2025 Johns Hopkins Updates: Cholangiocarcinoma

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Disclosures

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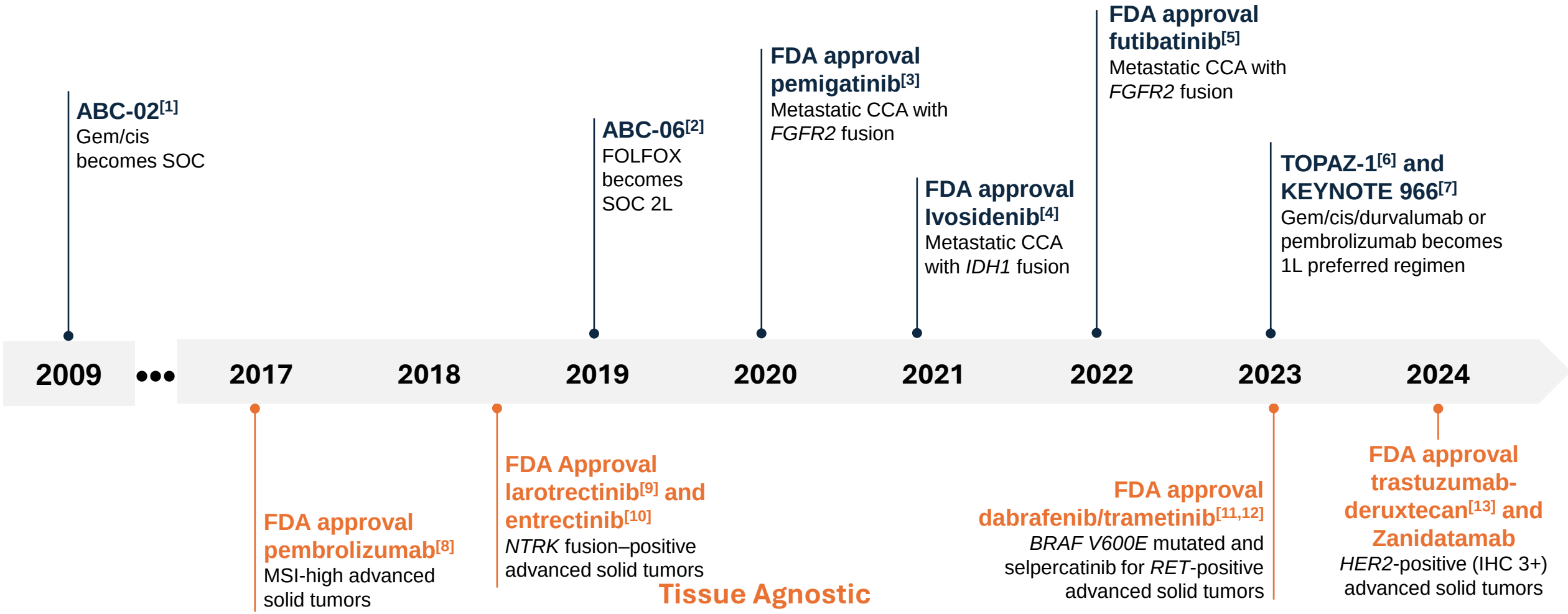
The Changing Therapeutic Landscape in the Management of Advanced Cholangiocarcinoma



- 1L, first line; 2L, second line; FDA, US Food and Drug Administration; FOLFOX, 5-fluorouracil, oxaliplatin, and leucovorin; SOC, standard of care.

- 1. Valle J, et al; ABC-02 Trial Investigators. N Engl J Med. 2010;362:1273-1281; 2. Lamarka A, et al. Lancet Oncol. 2021;22:690-701; 3. Pemigatinib [PI]. Approved 2020. Revised April 2020; 4. Ivosidenib [PI]. Approved 2018. Revised October 2023; 5. Futibatinib [PI]. Approved 2022. Revised September 2022; 6. Oh DY, et al. Future Oncol. 2023;19:2277-2289; 7. Kelley RK, et al; KEYNOTE-966 Investigators. Lancet. 2023;401:1853-1865; 8. Pembrolizumab [PI]. Approved 2014. Revised May 2017; 9. Larotrectinib [PI]. Approved 2018. Revised November 2018; 10. Entrectinib [PI]. Approved 2019. Revised August 2019; 11. Dabrafenib [PI]. Approved 2013. Revised June 2022; 12. Trametinib [PI]. Approved 2013. Revised June 2022; 13. Trastuzumab-deruxtecan [PI]. Approved 2019. Revised December 2019.

TOPAZ-1: Schema

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

Stratification factors
- Disease status
  - Initially unresectable versus recurrent
- Primary tumour location
  - ICC versus ECC versus GBC

R (1:1)
(N=685)

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

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

Primary endpoint
- OS

Key secondary endpoints
- PFS
- ORR
- DoR
- Safety

Exploratory endpoint
- Efficacy and safety by primary tumour location
  - ICC versus ECC versus GBC

He et al, ESMO GI 2022

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	17 (5.0)	12 (3.5)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status at randomization, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis,* n (%)		
Metastatic	303 (88.9)	286 (83.1)
Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression,* n (%)		
TAP ≥1%	197 (57.8)	205 (59.6)
TAP <1%	103 (30.2)	103 (29.9)

Oh et al, NEJM Evidence 2022

TOPAZ-1: UPDATED OS

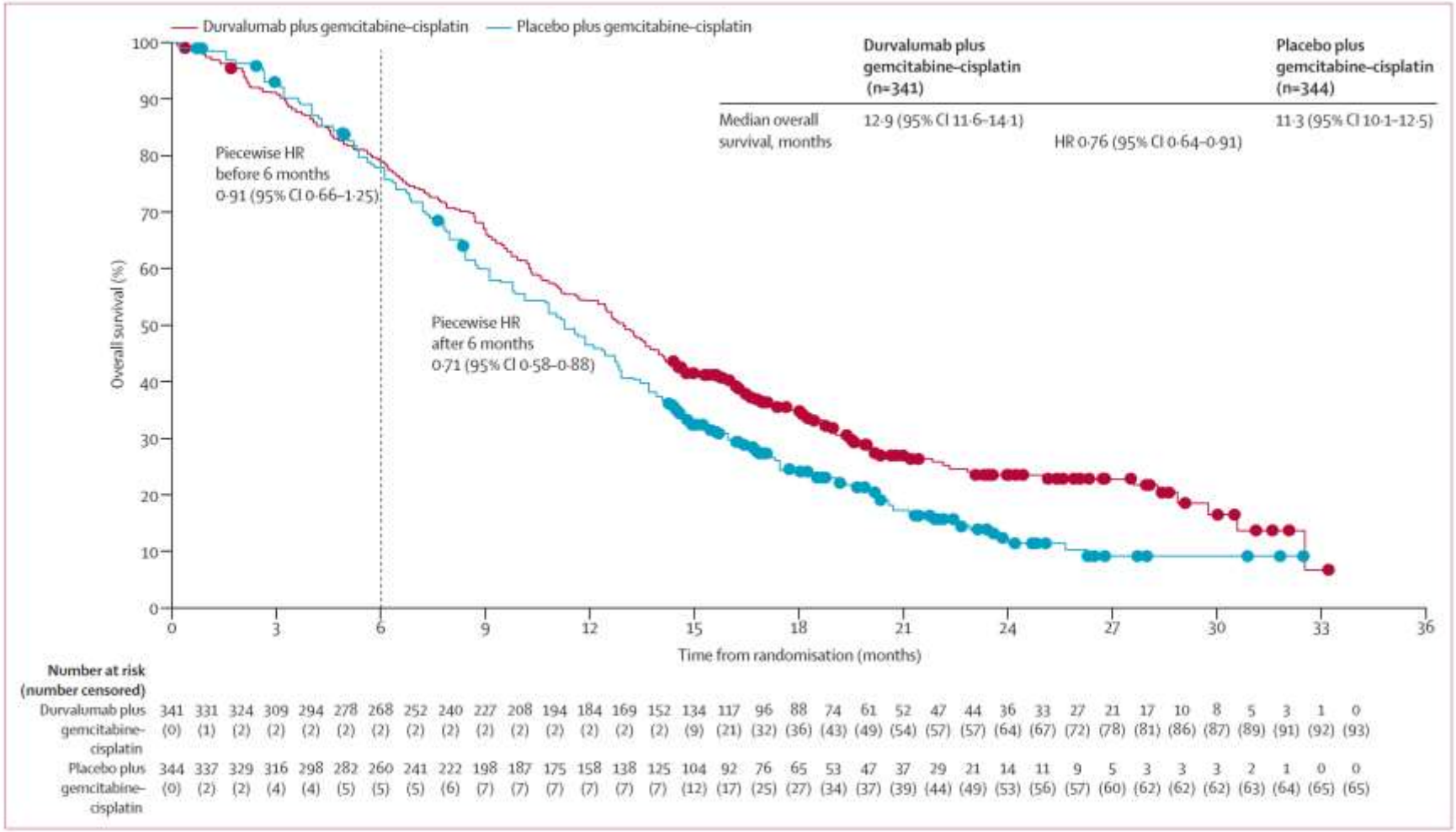
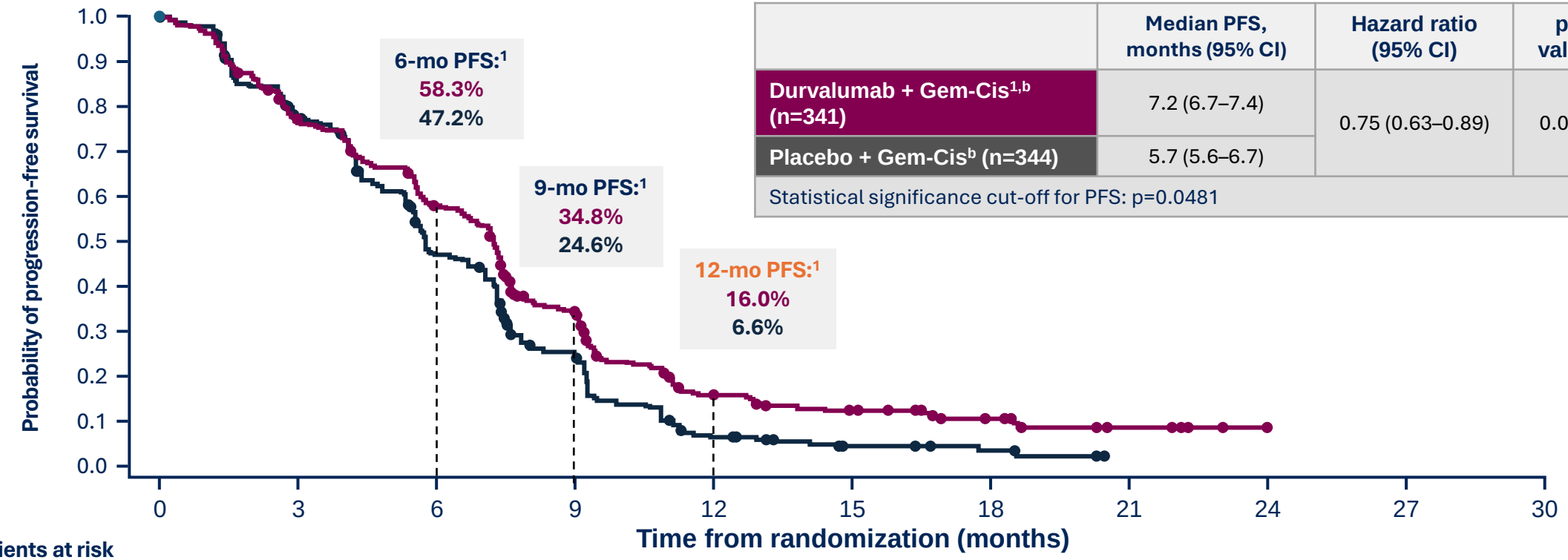


Figure 2: **Kaplan–Meier curve of overall survival in the full analysis set**
Data cut-off Feb 25, 2022. HR<1 favours durvalumab plus gemcitabine–cisplatin. HR=hazard ratio.

Oh et al, Lancet Gastroenterol Hepatol 2024

TOPAZ-1: Summary of Primary Results – PFS[a]

The combination of durvalumab + gem-cis showed statistically significant improvement in PFS, a key secondary endpoint of TOPAZ-1, when compared to placebo + gem-cis



	Median PFS, months (95% CI)	Hazard ratio (95% CI)	p-value
Durvalumab + Gem-Cis[1,b] (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + Gem-Cis[b] (n=344)	5.7 (5.6–6.7)		
Statistical significance cut-off for PFS: p=0.0481			

Number of patients at risk

Durvalumab + Gem-Cis	341	258	189	100	38	25	15	5	0
Placebo + Gem-Cis	344	255	149	71	17	7	4	0	0

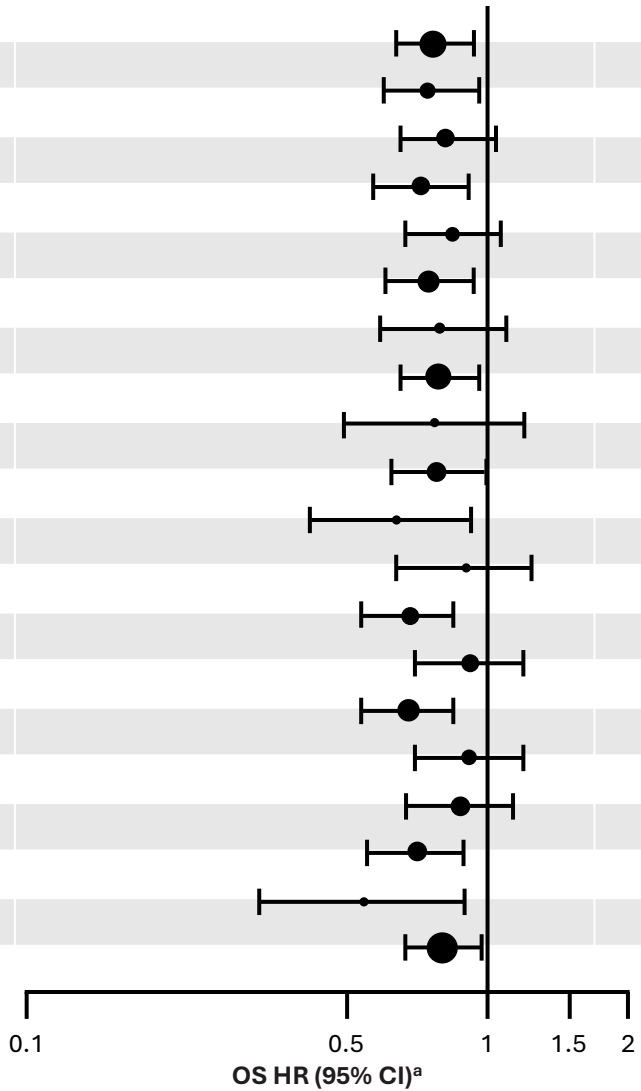
[a]At a pre-planned interim analysis, a statistically significant improvement in overall survival in the durvalumab arm compared with the placebo arm was observed. Therefore, the key secondary end point of progression-free survival was also formally evaluated at this interim analysis; [b]Median duration of follow-up (95% CI) was 9.2 (0.0–24.0) months with durvalumab + gem-cis and 6.9 (0.0–20.4) months with placebo + gem-cis.[1]

Oh et al, NEJM Evid 2022

TOPAZ-1: Subgroup Analysis of Overall Survival

The overall survival benefits observed in the durvalumab + gem-cis arm were generally consistent across all subgroups analyzed.

	Durvalumab + Gem-Cis n/N (%)	Placebo + Gem-Cis n/N (%)	OS HR (95% CI)[a]
All patients	248 / 341 (72.7)	279 / 344 (81.1)	0.76 (0.64–0.91)
Sex: male	126 / 169 (74.6)	148 / 176 (84.1)	0.75 (0.59–0.95)
Sex: female	122 / 172 (70.9)	131 / 168 (78.0)	0.81 (0.64–1.04)
Age at randomization: <65 years of age	123 / 181 (68.0)	150 / 184 (81.5)	0.72 (0.56–0.91)
Age at randomization: ≥65 years of age	125 / 160 (78.1)	129 / 160 (80.6)	0.84 (0.66–1.08)
PD-L1 expression: high (TAP ≥1%)	149 / 199 (74.9)	172 / 207 (83.1)	0.75 (0.60–0.93)
PD-L1 expression: low / negative (TAP <1%)	71 / 103 (68.9)	81 / 103 (78.6)	0.79 (0.58–1.09)
Disease status at randomization: initially unresectable	209 / 274 (76.3)	240 / 279 (86.0)	0.79 (0.65–0.95)
Disease status at randomization: recurrent	39 / 67 (58.2)	39 / 64 (60.9)	0.76 (0.49–1.20)
Primary tumor location: intrahepatic cholangiocarcinoma	136 / 190 (71.6)	153 / 193 (79.3)	0.78 (0.62–0.99)
Primary tumor location: extrahepatic cholangiocarcinoma	45 / 66 (68.2)	55 / 65 (84.6)	0.61 (0.41–0.91)
Primary tumor location: gallbladder cancer	67 / 85 (78.8)	71 / 86 (82.6)	0.90 (0.64–1.25)
Race: Asian	134 / 185 (72.4)	174 / 201 (86.6)	0.68 (0.54–0.85)
Race: non-Asian	114 / 156 (73.1)	105 / 143 (73.4)	0.92 (0.70–1.20)
Region: Asia	130 / 178 (73.0)	170 / 196 (86.7)	0.68 (0.54–0.85)
Region: rest of the world	118 / 163 (72.4)	109 / 148 (73.6)	0.91 (0.70–1.18)
WHO / ECOG performance status: (0) normal activity	126 / 173 (72.8)	125 / 163 (76.7)	0.87 (0.68–1.12)
WHO / ECOG performance status: (1) restricted activity	122 / 168 (72.6)	154 / 181 (85.1)	0.70 (0.55–0.89)
Diagnostic stage: locally advanced	22 / 38 (57.9)	45 / 57 (78.9)	0.54 (0.32–0.88)
Diagnostic stage: metastatic	226 / 303 (74.6)	234 / 286 (81.8)	0.80 (0.67–0.97)



Oh et al, NEJM Evid 2022

TOPAZ-1: Best Objective Response

n (%)	Durvalumab + Gem-Cis (n=341)	Placebo + Gem-Cis (n=343)
Responders[2,a]	**91 (26.7)**	**64 (18.7)**
Complete response[2]	7 (2.1)	2 (0.6)
Partial response[2]	84 (24.6)	62 (18.1)
Non-responders	**250 (73.3)**	**279 (81.3)**
Stable disease	200 (58.7)	220 (64.1)
Progressive disease[b]	47 (13.8)	51 (14.9)
Not evaluable	3 (0.9)	8 (2.3)

There was a higher proportion of responders (CR + PR) in the durvalumab + gem-cis arm versus the placebo + gem-cis arm

Oh et al, NEJM Evid 2022

TOPAZ-1: Adverse Events

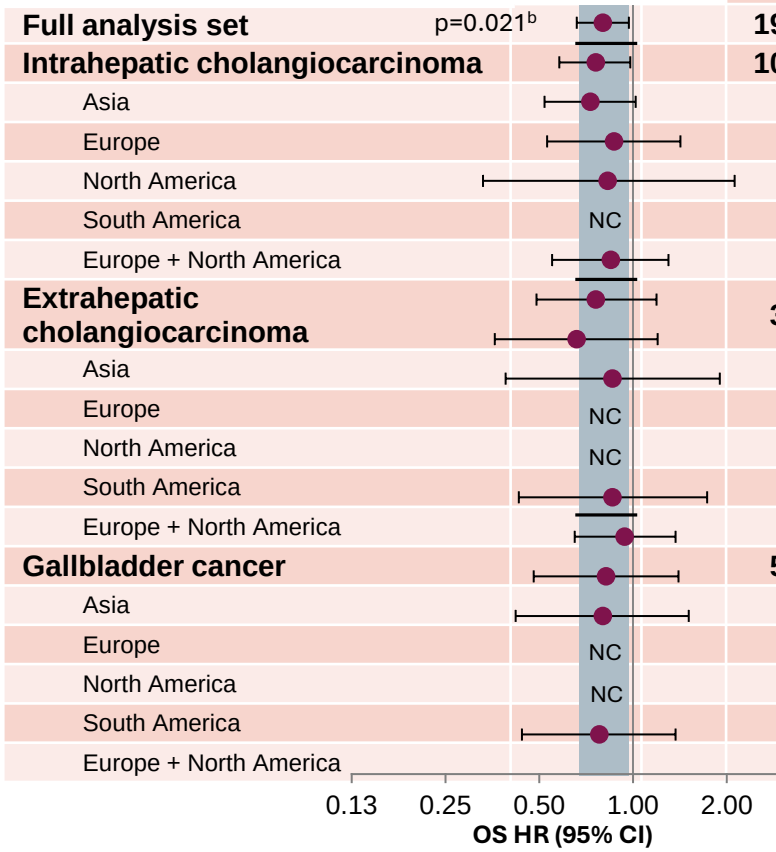
Event,[a] n (%)	Durvalumab + Gem-Cis (n=338)	Placebo + Gem-Cis (n=342)
Any AE	**336 (99.4)**	**338 (98.8)**
Any Grade 3/4 AE	250 (74.0)	257 (75.1)
Any AE leading to discontinuation	43 (12.7)	52 (15.2)
Any AE leading to death	13 (3.8)	14 (4.1)
Any TRAE	**314 (92.9)**	**308 (90.1)**
Any Grade 3/4 TRAE	206 (60.9)	217 (63.5)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any TRAE leading to death	2 (0.6)	1 (0.3)

The incidence of AEs and TRAEs (any, Grade 3 or 4 or leading to discontinuation of treatment or death) was similar between treatment arms and consistent with the safety profile observed at the primary analysis[1,2]

Oh et al, NEJM Evid 2022

TOPAZ-1: Primary Tumor Location

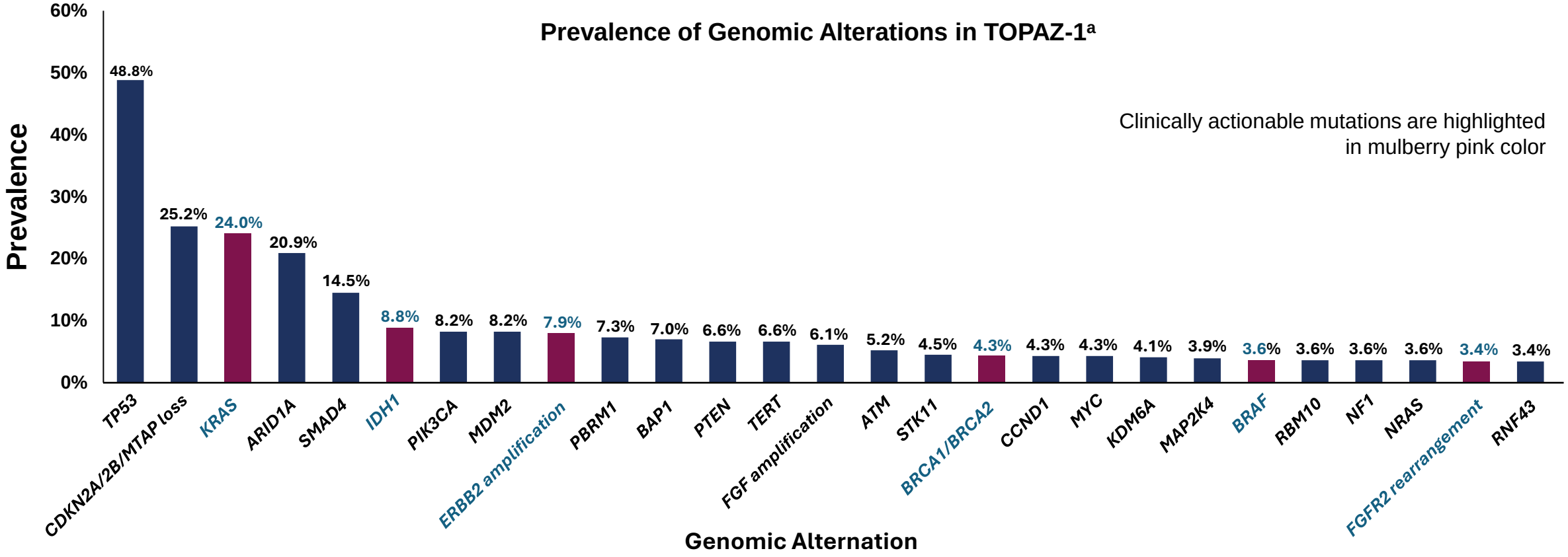
OS HRs were <1, favoring durvalumab, across primary tumor locations



	Durvalumab + Gem-Cis (N=341)		Placebo + Gem-Cis (N=344)		OS HR[a] (95% CI)
	Events, n/N (%)	Median OS (95% CI), mo	Events, n/N (%)	Median OS (95% CI), mo	
Full analysis set	**198/341 (58.1)**	**12.8 (11.1–14.0)**	**226/344 (65.7)**	**11.5 (10.1–12.5)**	**0.80 (0.66–0.97)[c]**
Intrahepatic cholangiocarcinoma	**105/190 (55.3)**	**13.5 (11.9–15.1)**	**126/193 (65.3)**	**11.5 (9.8–12.8)**	**0.76 (0.58–0.98)[d]**
Asia	60/100 (60.0)	13.0 (9.8–14.6)	81/111 (73.0)	11.4 (9.2–12.5)	0.73 (0.52–1.02)[d]
Europe	31/61 (50.8)	13.5 (9.5–18.8)	35/61 (57.4)	14.0 (8.0–18.3)	0.87 (0.53–1.42)[d]
North America	11/21 (52.4)	15.1 (6.8–NC)	9/18 (50.0)	13.3 (5.3–NC)	0.83 (0.33–2.12)[d]
South America	3/8 (37.5)	NR (2.3–NC)	1/3 (33.3)	NR (8.0–NC)	NC[e]
Europe + North America	42/82 (51.2)	13.7 (10.9–18.1)	44/79 (55.7)	13.6 (8.5–17.7)	0.85 (0.55–1.30)[d]
Extrahepatic cholangiocarcinoma	**38/66 (57.6)**	**12.7 (9.8–16.6)**	**42/65 (64.6)**	**12.1 (7.8–14.4)**	**0.76 (0.49–1.19)[d]**
Asia	18/35 (51.4)	16.6 (12.6–NC)	27/42 (65.3)	12.8 (7.7–17.3)	0.66 (0.36–1.20)[d]
Europe	14/23 (60.9)	9.1 (8.7–NC)	12/19 (63.2)	14.4 (7.0–NC)	0.86 (0.39–1.90)[d]
North America	5/6 (83.3)	11.0 (0.9–NC)	3/4 (75.0)	9.6 (3.4–NC)	NC[e]
South America	1/2 (50.0)	NR (10.0–NC)	0	NR	NC[e]
Europe + North America	19/29 (65.5)	9.8 (8.7–16.2)	15/23 (65.2)	12.1 (7.0–14.4)	0.86 (0.43–1.73)[d]
Gallbladder cancer	**55/85 (64.7)**	**10.7 (8.9–13.2)**	**58/86 (67.4)**	**11.0 (8.7–12.8)**	**0.94 (0.65–1.37)[d]**
Asia	25/43 (58.1)	13.3 (9.0–20.1)	29/43 (67.4)	12.6 (8.4-17.7)	0.82 (0.48–1.40)[d]
Europe	18/24 (75.0)	9.6 (5.2–11.1)	22/27 (81.5)	8.1 (4.9–11.0)	0.80 (0.42–1.51)[d]
North America	5/10 (50.0)	12.2 (2.6–NC)	4/6 (66.7)	10.2 (5.7–NC)	NC[e]
South America	7/8 (87.5)	8.1 (0.9–NC)	3/10 (30.0)[f]	NR (2.0–NC)	NC[e]
Europe + North America	23/34 (67.6)	10.3 (6.6–12.2)	26/33 (78.8)	8.7 (6.0–11.0)	0.78 (0.44–1.37)[d]

He et al. ESMO World GI 2022

TOPAZ-1 Impact of Mutation Status on Efficacy Outcomes: Genomic Alterations



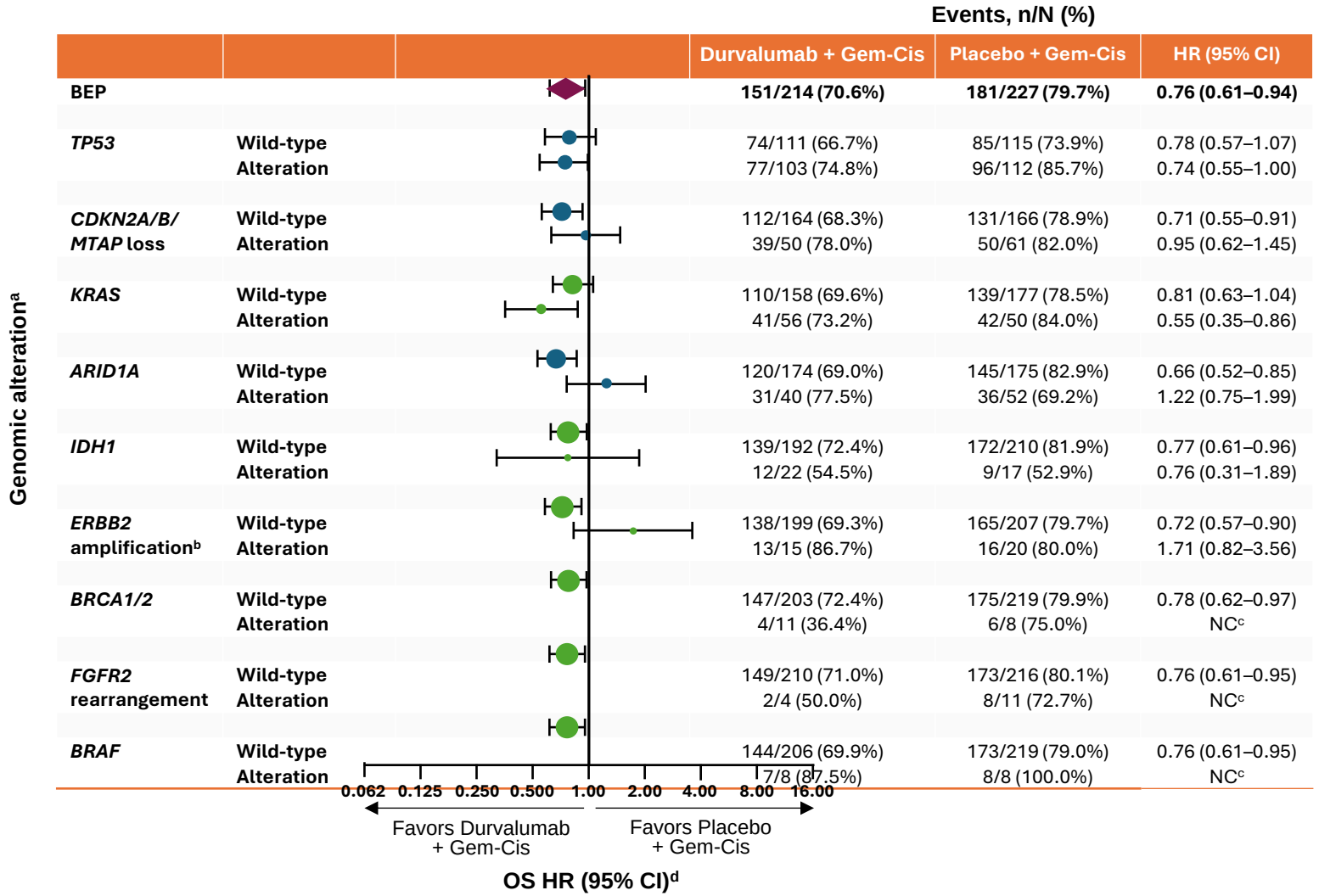
TP53, *CDKN2A/CDKN2B/MTAP*, *KRAS* and *ARID1A* were the most frequent genomic alterations in the TOPAZ-1 BEP; clinically actionable alterations in *IDH1*, *ERBB2*, *BRCA1/2*, *BRAF*, and *FGFR2* were also observed

[a]Genes with rates ≥3% are shown. Percentages are calculated out of the BEP, N=441.

TOPAZ-1: OS by Mutation Status

Durvalumab plus gem-cis is generally effective in patients with clinically actionable and high-prevalence genomic alterations

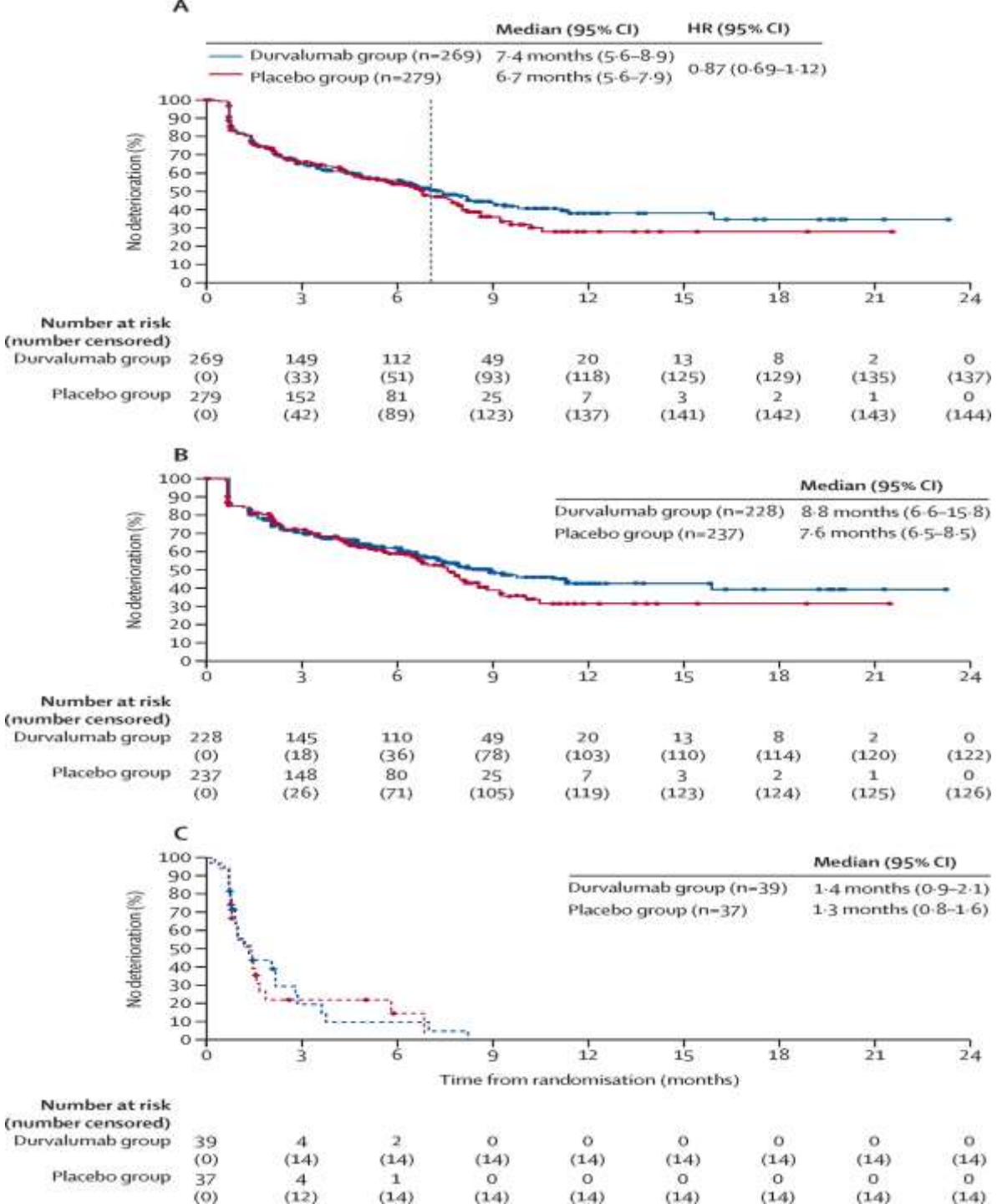
- Generally, similar OS benefit with durvalumab versus placebo was observed for patients with either wild-type or altered genotypes
- 95% CIs are wide for some genomic alterations due to their low prevalence



[a]Yellow indicates clinically actionable genomic alterations; [b]Correlation of *ERBB2* amplification with ERBB2 overexpression was not confirmed by immunohistochemistry or in-situ hybridization. It is unclear whether *ERBB2* amplification is associated with efficacy outcomes in this population; sample size is limited, and ongoing analysis is continuing to understand the outcomes in this subgroup; [c]HR not calculated if <20 total events occur across treatment arms; [d]Size of dot represents number of events.
Abbreviations and reference in slide notes.

TOPAZ-1: QOL

- No difference in time to deterioration in global health status or quality of life, functioning, and symptoms
- Median time to deterioration of global health status or quality of life was 7·4 months (95% CI 5·6 to 8·9) in the durvalumab group and 6·7 months (5·6 to 7·9) in the placebo group (hazard ratio 0·87 [95% CI 0·69 to 1·12])
- Authors concluded that the addition of durvalumab to gemcitabine and cisplatin “did not have a detrimental effect on patient-reported outcomes”



Burris et al, Lancet Oncol 2024

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R
1:1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W for 8 cycles

Placebo IV Q3W for ≤35 cycles (~2 yr)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W for 8 cycles

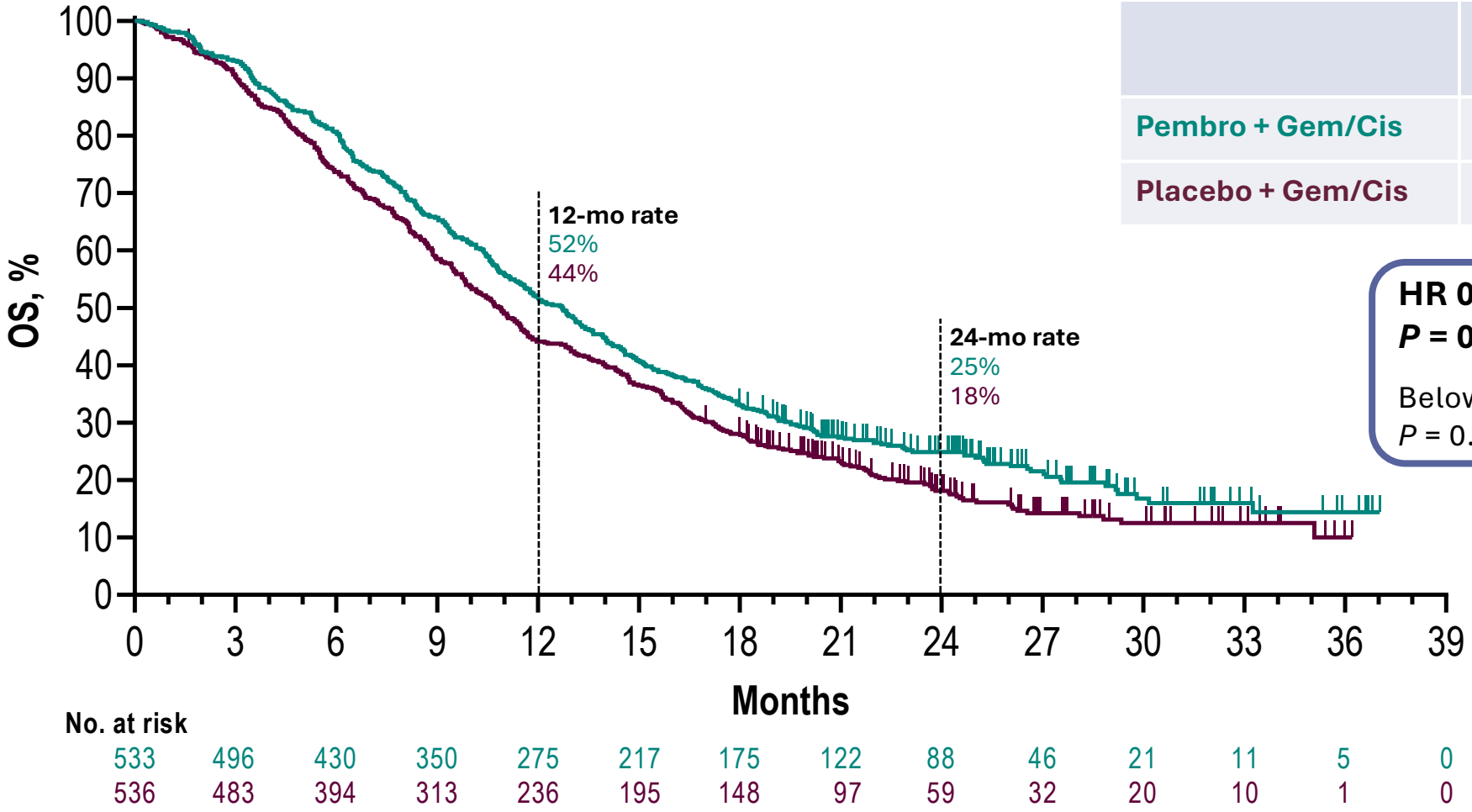
Stratification Factors

- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review (BICR) and safety

Kelley et al, AACR 2023

Overall Survival at Final Analysis



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**

Below the signficance boundary of *P* = 0.0200

Data cutoff date: December 15, 2022.

Kelley et al, AACR 2023

Conclusions

- Front-line therapy has evolved to include chemo plus immunotherapy as the backbone for CCA
- Ongoing trials are building on this backbone
- Exploratory analyses confirm that Gem/Cis + IO demonstrates survival benefits across all subgroups
- The addition of IO to Gem/Cis does not cause additive toxicity

Thank You!