VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
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Cáncer de origen digestivo no-colorrectal

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- Grant support: N/A
- Other: N/A

Outline

The best in 2024 about…

- Gastroesophageal adenocarcinoma
- Biliary tract cancer
- Pancreatic adenocarcinoma
- Hepatocellular carcinoma

The best in 2024 about…

Gastroesophageal adenocarcinoma

Curative setting:

- ESOPEC & TOP-GEAR: No place for RT in the perioperative setting → Change on the SoC
- KEYNOTE-585: Final analyzes → NEGATIVE
  - To be contextualized with MATTERHORN (awaited in 2025)

1st line, HER2-positive population

- KEYNOTE-811: Final analyzes → POSITIVE → Change on the SoC

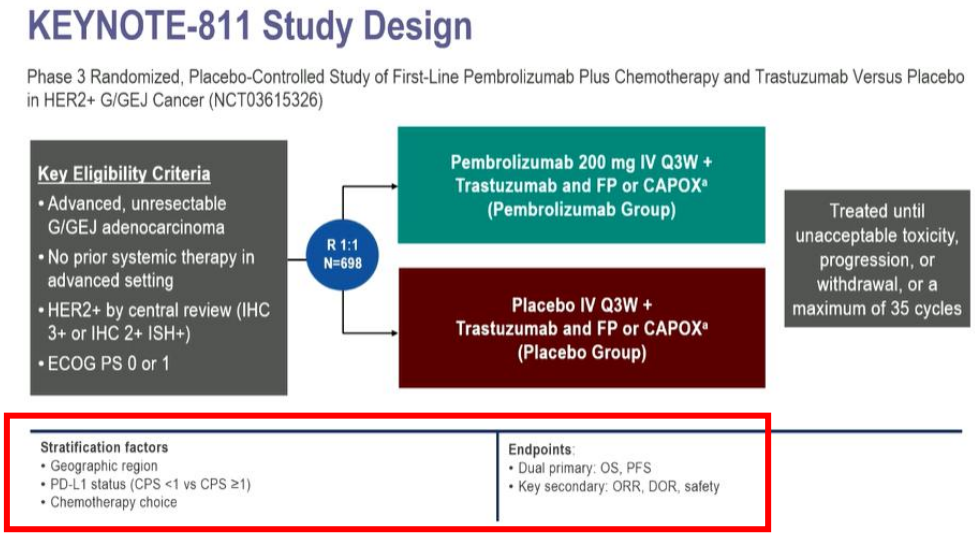
Hoppner ASCO 2024; Hoeppner NEJM 2025

Leong ESMO 2024; Leong NEJM 2025

Shitara ESMO 2024; Shitara Lancet 2024

Lonardi/Janjigian ESMO 2024; Janjigian NEJM 2024

KEYNOTE-811



IA1: ORR

- **74% vs 52%;** p=0.00006

IA2: mPFS

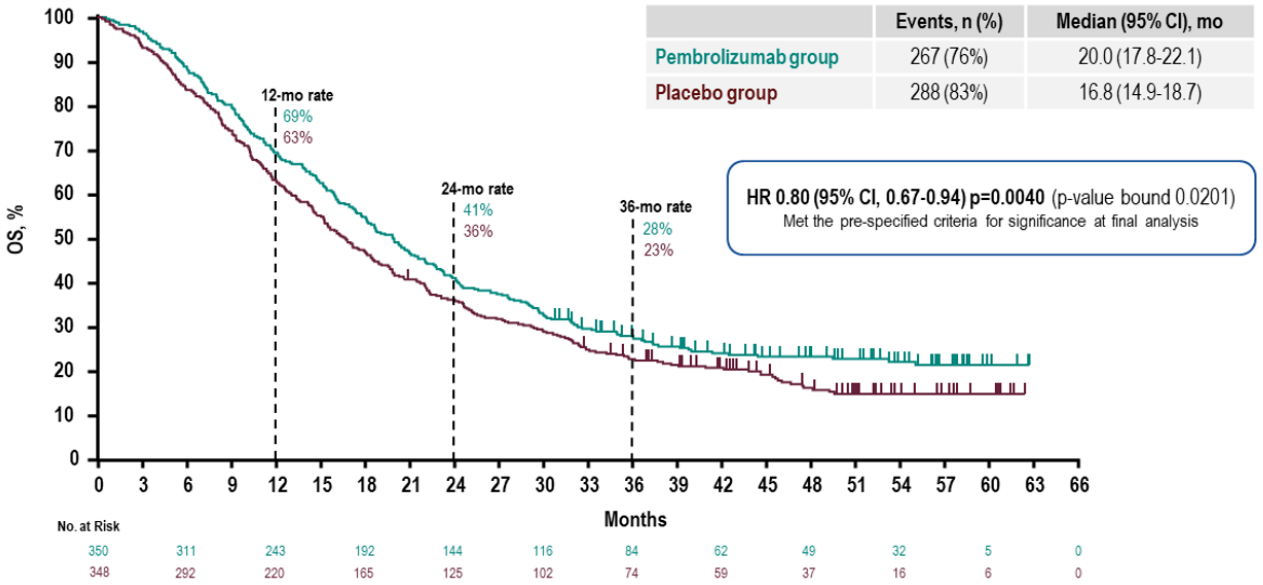
- mPFS: 10.0 vs. 8.1 mo in all patients (HR 0.72; p=0.0002)
- mPFS: **10.8 vs. 7.2 mo** in patients with **PD-L1 CPS ≥ 1** (HR 0.70)

ESMO 2024: Results of the **PP final analysis of OS**

Lonardi/Janjigian ESMO 2024; Janjigian NEJM 2024

KEYNOTE 811: Final analysis

Overall Survival at Final Analysis (ITT)



	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	267 (76%)	20.0 (17.8-22.1)
Placebo group	288 (83%)	16.8 (14.9-18.7)

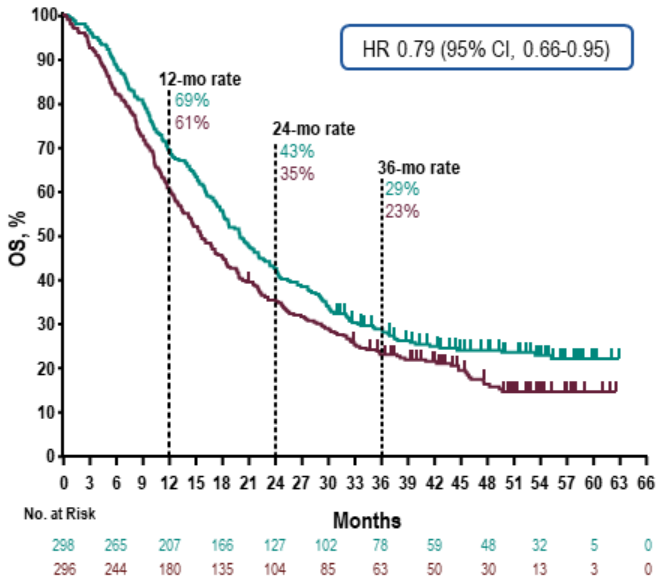
HR 0.80 (95% CI, 0.67-0.94) p=0.0040 (p-value bound 0.0201)
Met the pre-specified criteria for significance at final analysis

Lonardi/Janjigian ESMO 2024; Janjigian NEJM 2024

Antitumor Activity in CPS ≥1 Subgroup at Final Analysis

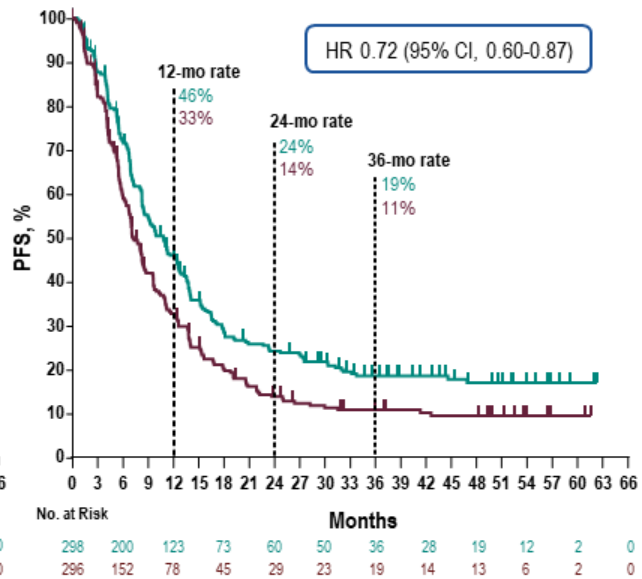
OS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	226 (76%)	20.1 (17.9-22.9)
Placebo group	244 (82%)	15.7 (13.5-18.5)



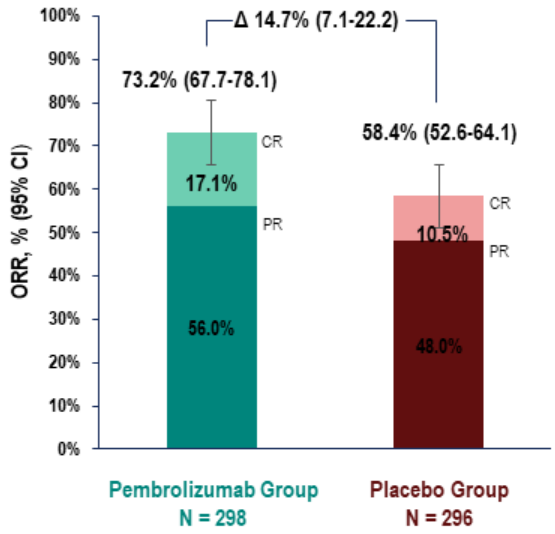
PFS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	221 (74%)	10.9 (8.5-12.5)
Placebo group	226 (76%)	7.3 (6.8-8.4)



ORR and DOR

	Responders, n	Median DOR (range), mo
Pembrolizumab group	218	11.3 (1.1+ -to 60.8+)
Placebo group	173	9.5 (1.4+ to 60.5+)

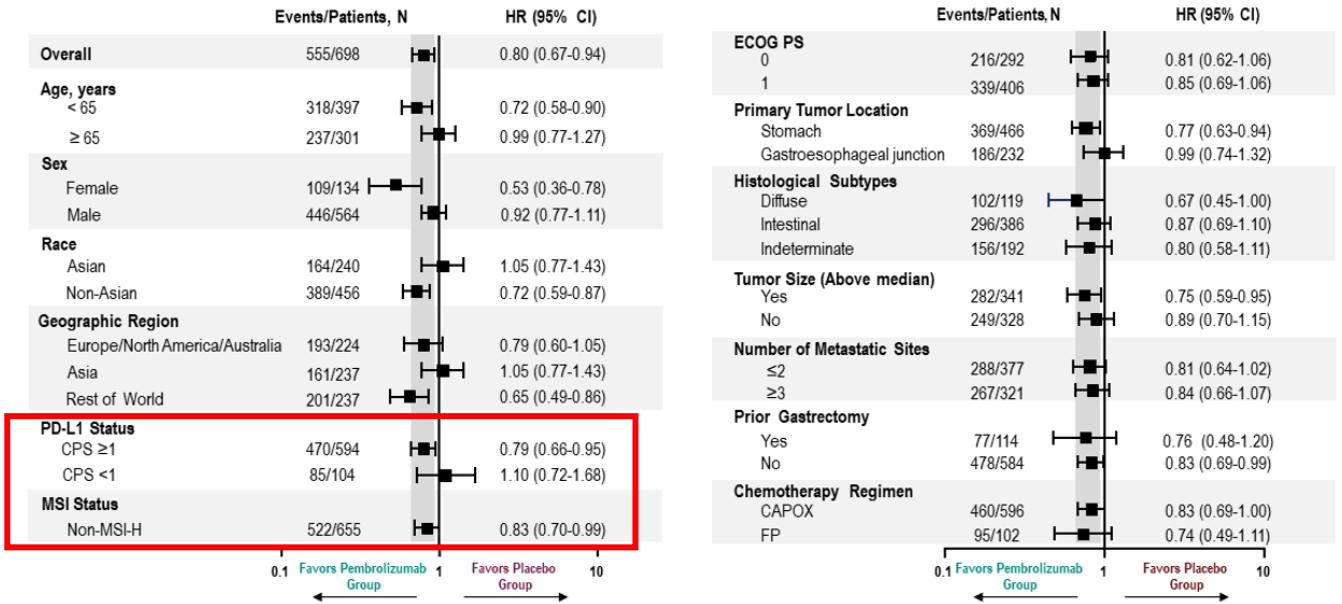


Data cutoff date: 20 Mar 2024. DOR, duration of response.

Lonardi/Janjigian ESMO 2024; Janjigian NEJM 2024

KEYNOTE 811: Final analysis

Overall Survival in Key Subgroups at Final Analysis (ITT)



Lonardi/Janjigian ESMO 2024; Janjigian NEJM 2024

KEYNOTE 811: CONCLUSIONS

- KEYNOTE-811 met pre-specified criteria (ORR, PFS, OS)

- Pembrolizumab received the EMA approval for **HER2-positive G/GEJ** adenocarcinoma with **PDL1 CPS ≥ 1**

The best in 2024 about…

Biliary Tract Cancer

Refractory setting

- Two studies for the HER2-positive population

FDA Approved

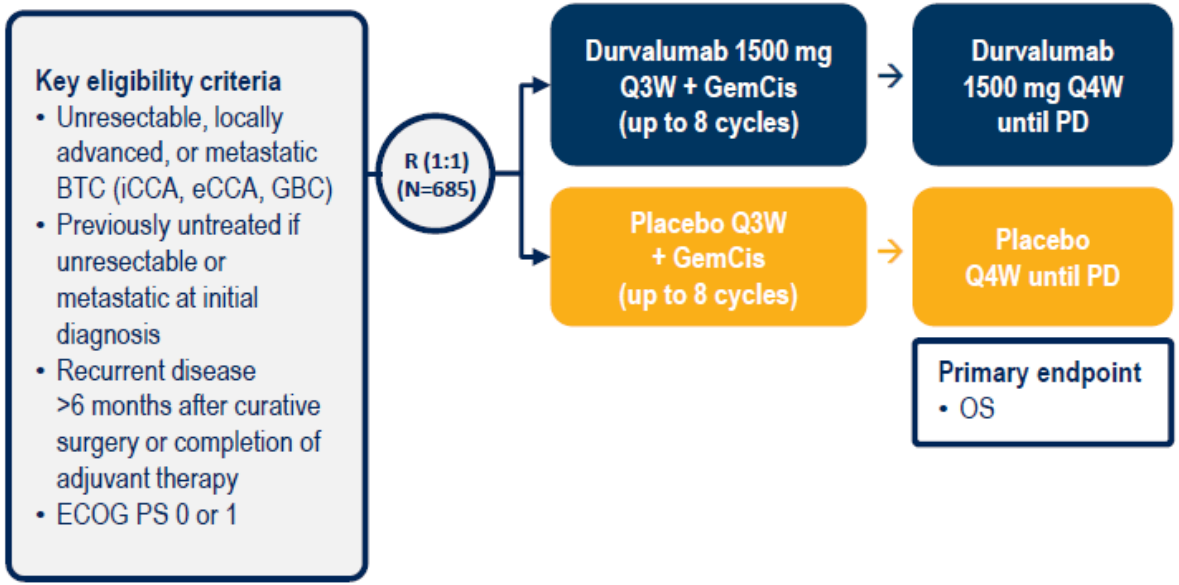
  - HERIZON-BTC-02: Ph2b Zanidatamab in the refractory setting (OS results)
  - HERB: Ph2 Trastuzumab deruxtecan in the refractory setting (Japan)

First-line setting

- TOPAZ-1 (3y FUP): POSITIVE → Change in SoC
- KEYNOTE-966 (3y FUP): POSITIVE → Change in SoC

Shubham Pant ASCO 2024
Ohba ASCO 2022; Ohba J Clin Oncol 2024
Oh ESMO GI 2024; Oh Lancet Gastrointestinal Hepatology 2024
Finn ASCO 2024

TOPAZ-1: Update OS (3y FUP)

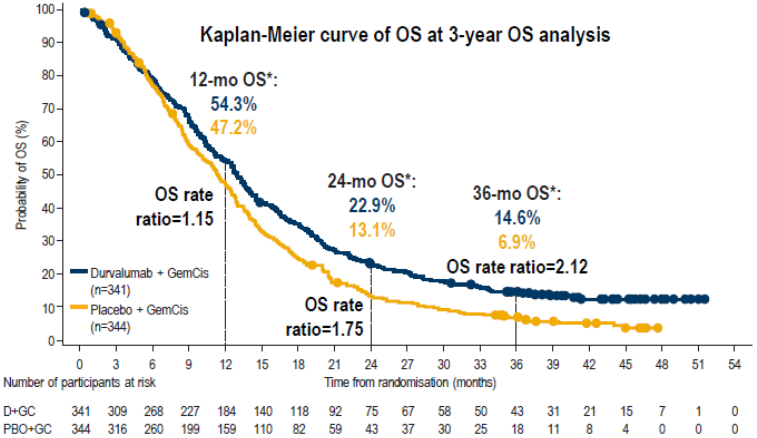


Oh ESMO GI 2024; Oh Lancet Gastrointestinal Hepatology 2024

TOPAZ-1: Update OS (3y FUP)

TOPAZ-1: 3-YEAR OS UPDATE

OS benefit with durvalumab + GemCis continued at the updated DCO



	Primary analysis[1,†] DCO: 11 Aug 2021		3-year OS analysis[‡] DCO: 23 Oct 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)	

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

Oh ESMO GI 2024; Oh Lancet Gastrointestinal Hepatology 2024

TOPAZ-1: Update OS (3y FUP)

SAFETY UPDATE

No meaningful changes in SAEs and treatment-related SAEs from previous analysis

- 13 participants in the durvalumab + GemCis arm and 0 in the placebo + GemCis arm remained on study treatment at the 3-year OS analysis
- Median duration of treatment was longer in the eLTS durvalumab + GemCis subgroup than the durvalumab + GemCis group of the FAS at the 3-year OS analysis (17.8 vs 7.3 months)

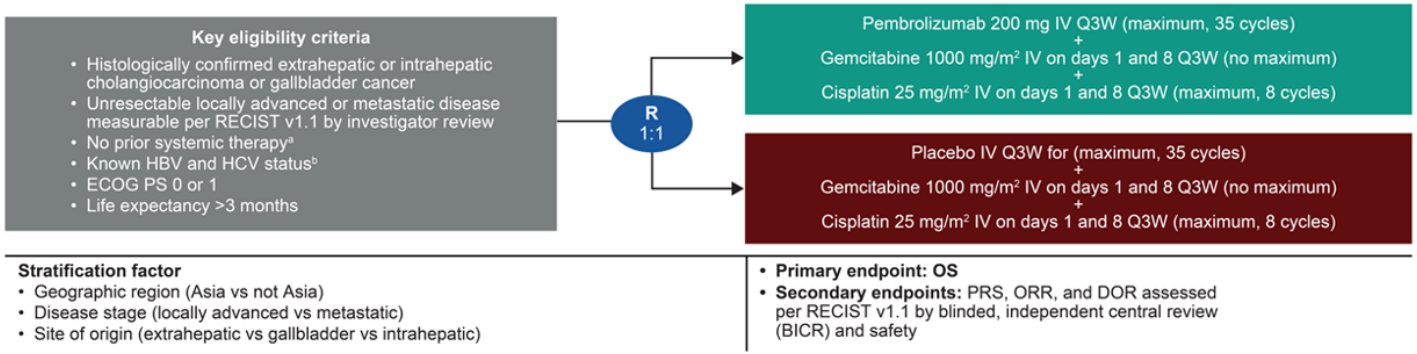
	90-day safety update (DCO: 25 Feb 2022)		3-year OS analysis (DCO: 23 Oct 2023)		eLTS (DCO: 23 Oct 2023)	
	D+GC n=338	PBO+GC n=342	D+GC n=338	PBO+GC n=342	D+GC n=58	PBO+GC n=30
SAEs, n (%)	**161 (47.6)**	**151 (44.2)**	**165 (48.8)**	**152 (44.4)**	**19 (32.8)**	**11 (36.7)**
Any SAE possibly related to study treatment, n (%)	52 (15.4)	59 (17.3)	52 (15.4)	59 (17.3)	5 (8.6)	3 (10.0)
Discontinued D / PBO due to AE, n (%)	**20 (5.9)**	**18 (5.3)**	**21 (6.2)**	**18 (5.3)**	**3 (5.2)**	**1 (3.3)**
Median (range) duration of D / PBO treatment, months	7.3 (0.1–31.0)	5.8 (0.2–26.6)	7.3 (0.1–50.9)	5.8 (0.2–28.4)	17.8 (3.4–50.9)	10.5 (2.2–28.4)

Despite a longer duration of exposure, the eLTS SAEs were comparable between arms and less frequent than in the FAS at the 3-year OS analysis

Oh ESMO GI 2024; Oh Lancet Gastrointestinal Hepatology 2024

KEYNOTE-966: Update OS (3y FUP)

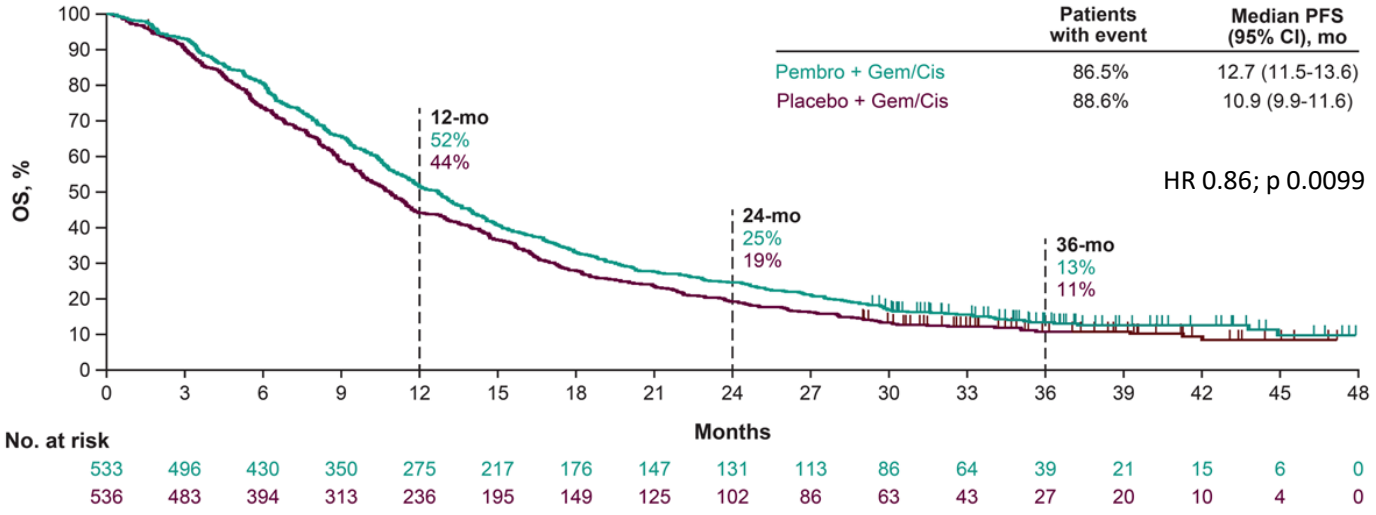
Study Design for KEYNOTE-966 (NCT04003636)



KEYNOTE-966: Update OS (3y FUP)

Finn MK-3475 KN966 ASCO 2024

Overall Survival

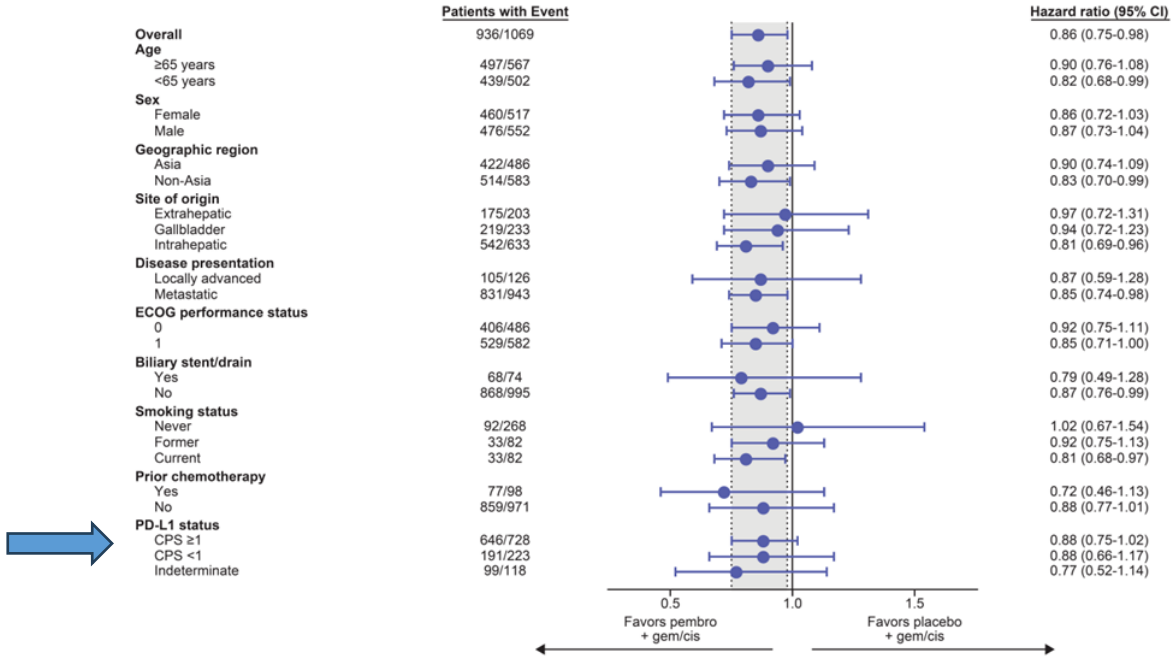


Finn ASCO 2024

KEYNOTE-966: Update OS (3y FUP)

Finn MK-3475 KN966 ASCO 2024

Overall Survival in Prespecified Subgroups



Finn ASCO 2024

KEYNOTE-966: Update OS (3y FUP)

Finn MK-3475 KN966 ASCO 2024

Adverse Event Summary

	Pembro + Gem/Cis (n = 529)	Placebo + Gem/Cis (n = 534)
Any	524 (99.1%)	532 (99.6%)
Treatment-related	493 (93.2%)	500 (93.6%)
Grade 3-4 as maximum grade	420 (79.4%)	399 (74.7%)
Treatment-related	370 (69.9%)	367 (68.7%)
Led to death	31 (5.9%)	50 (9.4%)
Treatment-related	8 (1.5%)[a]	3 (0.6%)[b]
Led to discontinuation of ≥1 study medication	140 (26.5%)	124 (23.2%)
Treatment-related	103 (19.5%)	82 (15.4%)
Led to discontinuation of all study medication	35 (6.6%)	39 (7.3%)
Treatment-related	18 (3.4%)	14 (2.6%)

[a]Adverse events leading to death (n = 1 each): abdominal abscess, cholangitis, lower respiratory tract infection, malignant neoplasm progression, myocardial infarction, pneumonitis, septic shock, and viral pneumonia.
[b]Adverse events leading to death (n = 1 each): hepatorenal syndrome, sepsis, and upper gastrointestinal hemorrhage.

Finn ASCO 2024

The best in 2024 about…

Pancreatic adenocarcinoma

First-line setting

- OPTIMIZE-1: Phase 1b/2 mFOLFIRINOX + mitazalimab (CD40 agonist): Primary analyses

Refractory setting

- RMC-6236: Phase 1 → first pan-RASi that shows efficacy in PDAC

Van Laethem ASCO 2024; Van Laethem Lancet Oncol 2024

Garrido-Laguna ASCO GI 2025

The best in 2024 about…

Hepatocarcinoma

Unresectable – first line

- Ph3 HIMALAYA (5y FUP): Treme-durva better than sorafenib, consequent with prior data
- Checkmate 9DW (first interim analysis; OS): ipi-nivo better than lenva or sora

Unresectable – intermediate stage: 2 phase 3 trials demonstrating the value of TACE + IO

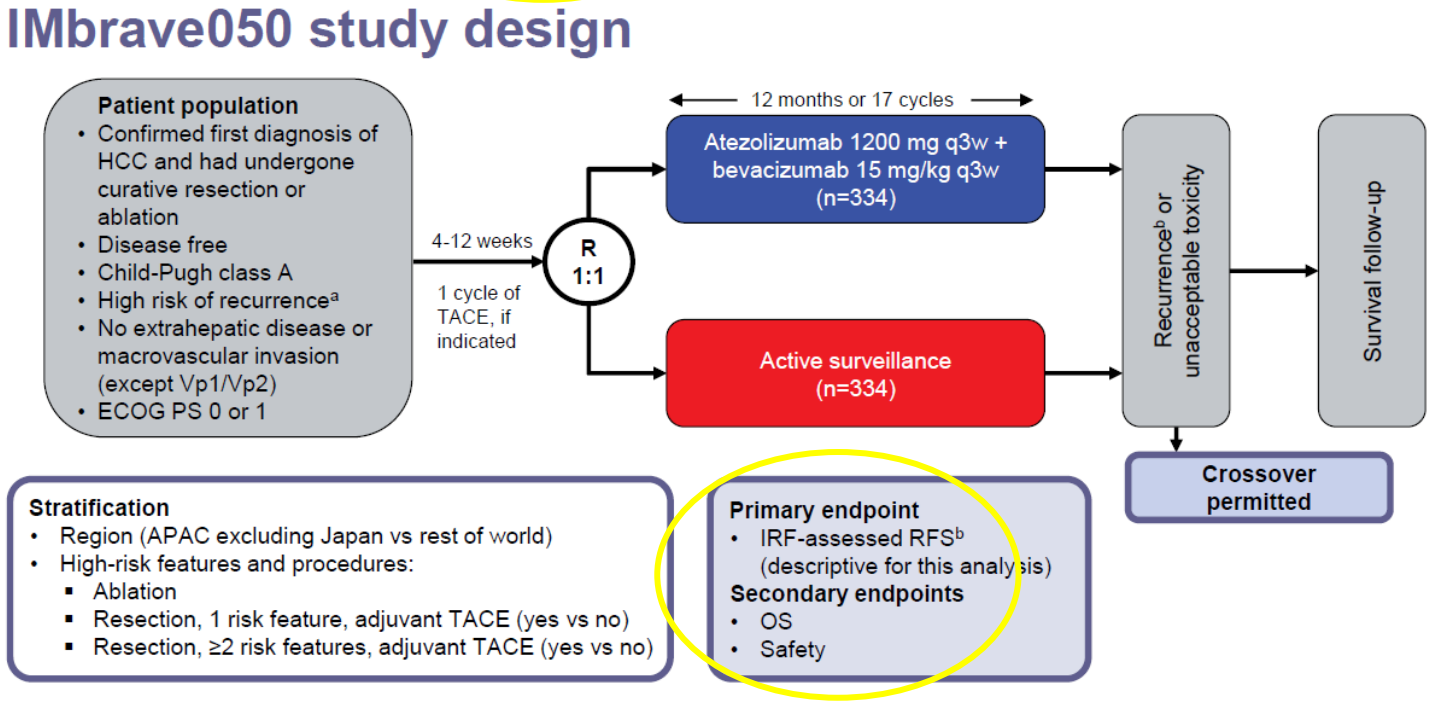
- Ph3 LEAP-012: TACE/lenva/pembro vs. TACE/pbo/pbo
  - TACE/lenva/prembro improved mPFS over TACE/pbo/pbo (14.6 vs 10mo (HR 0.66; p 0.0002))
- Ph3 EMERALD 1: TACE/durva/beva vs. TACE/durva vs. TACE
  - TACE/durva/beva improved mPFS over TACE (mPFS 15.0 vs 8.2mo (HR 0.77; p 0.032))

High-risk after resection/ablation: 1 phase 3 trial, first to discharge adjuvant IO

- IMbrave050 (updated with RFS and OS): Adjuvant atezo/beva → NEGATIVE

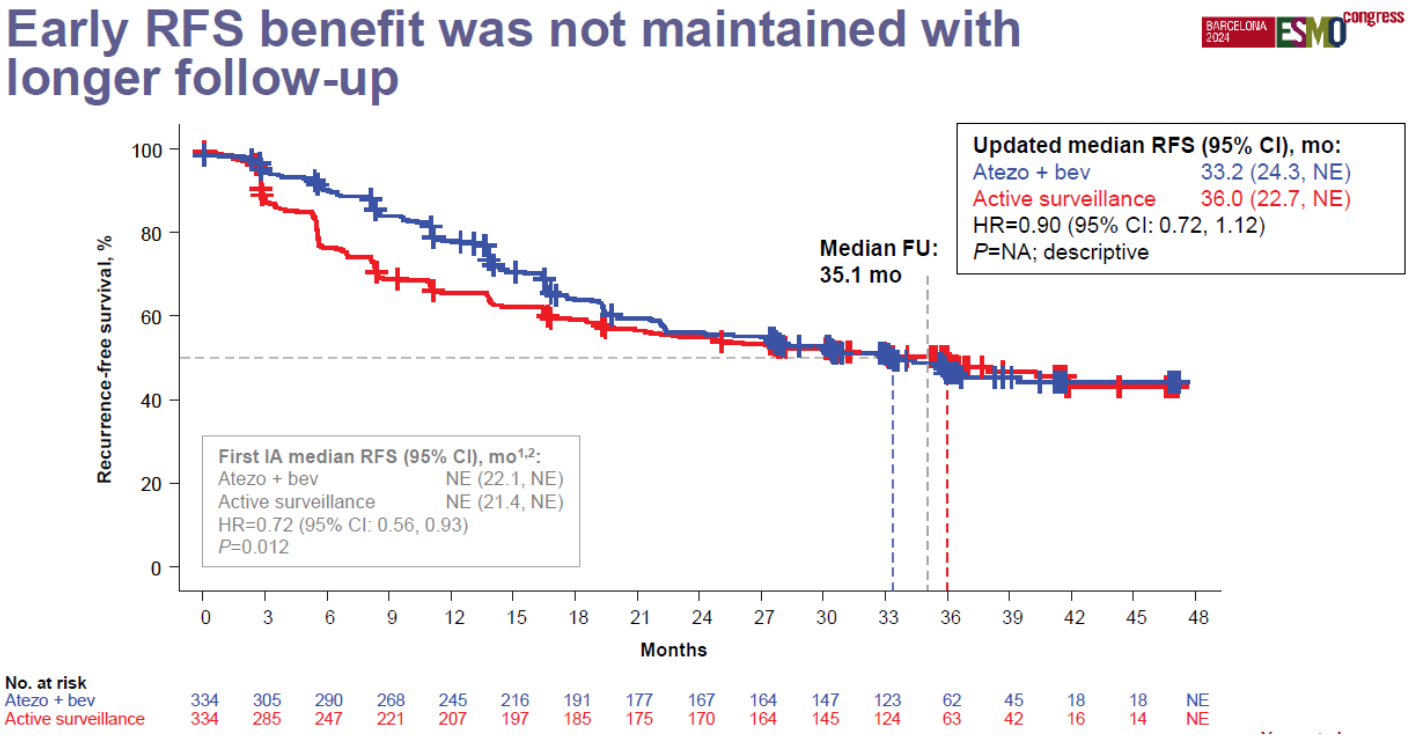
Rimassa ESMO 2024
Galle ASCO 2024
Llovet ESMO 2024
Lencioni ASCO GI 2024
Yopp ESMO 2024; Qin Lancet 2023

IMbrave050: Updated analysis with mature OS



[a]High-risk features include: tumour>5 cm, >3 tumours, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

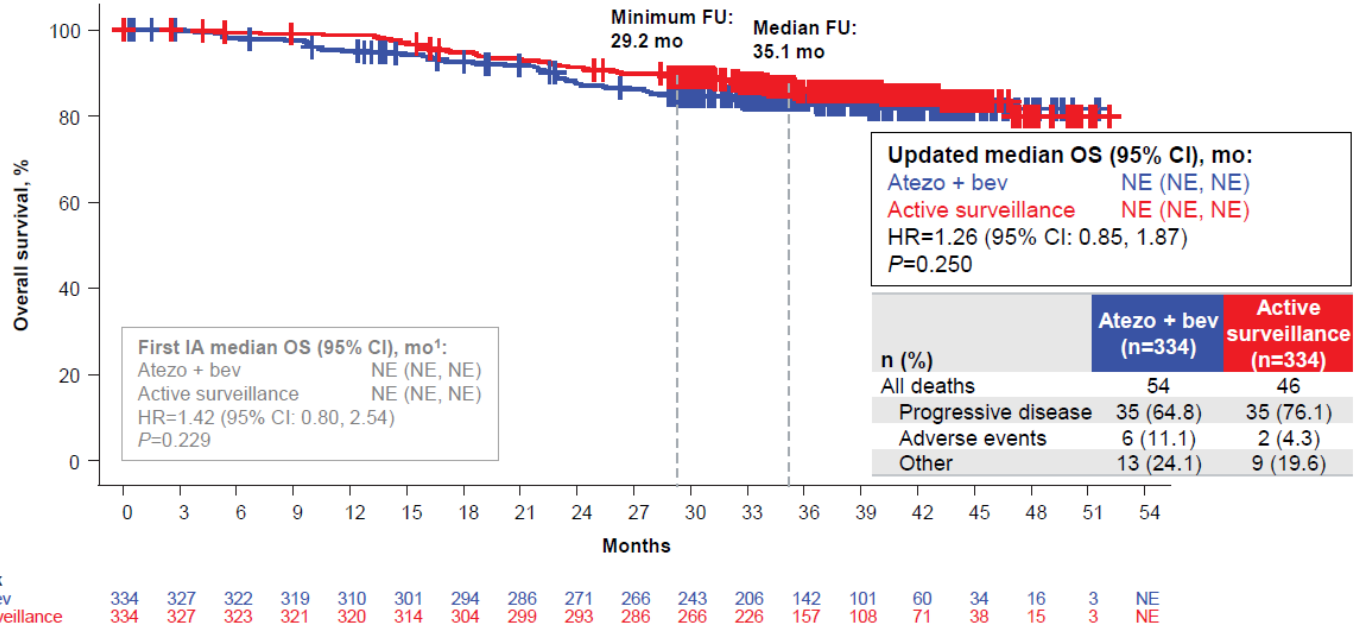
IMbrave050: Updated analysis with mature OS



Yopp ESMO 2024

IMbrave050: Updated analysis with mature OS

Updated OS remained immature but showed numerical improvement from the first IA



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	54	46
Progressive disease	35 (64.8)	35 (76.1)
Adverse events	6 (11.1)	2 (4.3)
Other	13 (24.1)	9 (19.6)

Yopp ESMO 2024

Conclusions: Practice changing studies

- **Gastroesophageal adenocarcinoma**
  - FLOT is the preferred perioperative option (ESOPEC & TOPGEAR)
  - Pembro + trastu + chemo in 1st line of HER2-positive PDL1 CPS-positive
- **Biliary tract cancer**
  - 1st line with Cis/Gem + durva (TOPAZ-1) or pembro (KN-966)
  - Zanidatamab and T-Dxd potential new options for HER2-positive
- **Pancreatic adenocarcinoma**
  - RASmt PDAC will be probably targetable in the future
- **Hepatocellular carcinoma**
  - Adjuvant IO don't work
  - TACE +/- IO/beva as new potential options for the intermediate stage
  - 1st line approaches with durva-treme (HIMALAYA) and nivo-ipi (CM9WD), as the "old" atezo/beva (IMbrave150)

Muchas gracias

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