AstraZeneca

Investor science conference call: American Society of Clinical Oncology Gastrointestinal (ASCO GI) Cancers Symposium 2022

Conference call for investors and analysts

24 January 2022

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Speakers

Dr Bruno Sangro
Investigator, HIMALAYA and Professor – Head Liver Unit and HPB Oncology Area, Clinica Universidad de Navarra

Dr Arndt Vogel
Steering Committee member, TOPAZ-1 and Professor - Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School

Susan Galbraith
Executive Vice President, Oncology Research and Development

Dave Fredrickson
Executive Vice President, Oncology Business Unit

Cristian Massacesi
Chief Medical Officer & Oncology Chief Development Officer (for Q&A)

Niko Andre
Global Franchise Head, Immuno-Oncology and Haematology (for Q&A)

Agenda

1. Introduction: AstraZeneca @ ASCO GI 2022
2. *Imfinzi* Phase III TOPAZ-1 trial
3. *Imfinzi* + tremelimumab Phase III HIMALAYA trial
4. Commercial opportunity
5. What's next for AstraZeneca in GI?
6. Closing and Q&A

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Introduction

Susan Galbraith

Executive Vice President,
Oncology R&D

Comprehensive portfolio to combat cancer

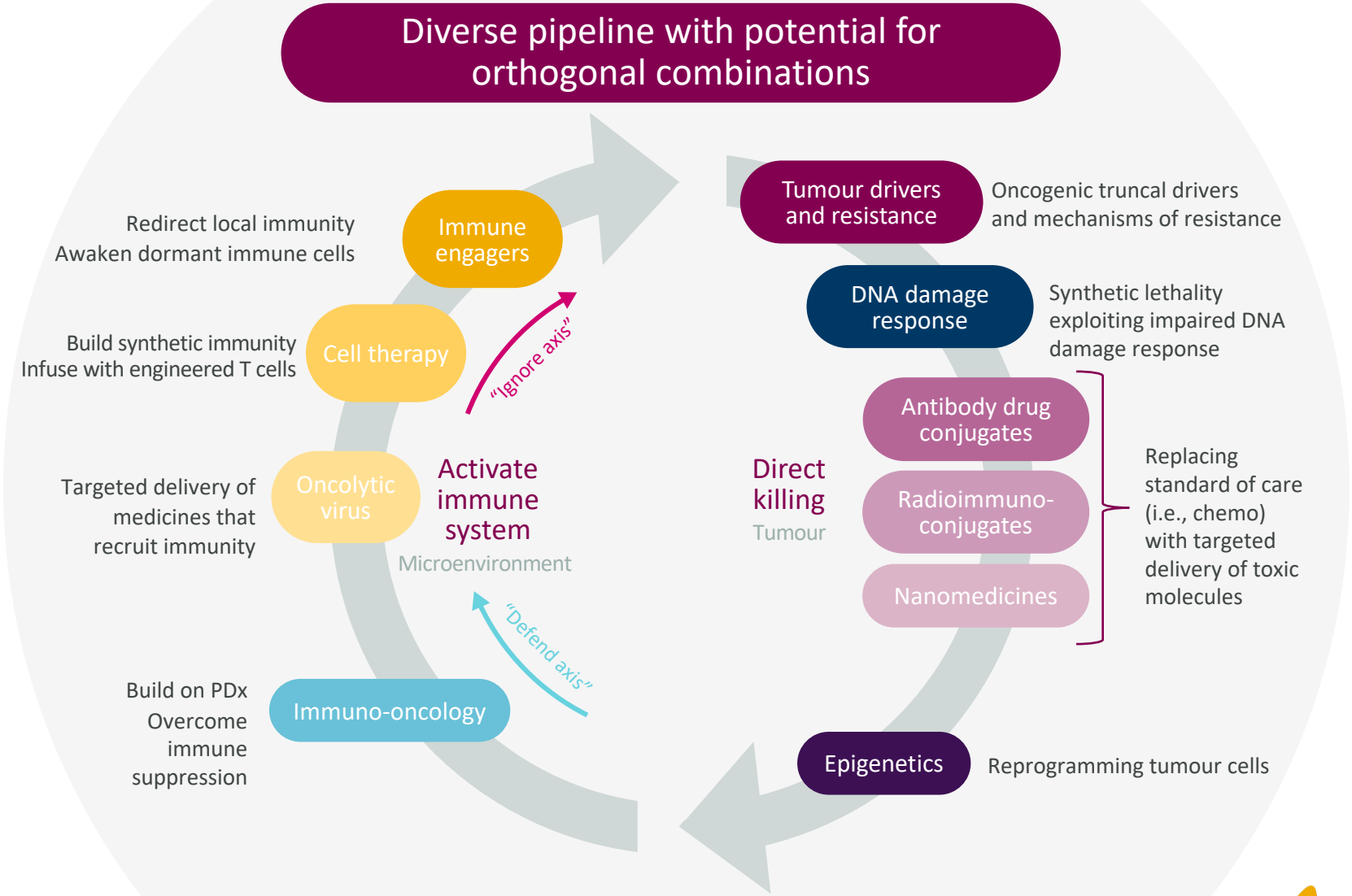
ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

IMFINZI®
durvalumab
Injection for Intravenous Use 50 mg/mL

Lynparza™
olaparib

TAGRISSO®
osimertinib

CALQUENCE®
(acalabrutinib) 100 mg capsules



Source: AstraZeneca.

ASCO GI 2022

ASCO® Gastrointestinal Cancers Symposium

21 abstracts with Four oral presentations

- **Two** Proffered paper oral presentations (late breakers)
- **Two** Mini oral presentations
- **17** Posters
- **21** Abstracts

Data highlights

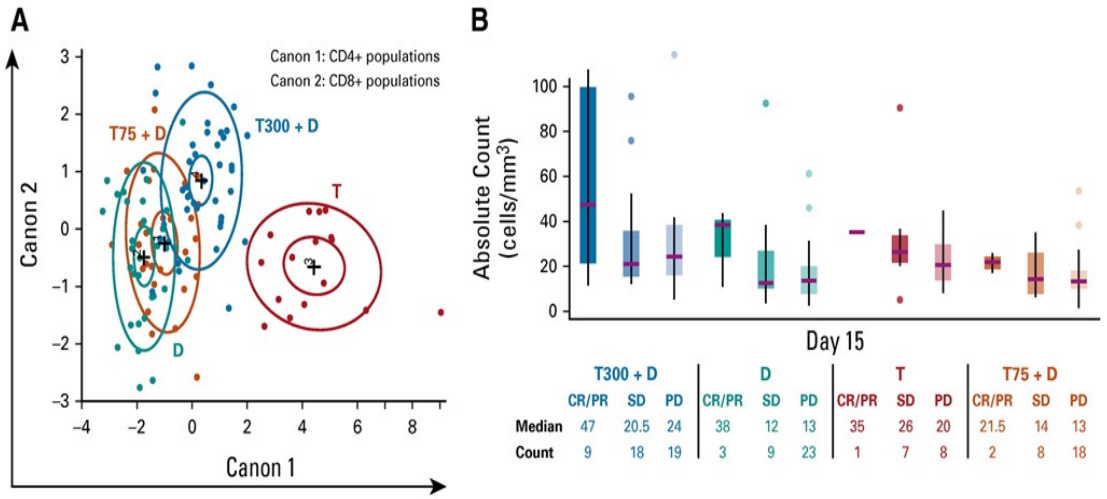
- ***Imfinzi* +/- tremelimumab in HCC**
  HIMALAYA
  Study 22
- ***Imfinzi* in BTC**
  TOPAZ-1
- ***Enhertu***
  DESTINY-Gastric01, DESTINY-Gastric03, DESTINY-CRC01

Source: ASCO GI 2022 accepted abstracts. Inclusive of externally sponsored research and partner-led trials. HCC = hepatocellular carcinoma; BTC = biliary tract cancer; CRC = colorectal cancer.

Imfinzi and tremelimumab

Phase II data in gastrointestinal cancers informed TOPAZ-1 and HIMALAYA designs

Study 22[1] HCC T-cell proliferation data



- 322 patients with advanced hepatocellular carcinoma randomised between arms

Median OS: T300+D - 18.7-mo; *Imfinzi* - 13.6-mo

Phase II trial in biliary tract cancer

- 121 patients enrolled with 1st-line biliary tract cancer
- *Imfinzi* (+/- tremelimumab) in combination with gemcitabine and cisplatin
- Combination was well tolerated

Median OS: 18.1-mo for *Imfinzi* + gem/cis

1. Kelley et al *J Clin Oncol* 39, 27: 2021 2991-3001 2. D-Y Oh et al ASCO 2020 *J Clin Oncol* 38, 15 suppl: 2020 4520. OS = overall survival; T300 = tremelimumab 300mg; mo = months; gem - = gemcitabine; cis = cisplatin

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Imfinzi TOPAZ-1

Dr Arndt Vogel

Steering Committee Member,
TOPAZ-1 Phase III trial

TOPAZ-1 trial design

A double-blind, multicentre, global, Phase III trial

Key eligibility

- Locally advanced or metastatic BTC (ICC, ECC, 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 tumor 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 objective

- Overall survival

Secondary objectives

- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

Patient demographics and baseline characteristics

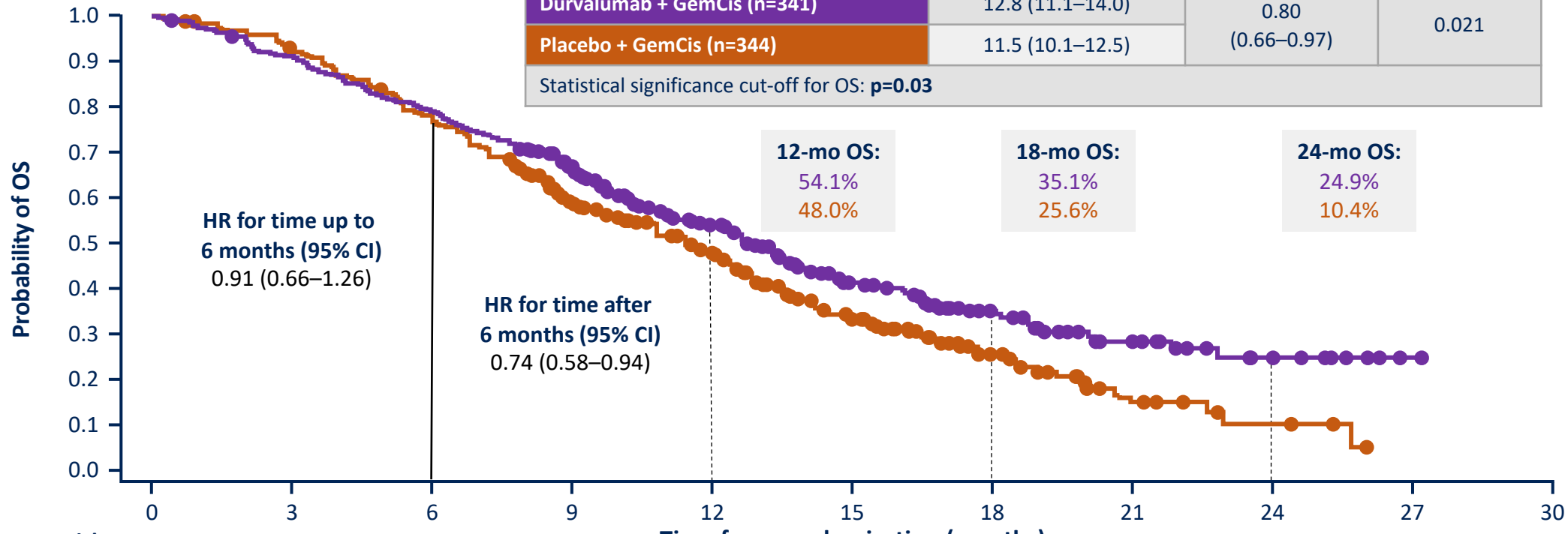
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	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)

**Data missing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Overall survival

	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**			



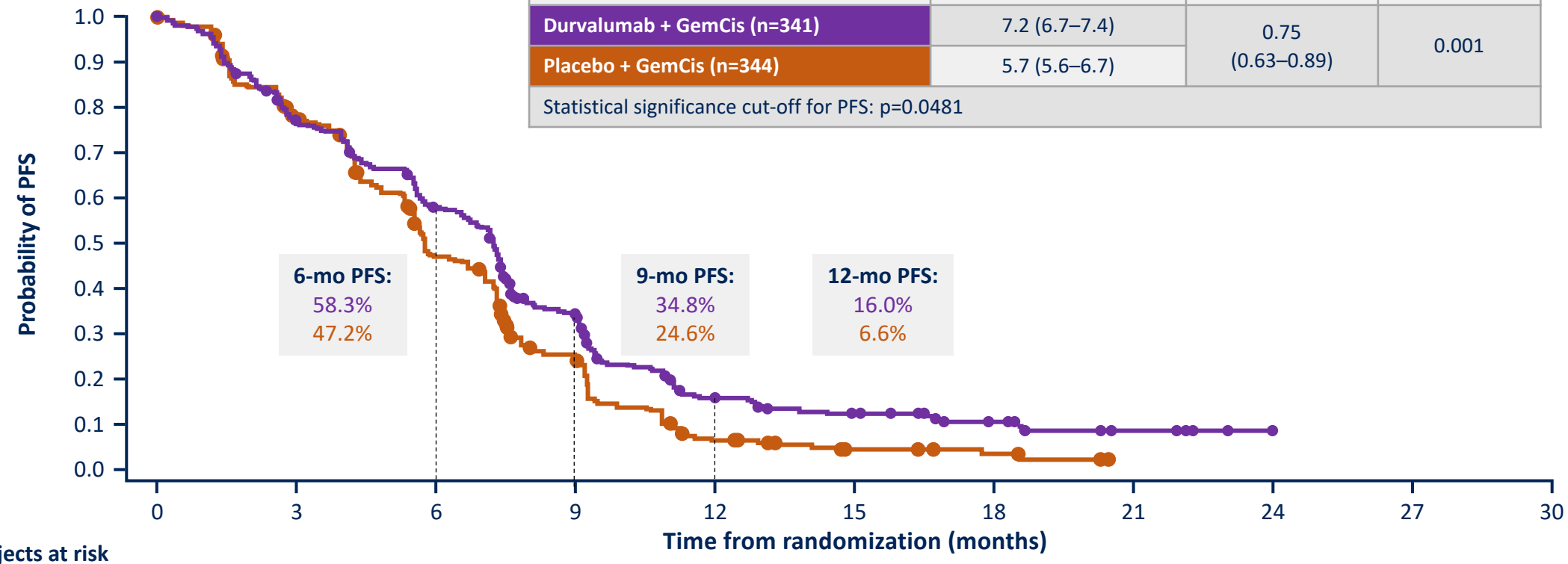
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

12 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.

Progression free survival

	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			

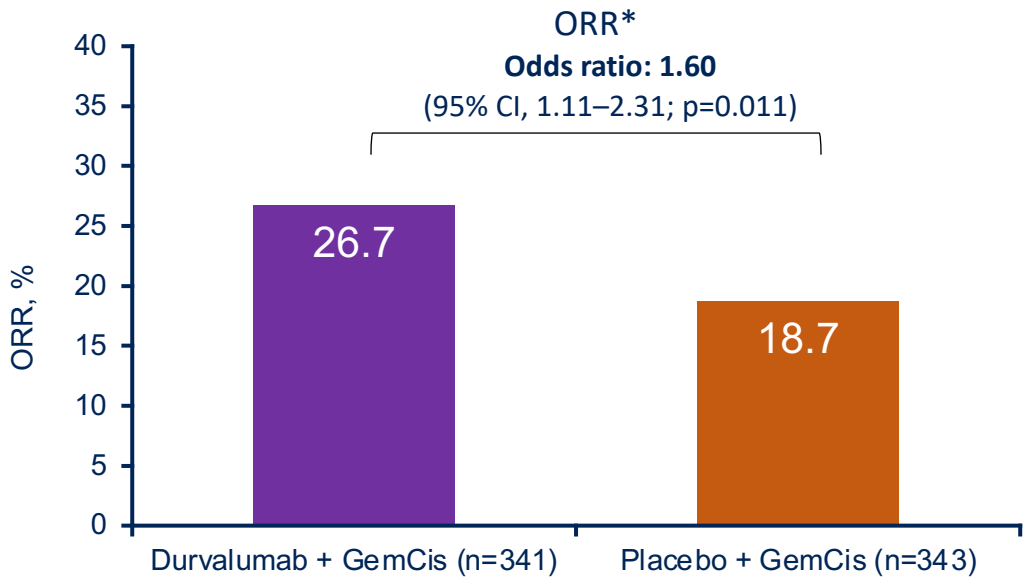


Number of subjects at risk									
Durvalumab + GemCis	341	258	189	100	38	25	15	5	0
Placebo + GemCis	344	255	149	71	17	7	4	0	0

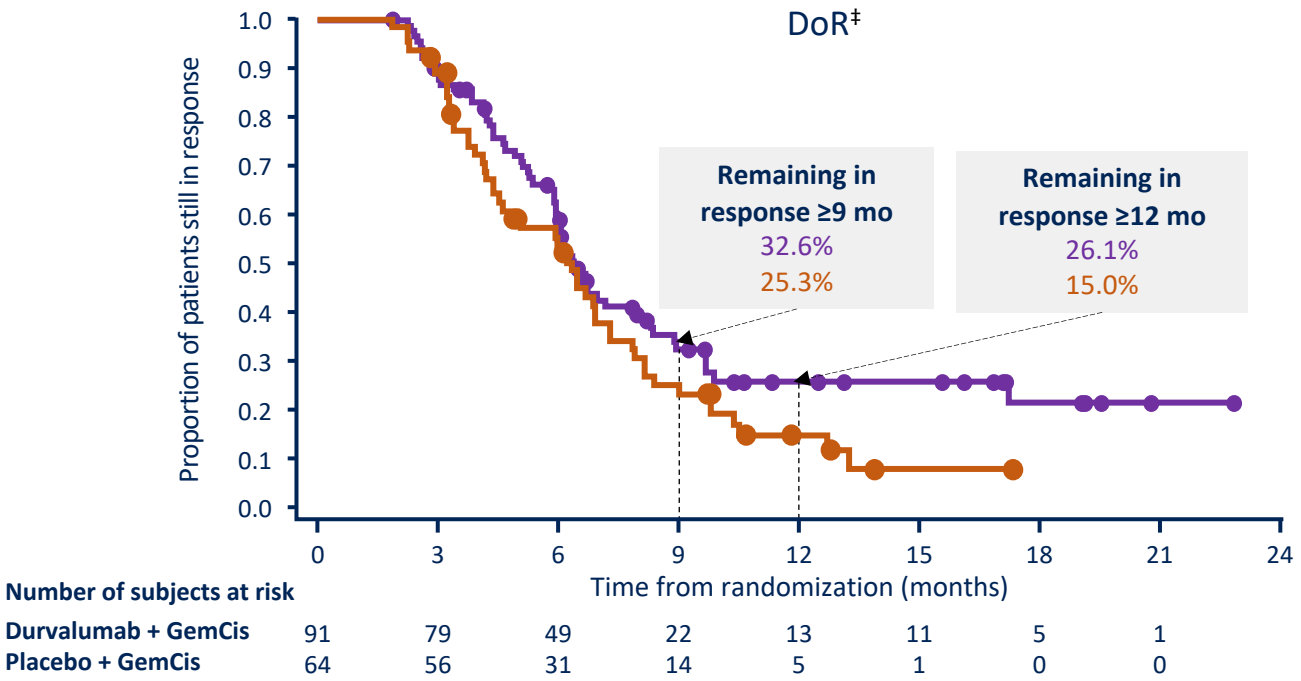
Median duration of follow-up (95% CI) was 9.2 (0.0–24.0) months with durvalumab + GemCis and 6.9 (0.0–20.4) months with placebo + GemCis.

CI, confidence interval; GemCis, gemcitabine and cisplatin; PFS, progression-free survival.

Tumour 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)

*By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. †Analysis of DCR was based on all patients in the full analysis set. ‡Analysis of DoR was based on patients in the full analysis set who had an objective response and measurable disease at baseline.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; GemCis, gemcitabine and cisplatin; mo, month; ORR, objective response rate; PR, partial response.

Summary of adverse events and treatment exposure

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median duration of exposure (range), months Durvalumab/placebo Gemcitabine Cisplatin	 7.33 (0.1–24.5) 5.19 (0.1–8.3) 5.13 (0.1–8.3)	 5.77 (0.2–21.5) 5.03 (0.2–8.6) 4.88 (0.2–8.5)
Event, n (%)		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)	308 (90.1)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)
Any serious AE	160 (47.3)	149 (43.6)
Any serious TRAE	53 (15.7)	59 (17.3)
Any AE leading to discontinuation	44 (13.0)	52 (15.2)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any AE leading to death	12 (3.6)	14 (4.1)
Any TRAE leading to death	2 (0.6)	1 (0.3)
Any immune-mediated AE	43 (12.7)	16 (4.7)

Conclusions

- TOPAZ-1 is the first global Phase III trial to report positive results testing immunotherapy plus chemotherapy as first-line treatment for advanced BTC
- TOPAZ-1 met its primary endpoint at the prespecified interim analysis: durvalumab plus GemCis demonstrated statistically significant and clinically meaningful prolonged overall survival compared with placebo plus GemCis
- Durvalumab did not add additional toxicity to that observed with GemCis, and no new safety signals were identified from the known safety profiles of each individual treatment

Durvalumab plus GemCis is an effective first-line therapy, and could become a new standard of care, for patients with advanced BTC

BTC, biliary tract cancer; GemCis, gemcitabine and cisplatin.

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Imfinzi + tremelimumab HIMALAYA

Dr Bruno Sangro

Principal Investigator,
HIMALAYA Phase III trial

HIMALAYA trial design

HIMALAYA was an open-label, multicenter, global, Phase III trial

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for locoregional therapy) and C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Macrovascular invasion: Y / N
- Etiology of liver disease: HBV / HCV / others
- Performance status: ECOG 0 / 1

R
N=1324

T300+D (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed* †
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST v1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

↓

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

OS *superiority* for durvalumab vs sorafenib

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

Baseline characteristics

Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Male sex, n (%)	327 (83.2)	323 (83.0)	337 (86.6)
Median age (range), years	65.0 (22–86)	64.0 (20–86)	64.0 (18–88)
Region, n (%) Asia (excluding Japan) Rest of world (including Japan)	 156 (39.7) 237 (60.3)	 167 (42.9) 222 (57.1)	 156 (40.1) 233 (59.9)
Viral etiology,*,† n (%) HBV HCV Nonviral	 122 (31.0) 110 (28.0) 161 (41.0)	 119 (30.6) 107 (27.5) 163 (41.9)	 119 (30.6) 104 (26.7) 166 (42.7)
ECOG PS, n (%) 0 1	 244 (62.1) 148 (37.7)	 237 (60.9) 150 (38.6)	 241 (62.0) 147 (37.8)
BCLC,† n (%) B C	 77 (19.6) 316 (80.4)	 80 (20.6) 309 (79.4)	 66 (17.0) 323 (83.0)

Characteristic	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Child-Pugh classification,† n (%) A B Missing	 392 (99.7) 0 1 (0.3)	 388 (99.7) 1 (0.3) 0	 386 (99.2) 3 (0.8) 0
ALBI grade, n (%) 1 2 3	 217 (55.2) 174 (44.3) 1 (0.3)	 198 (50.9) 189 (48.6) 2 (0.5)	 203 (52.2) 185 (47.6) 1 (0.3)
MVI,† n (%)	103 (26.2)	94 (24.2)	100 (25.7)
EHS,† n (%)	209 (53.2)	212 (54.5)	203 (52.2)
PD-L1 positive,‡ n (%)	148 (37.7)	154 (39.6)	148 (38.0)
AFP ≥400 ng/ml,† n (%)	145 (36.9)	137 (35.2)	124 (31.9)

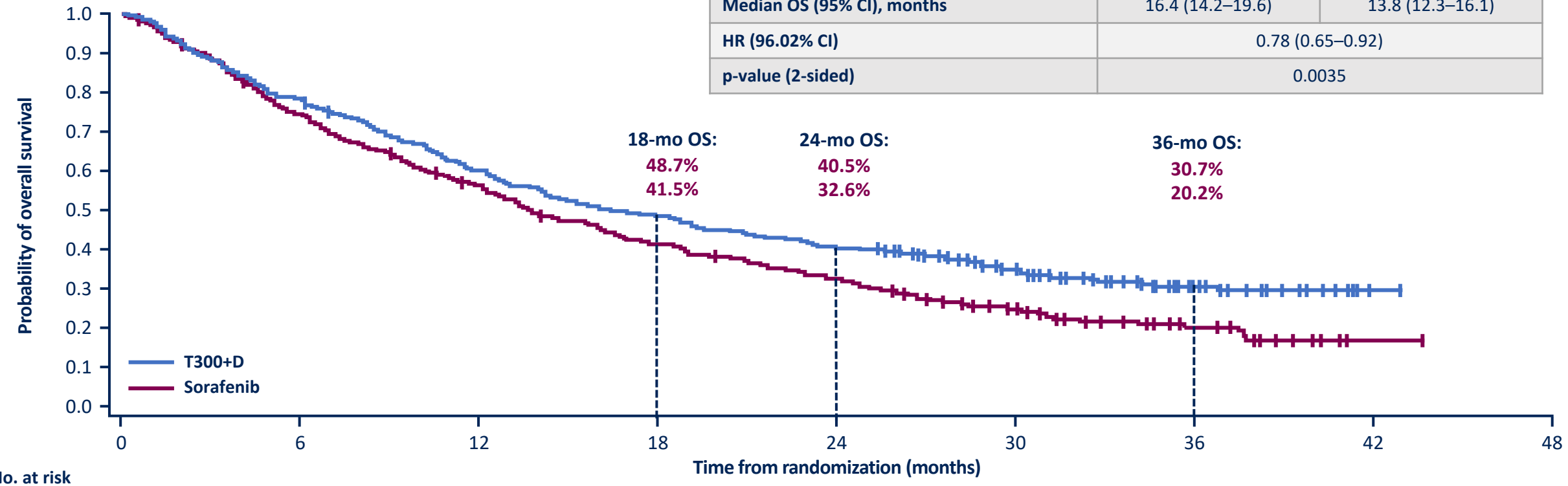
*HBV: patients who tested positive for HBsAg or anti-HBc with detectable HBV DNA; HCV: patients who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified. †Determined at screening. ‡Defined as tumor area positivity score ≥1%.

T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Overall survival

T300+D versus sorafenib

	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk								
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

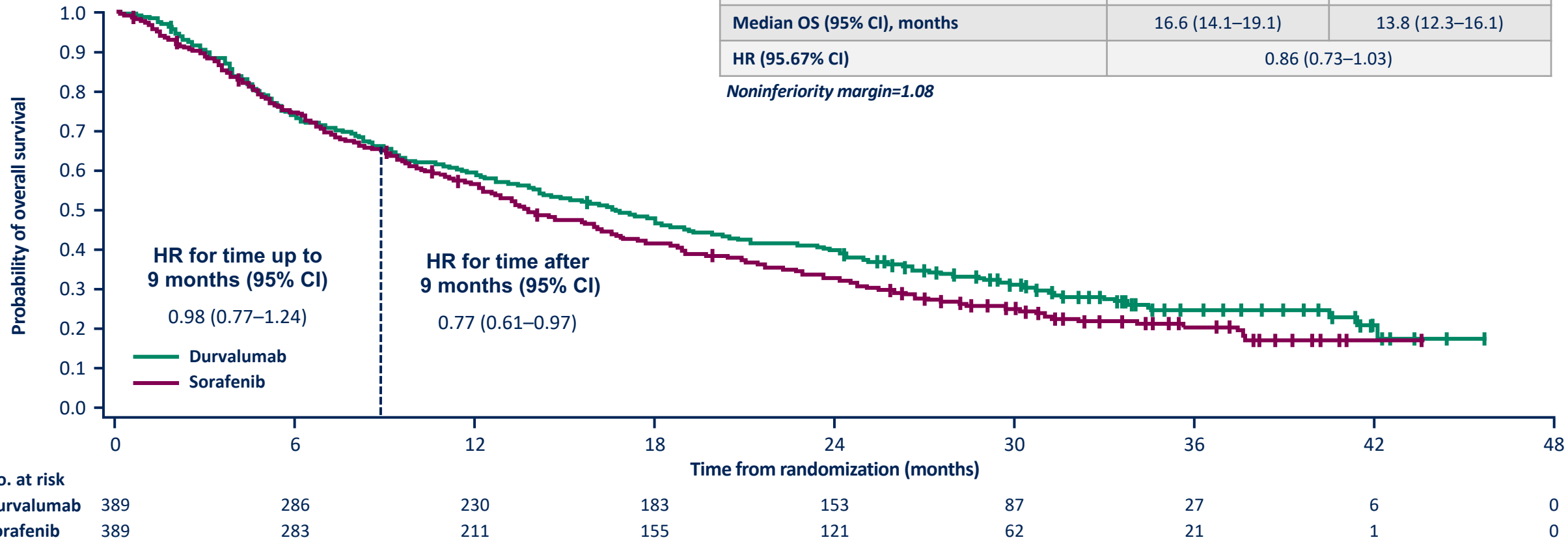
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Overall survival

Durvalumab versus sorafenib

	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08



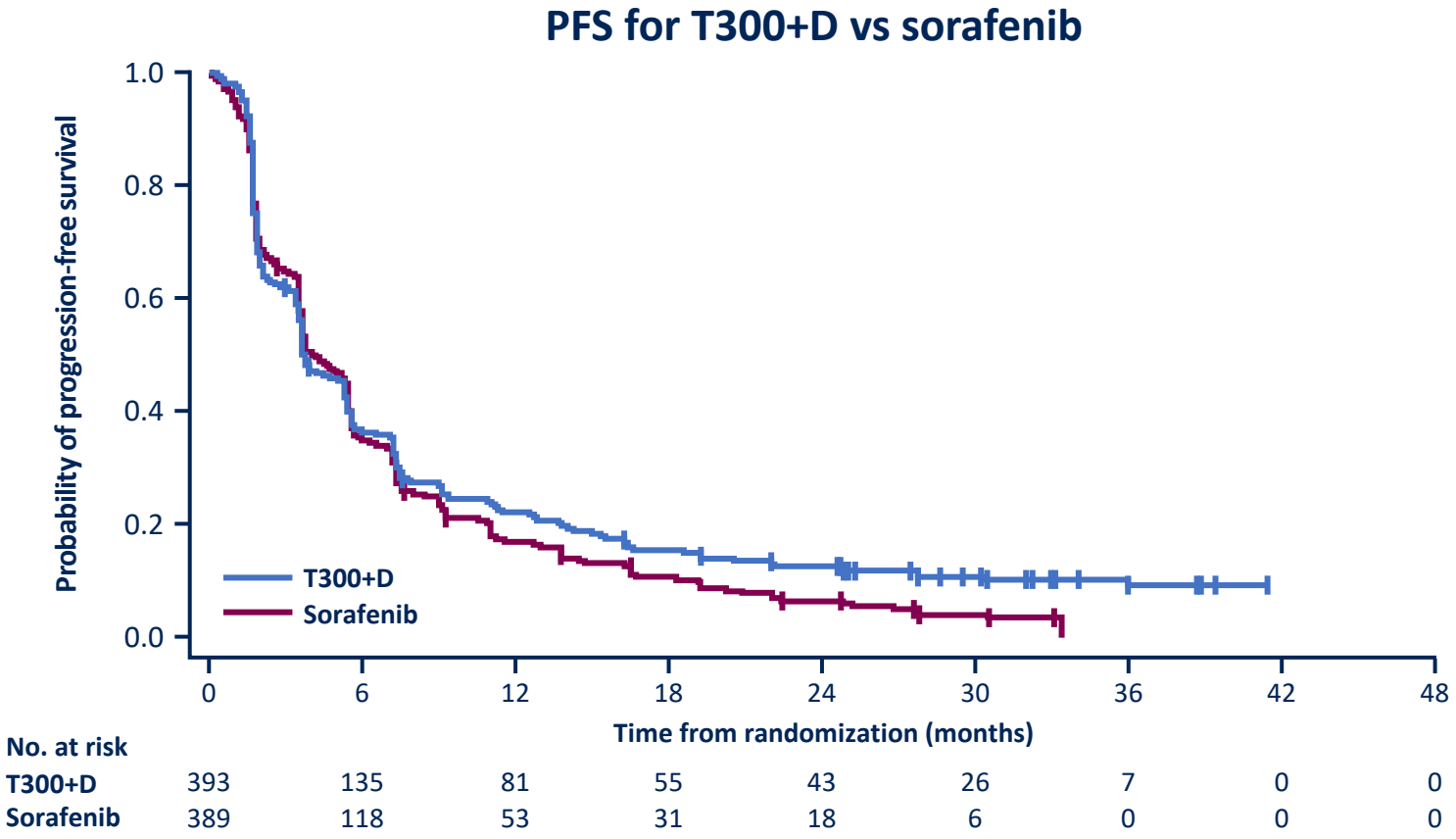
No. at risk								
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival.

Progression free survival

T300+D vs sorafenib



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

**Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.

CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.

Safety and tolerability

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)[†]	0	3 (0.8)[‡]
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.

*Treatment-related was as assessed by investigator. [†]Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1). [‡]Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).

AE, adverse event; SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

Treatment-related hepatic or haemorrhage SMQ events

Event, n (%)	T300+D (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with hepatic SMQ TRAE	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
Patients with hemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)	5 (1.3)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	22 (5.7)	9 (2.3)	25 (6.4)	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	0	0	2 (0.5)	0
Hepatic encephalopathy	0	0	0	0	2 (0.5)	1 (0.3)
International normalized ratio increased	4 (1.0)	1 (0.3)	0	0	0	0
Esophageal varices hemorrhage	0	0	0	0	0	0

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Treatment-related was as assessed by investigator.

SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

Conclusions

- The HIMALAYA study was a large, Phase 3 study that included a global, heterogeneous population, representative of patients with uHCC
- A single priming dose of tremelimumab plus regular interval durvalumab with the STRIDE (T300+D) regimen statistically significantly improved overall survival versus sorafenib
  - Median overall survival was 16.4 months for STRIDE (T300+D) and 13.8 months for sorafenib
  - STRIDE (T300+D) appeared to provide a long-term survival benefit, with a landmark 36-month overall survival of 30.7%
- Overall survival for durvalumab monotherapy was noninferior to sorafenib, with a favorable benefit-risk profile
- Both STRIDE (T300+D) and durvalumab monotherapy had manageable safety profiles, with lower rates of grade 3/4 TRAEs and TRAEs leading to discontinuation than sorafenib and no increase in liver toxicity or bleeding risk

The STRIDE (T300+D) regimen and durvalumab monotherapy may represent new treatment options for patients with uHCC

3

Commercial opportunity

Dave Fredrickson

Executive Vice President,
Oncology Business Unit

TOPAZ-1 has the potential to become the first-ever IO therapy available for first-line, advanced biliary tract cancer patients

Lack of innovation in biliary tract cancer

10+ years
without innovation on top of standard of care

5% to 15%
of all patients with BTC surviving only five years[1]

75%
of BTC patients present with advanced, unresectable BTC[2]

*~ **50,000** people in the US, Europe and Japan and about **210,000** people worldwide are diagnosed with BTC each year[3]*

TOPAZ-1 has practice-changing potential

- Trial stopped early at an interim analysis due to clear efficacy, with almost

1 in 4 patients **alive at two years** versus one in 10 on chemotherapy alone

- Potential new standard of care in this historically underserved cancer

Regulatory submissions in H1 2022

- Safety: no AE-related increase in discontinuations

First IO therapy to demonstrate long-term survival in first-line advanced BTC

1. Turkes F, *et al*. *Gastroenterol Res Pract.* 2019; 2019:7698786. 2. Vienot A and Neuzillet C. *Clin Res Hepatol Gastroenterol.* 2020;44:810-824 3. Siegel R, *et al*. *CA Cancer J Clin.* 2020; 70: 7-30. and Nakachi K, *et al. Japanese Journal of Clinical Oncology*. 2018; 48(4): 392-395. and 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. AE = adverse events.

HIMALAYA – an innovative IO regimen delivering survival benefit to patients with advanced, unresectable hepatocellular carcinoma

Large unmet need in liver cancer

3rd

leading cause of cancer death worldwide[1]

7%

five-year survival in advanced HCC[2]

At least 40%

of treatment eligible first-line advanced HCC patients are at risk of bleeding[3]

*~**80,000** people in the US, Europe and Japan and **260,000** people in China present with advanced, unresectable HCC each year[4]*

Innovative STRIDE regimen with tremelimumab

- First IO+IO combination in first-line advanced, unresectable HCC
- Only Phase III trial to show benefit of single, priming dose of CTLA-4
- Impressive three-year landmark OS data with almost

1 in 3

patients **alive at three years** on STRIDE regimen versus one in five on sorafenib

Clear efficacy, safety and simplicity for patients

- *Imfinzi* monotherapy non-inferior to sorafenib, with numerical advantage in OS
- No increased bleeding risk or severe liver toxicity seen in trials
- Exceptional safety profile

Regulatory submissions in H1 2022

IO-only combination strategy simplifies patient management

1. ASCO. Liver Cancer: Accessed January 2022. 2. Sayiner M, et al. *Digestive Diseases and Sciences. 2019; 64: 910-917.* 3. Boregowda et al. *World J Gastrointest Pharmacol Ther*. 2019 Jan 21; 10(1): 1–21. 4. AstraZeneca data on file. Kantar Health. 2021. STRIDE = single tremelimumab regular interval durvalumab; IO = immuno-oncology; CTLA-4 = cytotoxic T-lymphocyte associated protein 4.

4

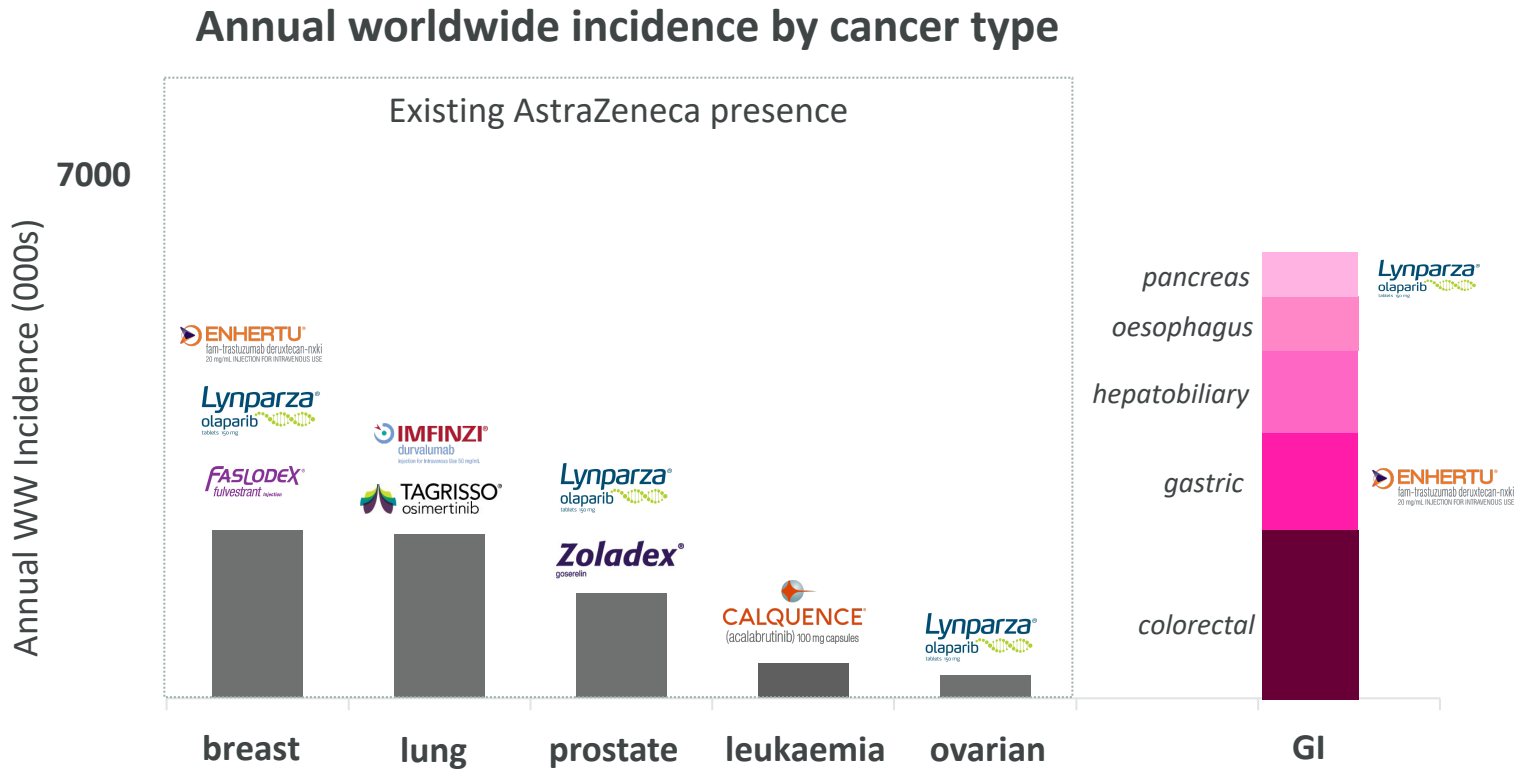
What's next in GI?

Susan Galbraith

Executive Vice President,
Oncology R&D

GI tumours are the next pillar for AstraZeneca in oncology

complementing strong presence in lung & breast



Levels of heterogenicity seen in GI cancers shows the need for a varied arsenal of medicines across the GI cancer landscape

Source: Globocan (Globocan 2020 Estimates of Incidence and Mortality Worldwide; GLOBOCAN Cancer Today, 2018). WW = worldwide; GI = gastrointestinal.

AZ poised to become a leader in GI cancers

Late-stage clinical programmes

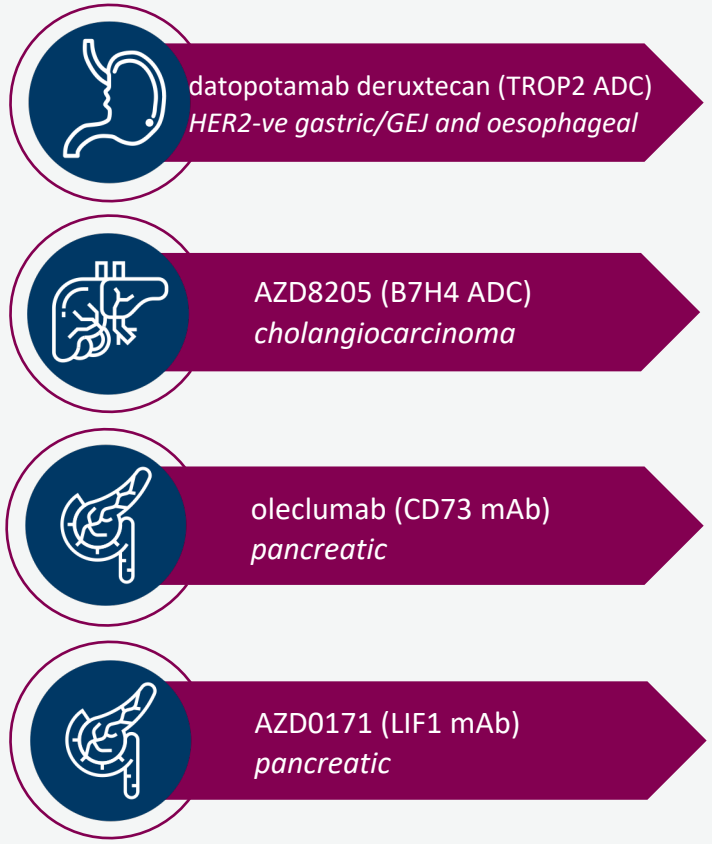
IMFINZI®
durvalumab
Injection for Intravenous Use 50 mg/mL

- EMERALD-1: locoregional HCC; data H2 2022
- EMERALD-2: adjuvant HCC; data 2022 +
- MATTERHORN: resectable gastric / GEJ; data 2022+
- KUNLUN: locally-advanced oesophageal; data 2022+

ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

- DESTINY-Gastric03: HER2+ gastric / GEJ; data 2022+
- DESTINY-Gastric04: 2L gastric / GEJ; data 2022+
- DESTINY-Gastric06: 3L HER2+ CN; data 2022+
- DESTINY-CRC02: 3L HER2+ CN; data 2022+
- DESTINY-PT01: CRC, liver and gastric; data 2022+
- DESTINY-PT02: BTC and pancreatic; data 2022+

Selected early-stage



GEJ = gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; CN = China; PT= pan-tumor; TROP2 = trophoblast cell surface antigen 2; HER2-ve = HER2-negative; B7H4 = v-set domain-containing T-cell activation inhibitor 1; ADC = antibody drug conjugate; CD73 = cluster of differentiation 73; mAb = monoclonal antibody; LIF1 = leukaemia inhibitory factor 1.

5

Closing and Q&A

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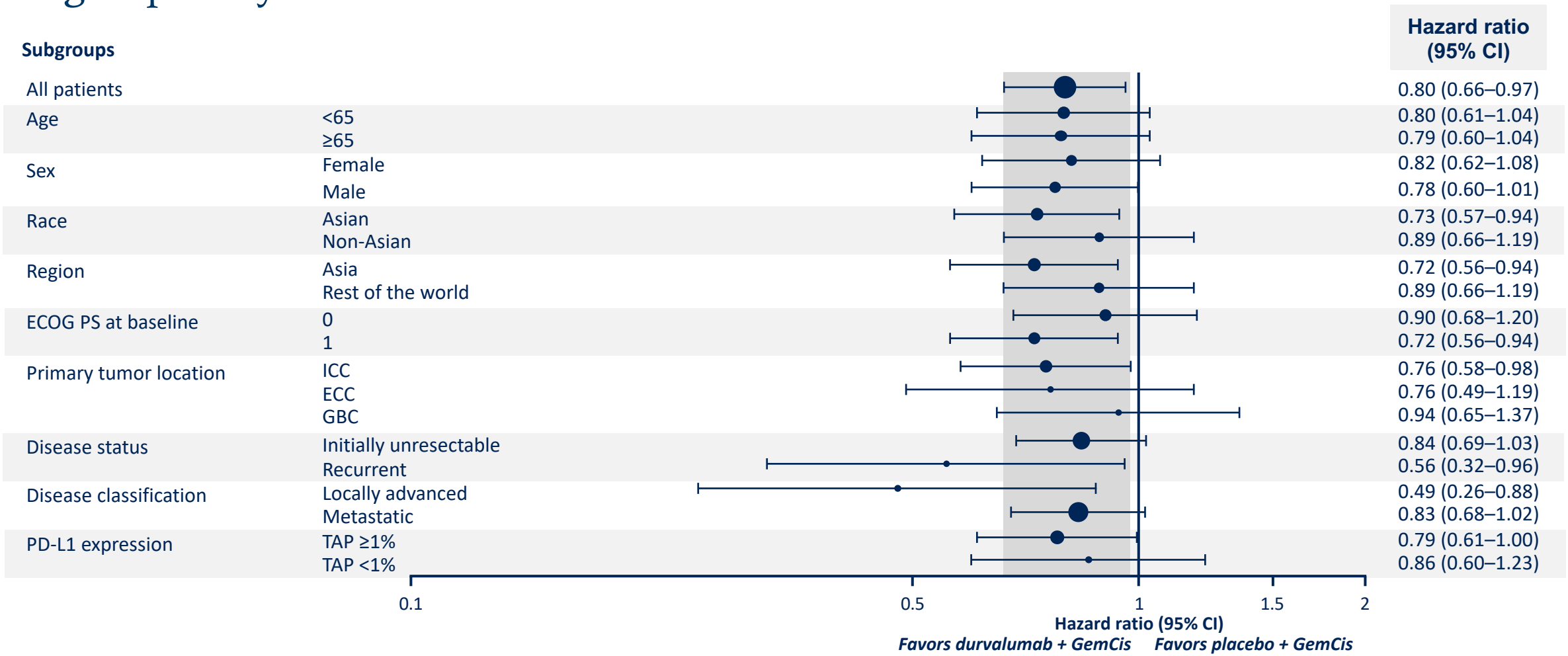
A

Appendix

TOPAZ-1

Overall survival

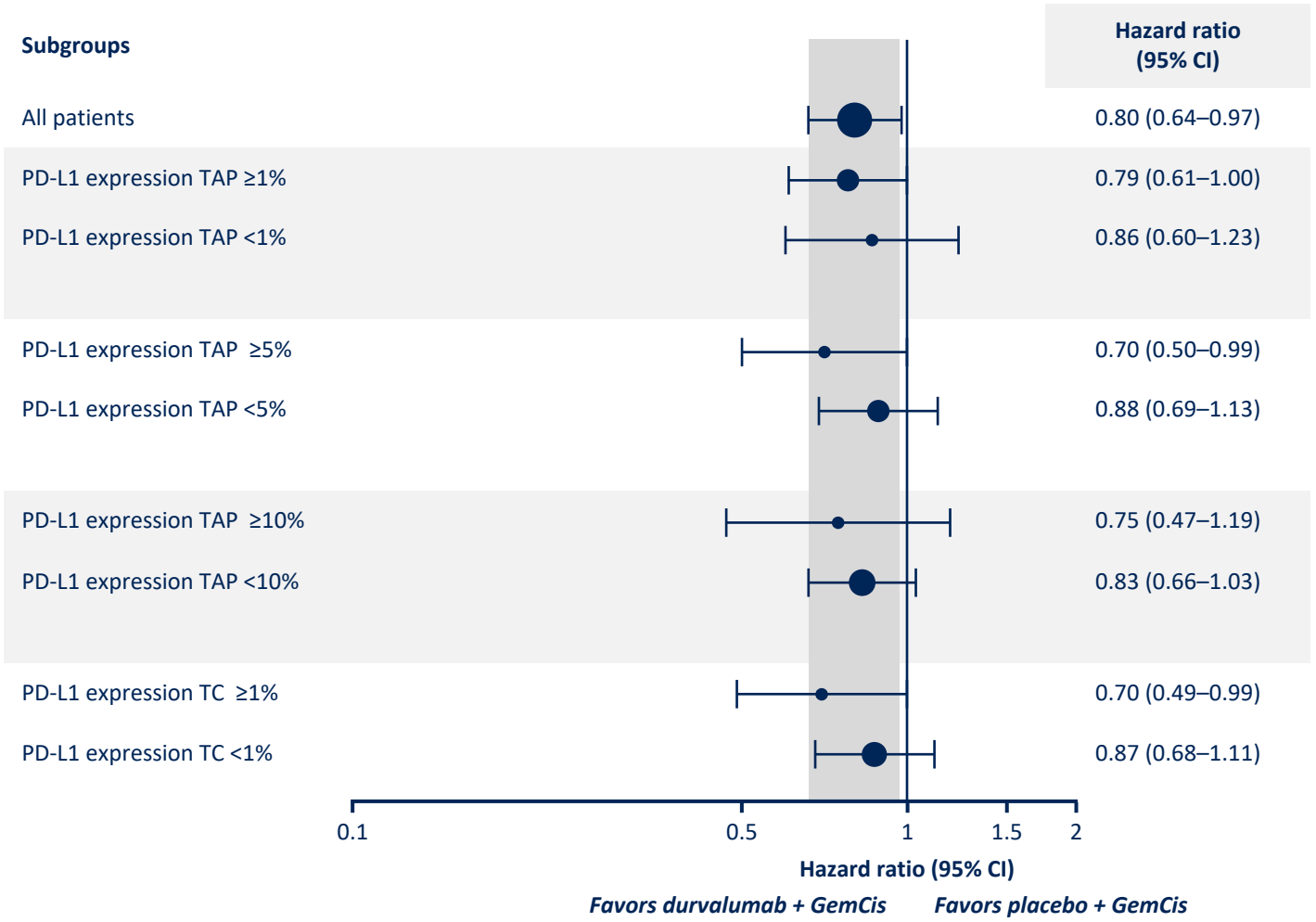
Subgroup analysis



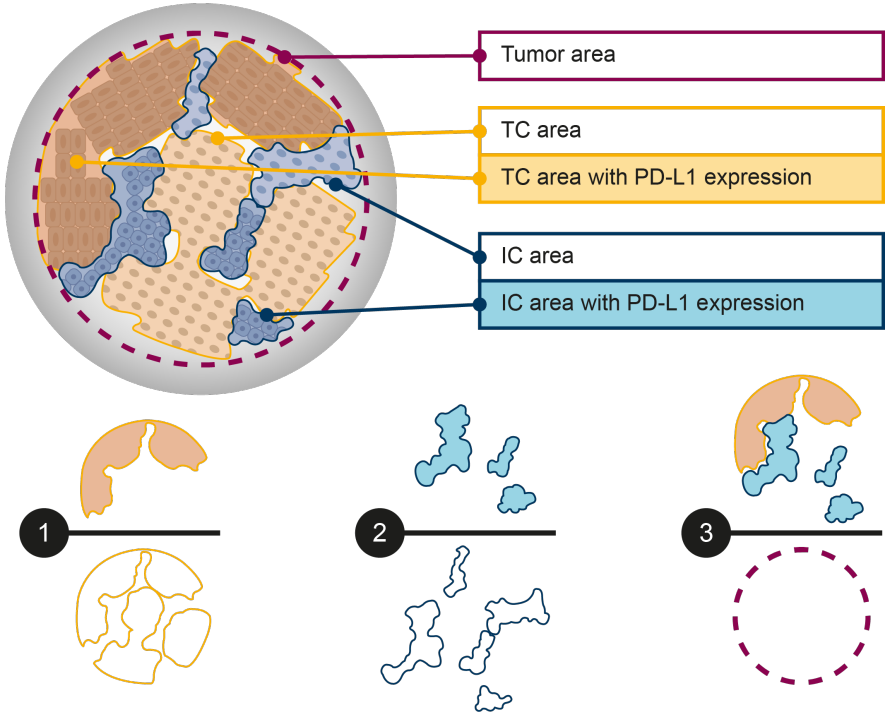
CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Overall survival in subgroups

by PD-L1 expression



Tumor Area Positivity (TAP) score using the Ventana PD-L1 (SP263) Assay



1. TC: proportion of TCs with PD-L1 membrane staining at any intensity
2. IC: proportion of tumor-associated ICs with PD-L1 cytoplasmic/membrane staining at any intensity
3. **Combined TCs and ICs:** Proportion of tumour area occupied by TCs with membrane and ICs with cytoplasmic/membrane PD-L1 staining at any intensity (TAP score)

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

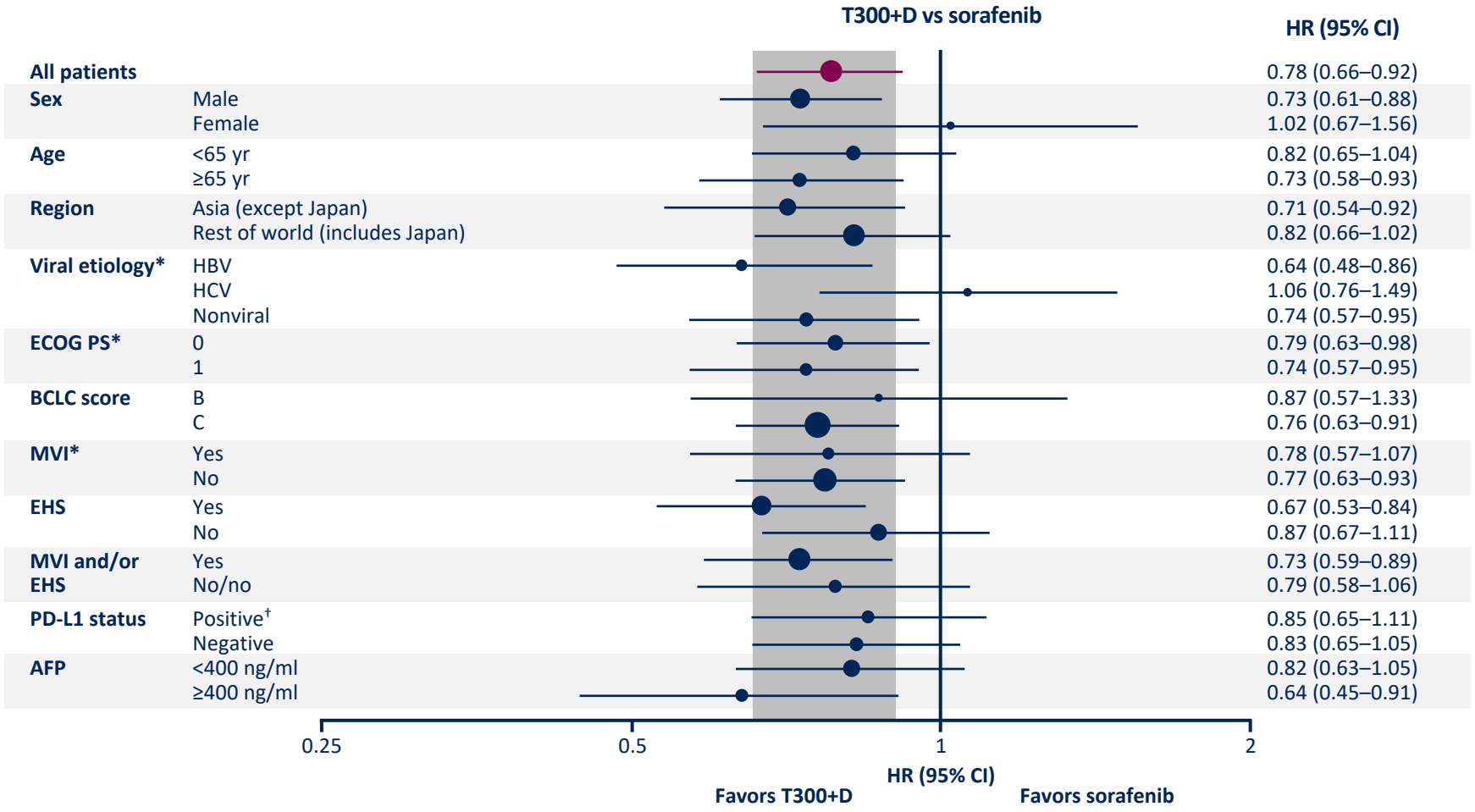
Grade 3/4 adverse events

Event, n (%)	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Any grade 3/4 AE (≥5%)		
Anemia	80 (23.7)	77 (22.5)
Neutrophil count decreased	71 (21.0)	88 (25.7)
Neutropenia	68 (20.1)	72 (21.1)
Platelet count decreased	33 (9.8)	29 (8.5)
Cholangitis	22 (6.5)	11 (3.2)
Thrombocytopenia	16 (4.7)	18 (5.3)
White blood cell count decreased	15 (4.4)	20 (5.8)
Any grade 3/4 TRAE (≥2%)		
Neutrophil count decreased	70 (20.7)	87 (25.4)
Neutropenia	65 (19.2)	69 (20.2)
Anemia	64 (18.9)	64 (18.7)
Platelet count decreased	27 (8.0)	26 (7.6)
White blood cell count decreased	14 (4.1)	20 (5.8)
Thrombocytopenia	12 (3.6)	18 (5.3)
Fatigue	9 (2.7)	8 (2.3)
Leukopenia	7 (2.1)	2 (0.6)
Asthenia	4 (1.2)	7 (2.0)

HIMALAYA

Forest plot of overall survival

T300+D versus sorafenib in patient subgroups



*Stratification factor. †Defined as tumor area positivity score ≥1%.

T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Immune-mediated adverse events

Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

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