Mahipal, Aparna Kalyan, Milind M. Javle, Carol Aghajanian, Benjamin R. Tan, Puneet S. Cheema, Anuj K. Patel, Renuka V. Iyer, Robin Kate Kelley, Jaykumar Ranchodbhai Thumar, Anthony B. El-Khoueiry, E. Gabriela Chiorean, Howard S. Hochster, Philip Agop Philip

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

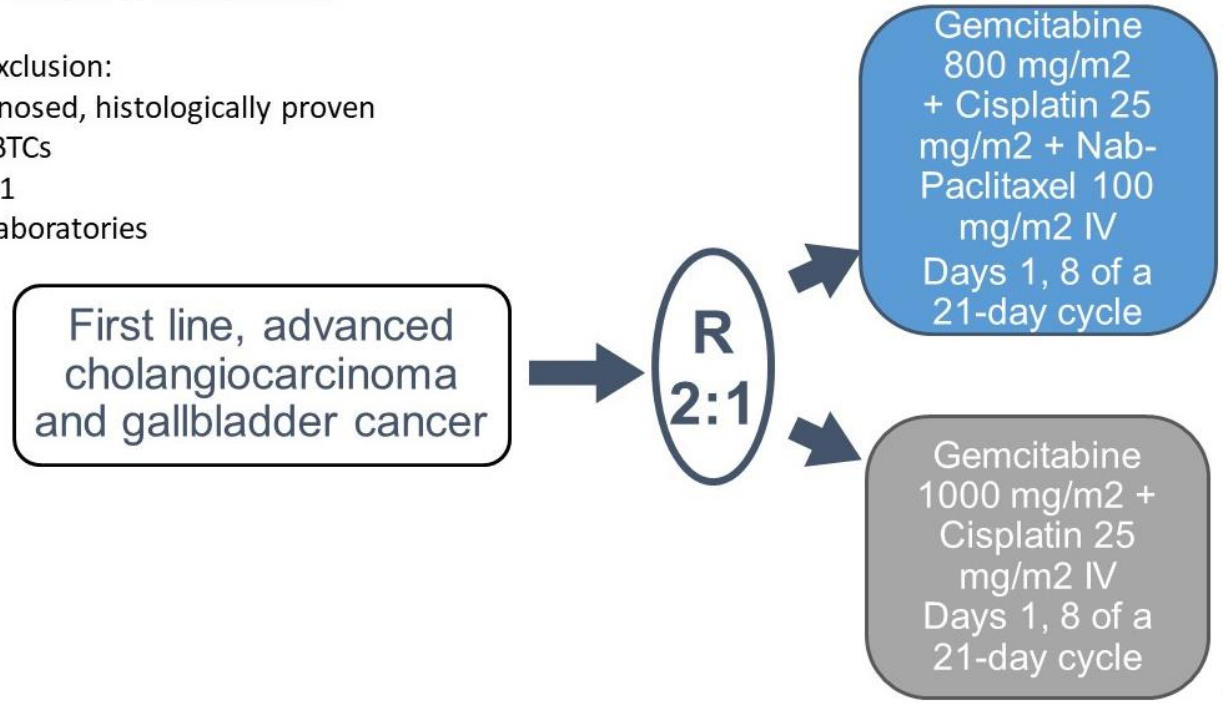
SWOG 1815: Background

- In advanced biliary tract cancers, mOS remains ~12m with gemcitabine based regimens
- In Phase II trial, Gemcitabine /Cisplatin /Nab-paclitaxel had a promising mOS of 19.2 m
- This prompted SWOG 1815 to evaluate Gem/Cis/Nab-paclitaxel vs. Gem/Cisplatin in 1L of advanced biliary tract cancers

SWOG 1815: 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



N = 441

FIRST PATIENT IN: 2/2019

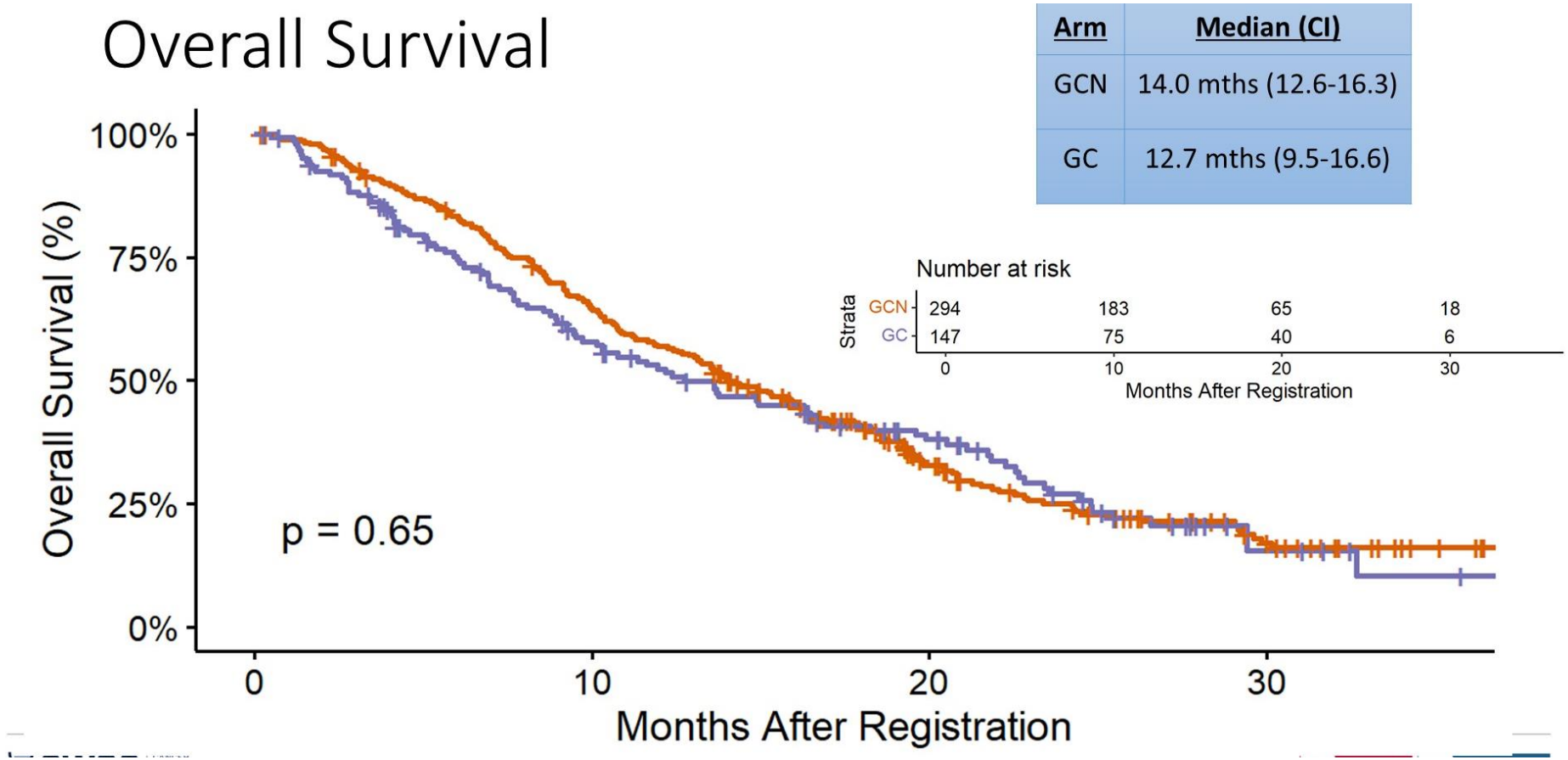
CLOSED TO ACCRUAL 2/15/2021

Restage every 3 cycles until progression

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

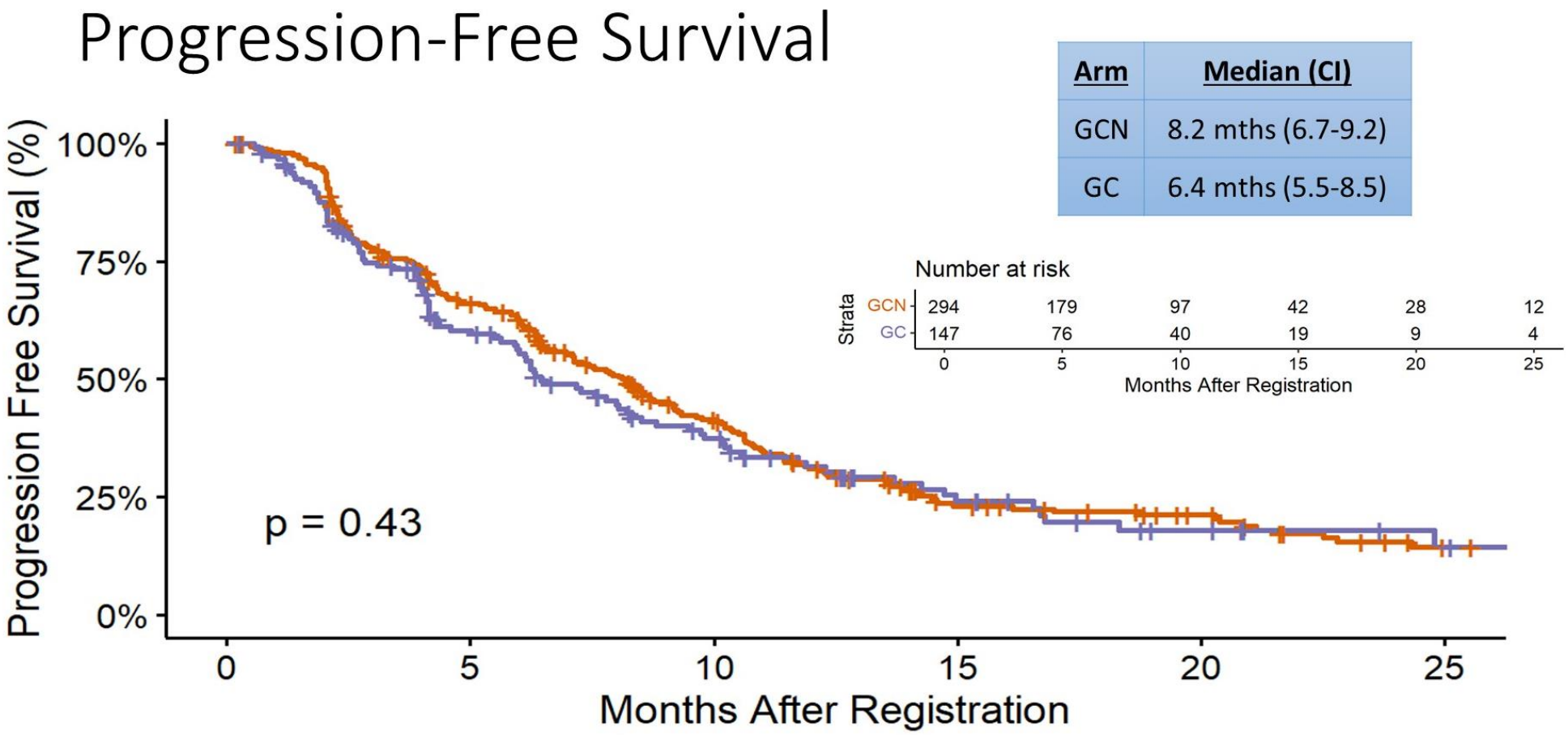
Archival blood and tissue specimens to be banked

SWOG 1815:



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

SWOG 1815:



Arm	Median (CI)
GCN	8.2 mths (6.7-9.2)
GC	6.4 mths (5.5-8.5)

SWOG 1815: Survival by Disease site

Overall Survival (months)

Disease Site	GCN (CI)	GC (CI)
Intrahepatic CCA	13.6 (11.7-16.1)	13.6 (9.5-19.6)
Extrahepatic CCA	15.8 (9.2-18.5)	16.3 (5.1-29.4)
★ Gallbladder Adenocarcinoma	17.0 (11.3-20.7)	9.3 (7.0-22.2)

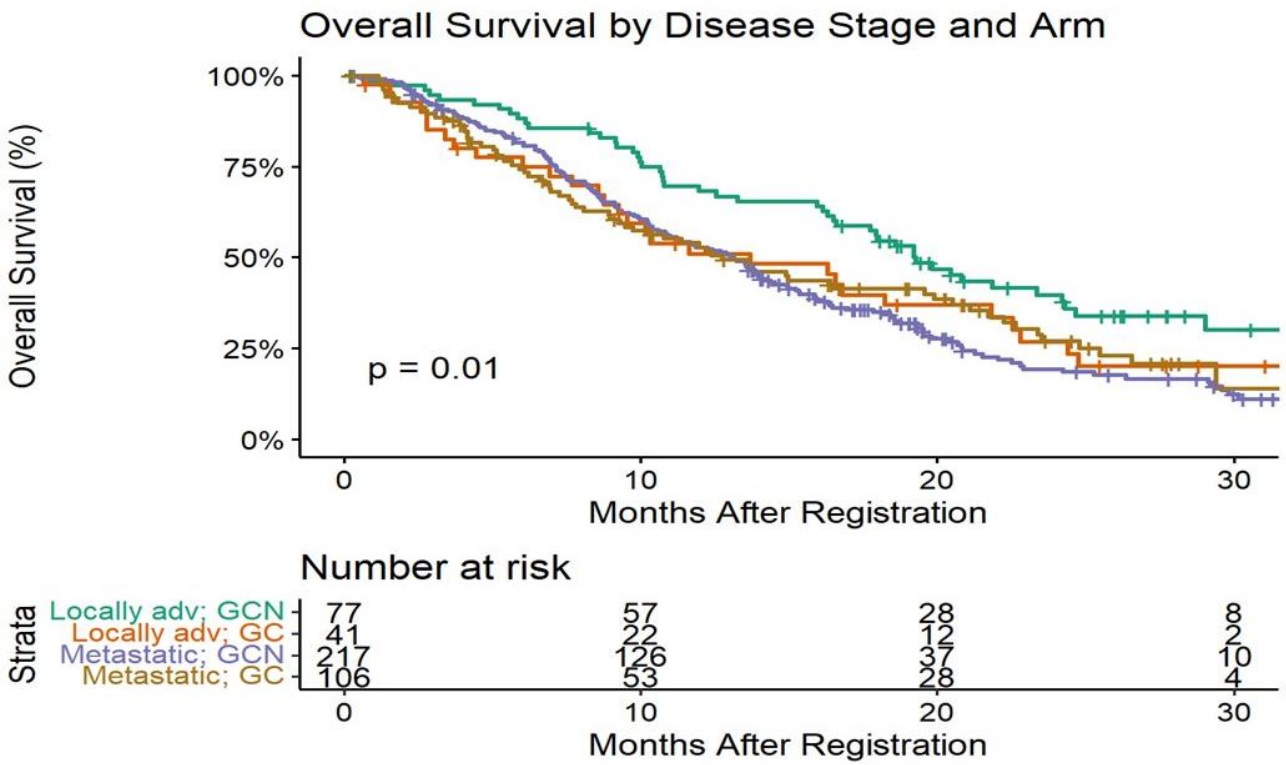
Progression Free Survival (months)

Disease Site	GCN (CI)	GC (CI)
Intrahepatic CCA	8.1 (6.4-9.3)	7.3 (5.9-9.7)
Extrahepatic CCA	7.1 (4.2-10.4)	7.8 (4.0-16.8)
★ Gallbladder Adenocarcinoma	9.6 (6.2- 14.6)	5.6 (3.9-8.8)

No significant differences between GCN and GC by disease site

Trends towards better survival with GCN in gallbladder cancer, but numbers are small

SWOG 1815: Survival by Disease stage



Median Overall Survival

Disease Stage	GCN (mths)	GC (mths)
Locally-Advanced	19.2	13.7
Metastatic	13.1	12.7

SWOG 1815: 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 1815: Conclusions

- The addition of nab-paclitaxel to gemcitabine and cisplatin did not improve OS in newly diagnosed advanced biliary tract cancer
- The GCN regimen had significantly more grade 3-5 hematologic toxicities, though treatment discontinuation rate did not significantly vary between treatment arms.
- Exploratory analysis suggest improved OS in patients with locally advanced disease or gall bladder cancer
- Consider biomarker analyses may identify subsets of patients who could benefit from GCN

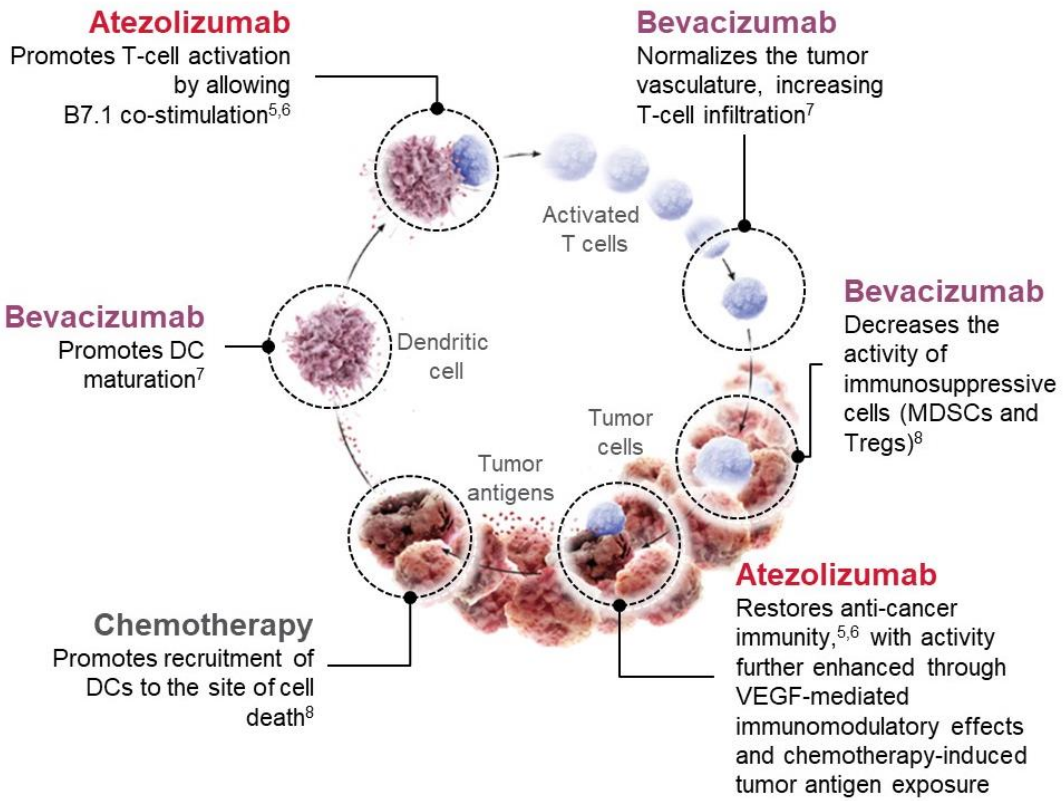
Imbrave 151: A Phase 2 randomized, double-blind, placebo-Controlled study of Bevacizumab in combination with atezolizumab and Gem/Cisplatin in Patients with advanced biliary tract cancer

Anthony B. El-Khoueiry, Zhenggang Ren, Hongjae Chon, Joon Oh Park, Jin Won Kim, Tiziana Pressiani, Daneng Li, Lyudmila Zhukova, Ming-Huang Chen, Stephen Paul Hack, Stephanie Wu, Bo Liu, Yulei Wang, Teresa Macarulla

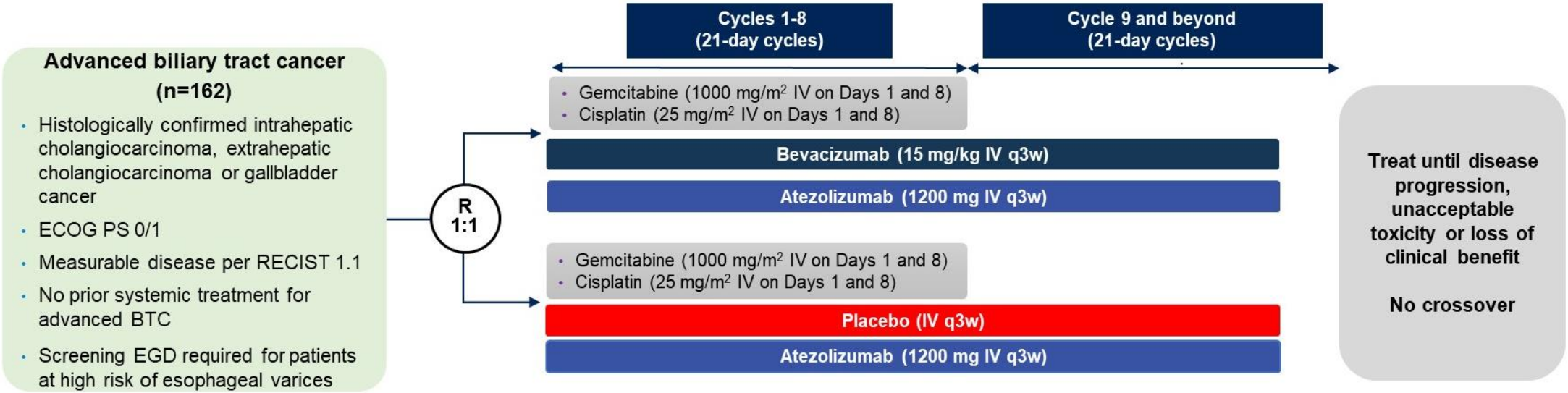
IOWA

Imbrave 151: Background

- Gemcitabine + Cisplatin +/- Durvalumab is the standard first line treatment for advanced biliary tract cancer (TOPAZ-1)
- VEGF blockade coupled with cytotoxic chemotherapy can augment responses to PD-L1 inhibition (promote an immune permissive tumor microenvironment).



Imbrave 151: Study Design



Stratification factors

- Anatomical location of primary tumor (iCCA, eCCA or GBC)
- Metastatic disease (yes or no)
- Geographic region (Asia vs rest of world)

Key endpoints

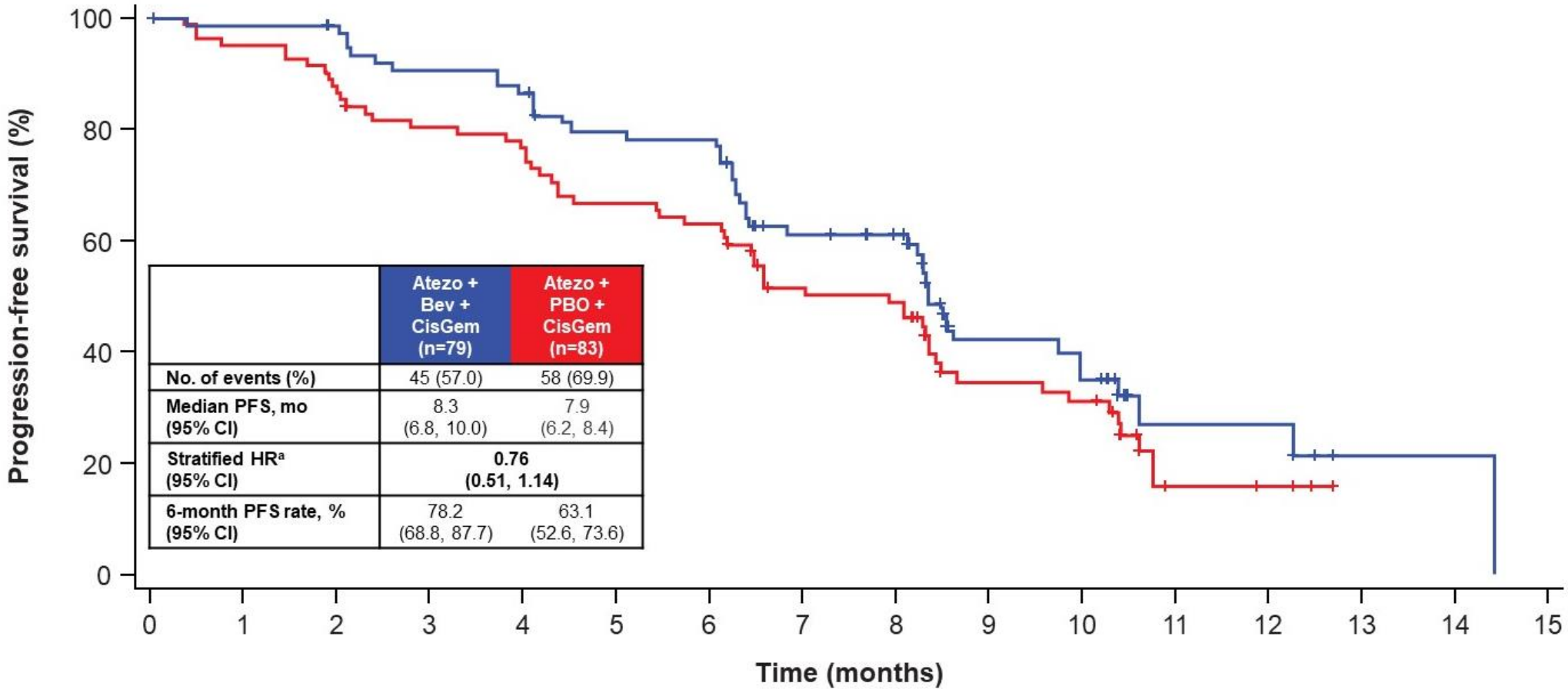
- **Primary endpoint:** PFS[a]
- **Key secondary endpoints:** ORR,[a] duration of response,[a] DCR,[a] OS, safety, PRO/QOL
- **Exploratory endpoints:** 6-month PFS and OS rates, biomarkers, PRO-CTCAE

Imbrave 151: Baseline Characteristics

	Atezo + Bev + CisGem (n=79)	Atezo + PBO + CisGem (n=83)	All patients (n=162)
Median age (range), years	61.0 (36-79)	65.0 (37-79)	63.0 (36-79)
Age < 65 years, n (%)	51 (64.6)	38 (45.8)	89 (54.9)
Male, n (%)	49 (62.0)	38 (45.8)	87 (53.7)
Race, n (%)			
White	41 (51.9)	46 (55.4)	87 (53.7)
Asian	37 (46.8)	35 (42.2)	72 (44.4)
Region,[a] n (%)			
Asia	34 (43.0)	35 (42.2)	69 (42.6)
Rest of world	45 (57.0)	48 (57.8)	93 (57.4)
Baseline ECOG PS, n (%)			
0	42 (53.2)	43 (51.8)	85 (52.5)
1	37 (46.8)	40 (48.2)	77 (47.5)
PD-L1 (TAP)[a] status at baseline, n (%)	n=58	n=63	n=121
< 1%	35 (60.3)	33 (52.4)	68 (56.2)
≥ 1%	23 (39.7)	30 (47.6)	53 (43.8)
Metastatic disease,[a] n (%)	n=75	n=80	n=155
Yes	63 (84.0)	64 (80.0)	127 (81.9)
No	12 (16.0)	16 (20.0)	28 (18.1)
Anatomical location of primary tumor,[b] n (%)			
iCCA	45 (57.0)	43 (51.8)	88 (54.3)
eCCA	13 (16.5)	17 (20.5)	30 (18.5)
GBC	21 (26.6)	23 (27.7)	44 (27.2)
Median CA19.9 at baseline (range), kU/L	46.3 (0-199970.0)	66.9 (0-335091.0)	57.2 (0-335091.0)
Prior BTC surgery, n (%)	22 (27.8)	32 (38.6)	54 (33.3)

Atezo, atezolizumab; Bev, bevacizumab; BMI, body mass index; CisGem, gemcitabine plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; PBO, placebo; PD-L1, programmed cell death ligand 1; TAP, tumor area positive score. [a]Per VENTANA SP-263 PD-L1 assay. [b]Per electronic case report form.

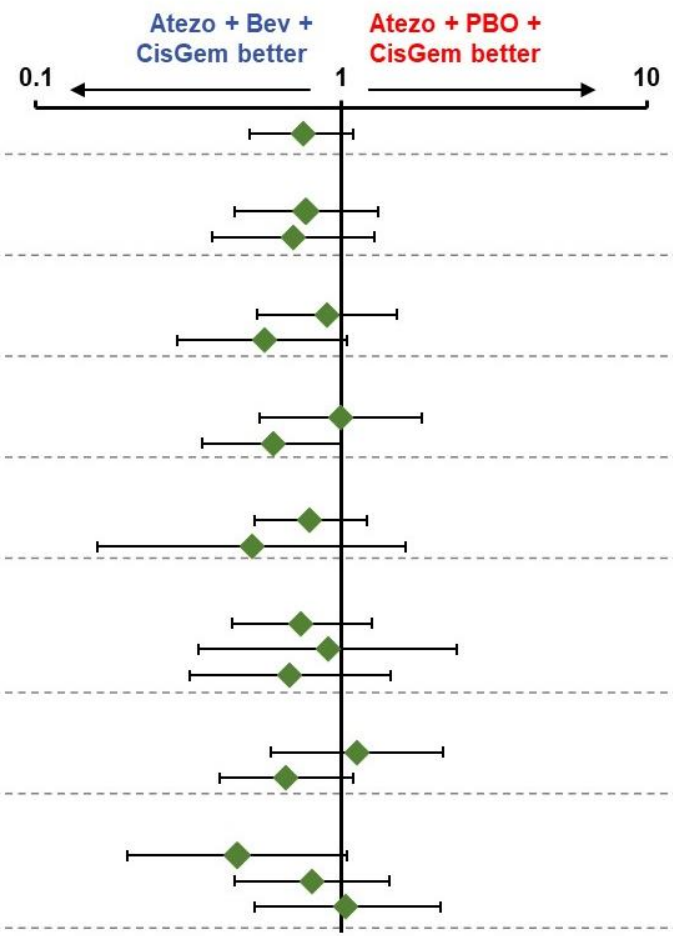
Imbrave 151: PFS



	Atezo + Bev + CisGem (n=79)	Atezo + PBO + CisGem (n=83)
No. of events (%)	45 (57.0)	58 (69.9)
Median PFS, mo (95% CI)	8.3 (6.8, 10.0)	7.9 (6.2, 8.4)
Stratified HR[a] (95% CI)	0.76 (0.51, 1.14)	
6-month PFS rate, % (95% CI)	78.2 (68.8, 87.7)	63.1 (52.6, 73.6)

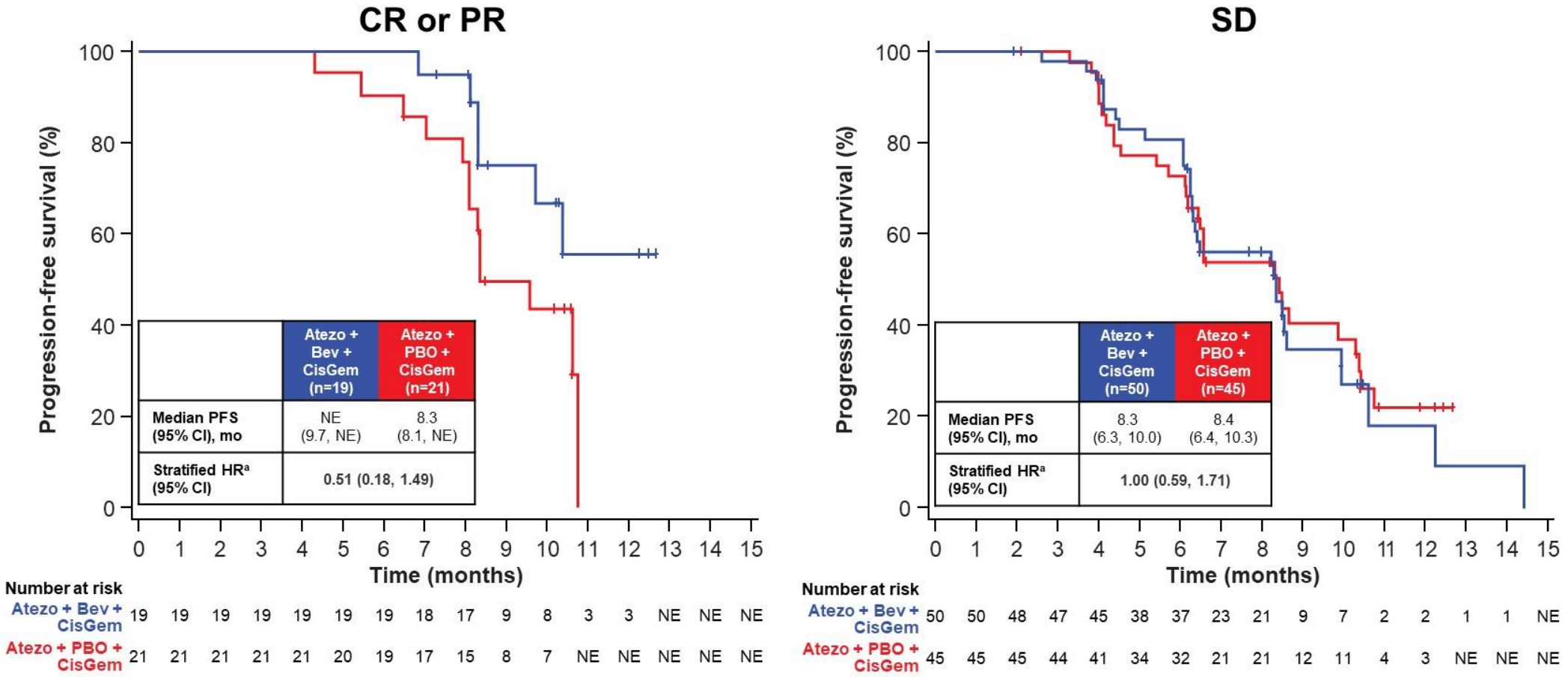
Imbrave 151: PFS subgroup analysis

Subgroup	Atezo + Bev + CisGem (n=79)			Atezo + PBO + CisGem (n=83)		HR	95% CI
	N	n	Median, mo	n	Median, mo		
All patients[a]	162	79	8.3	83	7.9	0.76	(0.51, 1.14)
Age, years[b]							
<65	89	51	8.3	38	8.1	0.77	(0.45, 1.32)
≥65	73	28	8.5	45	6.6	0.70	(0.38, 1.29)
Sex[b]							
Male	87	49	8.3	38	8.1	0.90	(0.53, 1.52)
Female	75	30	10.6	45	7.0	0.56	(0.29, 1.05)
Geographic region[b]							
Asia	69	34	8.3	35	8.3	1.00	(0.54, 1.83)
Rest of world	93	45	8.6	48	6.6	0.60	(0.35, 1.01)
Metastatic disease[b]							
Yes	127	63	8.3	64	7.0	0.79	(0.52, 1.22)
No	28	12	14.4	16	6.5	0.51	(0.16, 1.62)
Location of primary tumor[b]							
Intrahepatic (iCCA)	88	45	8.5	43	8.3	0.74	(0.44, 1.26)
Extrahepatic (eCCA)	30	13	8.1	17	8.3	0.91	(0.34, 2.39)
Gallbladder carcinoma	44	21	8.5	23	6.5	0.68	(0.32, 1.45)
Surgery[b]							
Yes	54	22	8.1	32	8.3	1.13	(0.59, 2.16)
No	108	57	8.5	51	6.6	0.66	(0.40, 1.10)
PD-L1 category 1[b,c]							
Unknown	41	21	8.6	20	5.1	0.46	(0.20, 1.05)
TAP<1%	68	35	8.3	33	8.3	0.80	(0.45, 1.44)
TAP ≥1%	53	23	8.1	30	8.1	1.04	(0.52, 2.11)



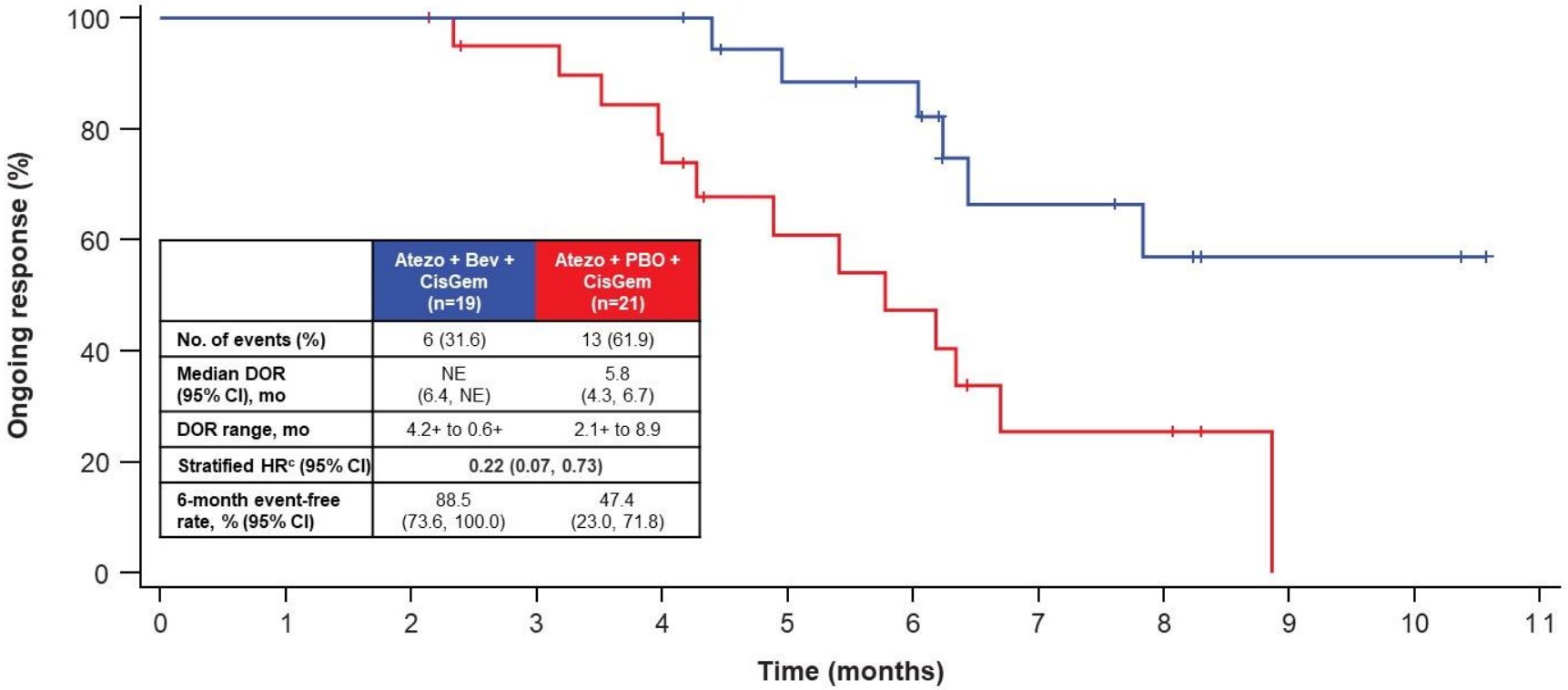
Median follow-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; PBO, placebo; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TAP, tumor area positive score.
[a]Stratified analysis. [b]Unstratified Cox regression analysis. [c]Per VENTANA SP-263 PD-L1 assay.

Exploratory post hoc analysis: PFS in patients with CR or PR, or with SD



Median follow-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; CR, complete response; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NE, not estimable; PBO, placebo; PFS, progression-free survival; PR, partial response; SD, stable disease. [a]Stratified analysis. Stratification factors are location of primary tumor (iCCA vs eCCA vs GBC) and geographic region (Asia vs rest of world).

Imbrave 151: DOR

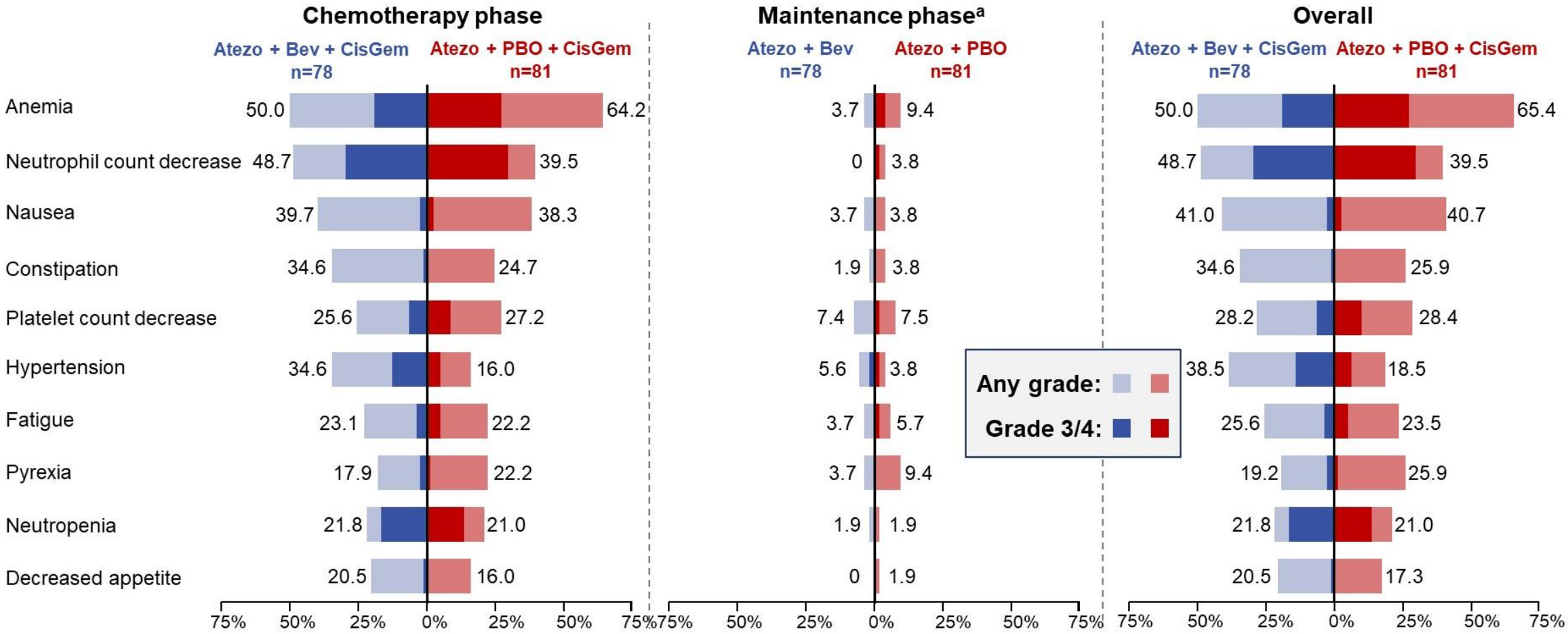


	Atezo + Bev + CisGem (n=19)	Atezo + PBO + CisGem (n=21)
No. of events (%)	6 (31.6)	13 (61.9)
Median DOR (95% CI), mo	NE (6.4, NE)	5.8 (4.3, 6.7)
DOR range, mo	4.2+ to 0.6+	2.1+ to 8.9
Stratified HR[c] (95% CI)	0.22 (0.07, 0.73)	
6-month event-free rate, % (95% CI)	88.5 (73.6, 100.0)	47.4 (23.0, 71.8)

Number at risk												
Atezo + Bev + CisGem	19	19	19	19	19	15	14	8	6	3	3	NE
Atezo + PBO + CisGem	21	21	21	18	15	9	7	3	3	NE	NE	NE

w-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; DOR, duration of response; eCCA, cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NE, not estimable; PBO, placebo. [a]Stratified analysis. Stratification factors are location of primary tumor (CA vs GBC) and geographic region (Asia vs rest of world).

AEs with ≥20% incidence by treatment phase



Median follow-up duration: 10.8 months. CCOD: May 16, 2022. AE, adverse event; Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CisGem, gemcitabine plus cisplatin; PBO, placebo. [a]Maintenance phase started at Cycle 9 after the completion of 8 cycles of combination chemotherapy treatment administered on a 21-day cycle.

Imbrave 151: Conclusions

- The addition of bevacizumab to atezolizumab + GemCis resulted in modestly improved PFS (HR = 0.76)
  - The median PFS was similar in both arms (8.3 vs 7.9m)
  - 6-mth PFS rate was higher in the bevacizumab arm (78.2% vs 63.1%)
- Longer median duration of response at 6 months for the bevacizumab arm
- Potential subset of patient that derives benefit from this regimen
- OS results are pending