ESMO 2020 (Virtual) Congress Report

Solid tumors:
PD-1/PD-L1 inhibition and PARP inhibition
Focus on GI and ovarian cancers

memo inOncology
A Congress Resource for Oncology & Haematology Specialists

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Contents – GI cancers

GI cancers

GI: Gastrointestinal. GC: Gastric cancer. GEJC: Gastroesophageal junction cancer. EAC: esophageal adenocarcinoma.1L: First line.

Contents – Ovarian cancer and other solid tumors

Ovarian cancer

Other solid tumors

GI Cancers

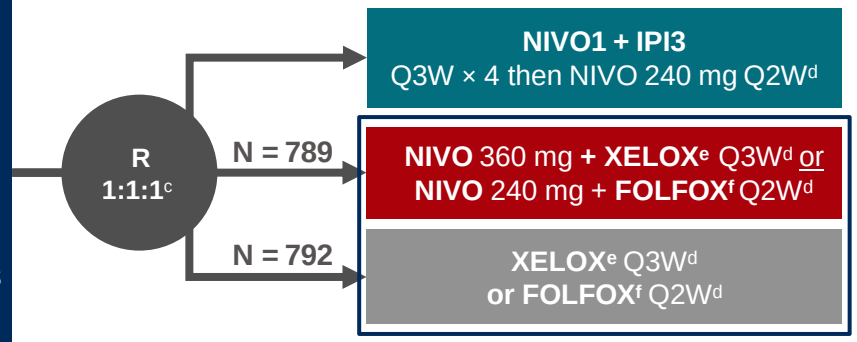
CheckMate 649

PD-1i plus chemotherapy vs chemotherapy in gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: Nivolumab

Checkmate 649 Study design

Randomized, open-label, pivotal phase 3 trial evaluating nivolumab plus chemotherapy vs chemotherapy alone as a first-line treatment for metastatic gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1



Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1 or all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- **ORR**[g]

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)

N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

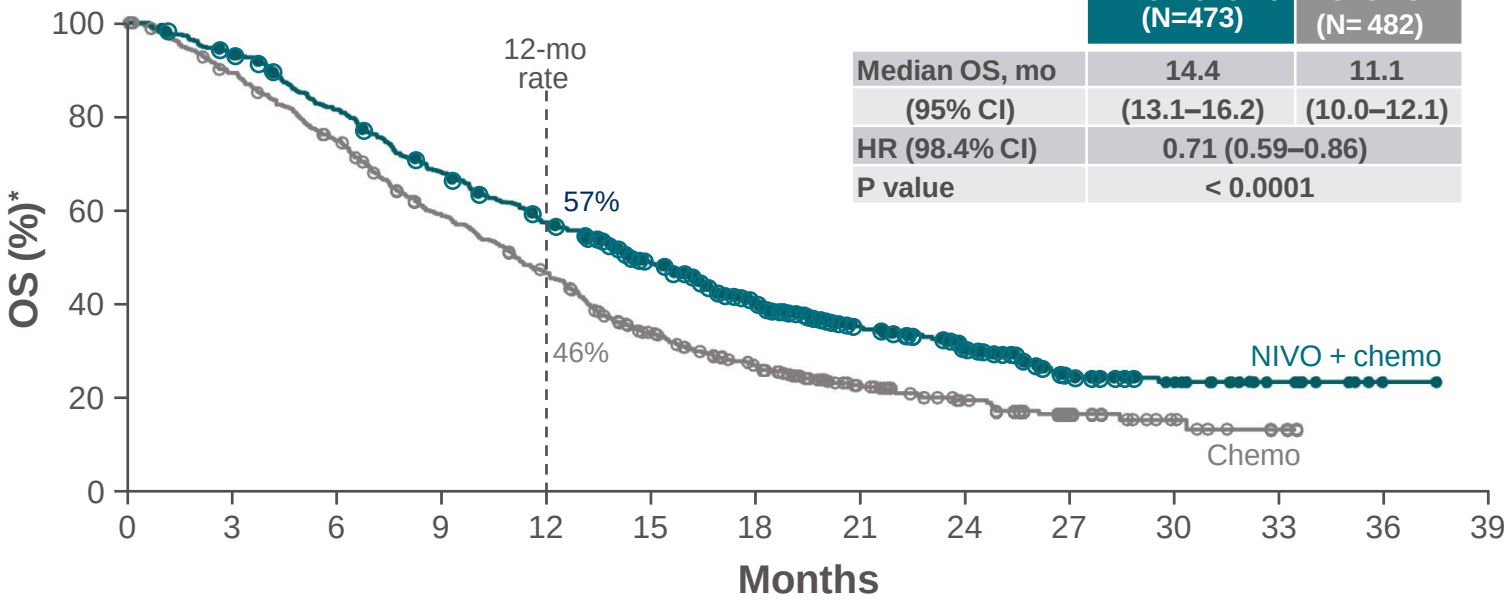
At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[*]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

BICR: Blinded independent committee review. CPS: Combined positive score. ECOG PS: Eastern cooperative oncology group performance status. GEJ: Gastroesophageal junction. IHC: Immunohistochemistry. IPI: Ipilimumab. NIVO: nivolumab: ORR: Objective response rate. OS: Overall survival. PD-L1: Programmed death ligand 1. PFS: Progression-free survival.
Moehler, M. et al, 2020. Abstract LBA6 presented at ESMO 2020.

Primary endpoint: Overall survival (OS)

PD-L1 combined positive score (CPS) ≥ 5



	Nivo + chemo (N=473)	Chemo (N= 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1–16.2)	(10.0–12.1)
HR (98.4% CI)	0.71 (0.59–0.86)	
P value	< 0.0001	

No. at risk														
Nivo + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

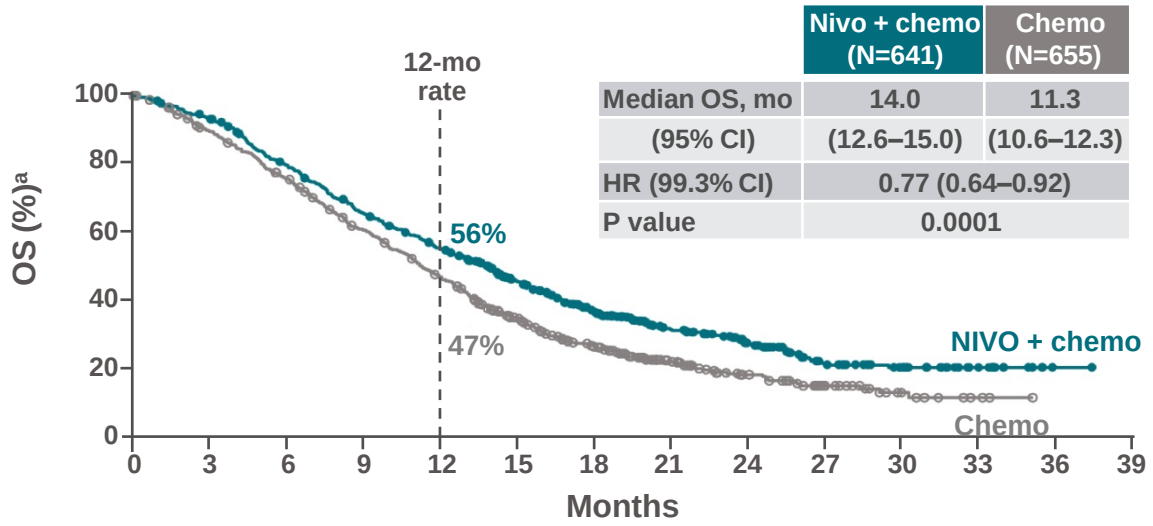
- Superior OS, 29% reduced risk of death, and a 3.3-month improvement in median OS with nivolumab+ chemotherapy vs chemotherapy in patients whose tumors expressed PD-L1 CPS ≥5

*Minimum follow-up 12.1 months.

OS: Overall survival. CI: Confidence interval. CPS: Combined positive score. HR: Hazard ratio. PD-L1, programmed death ligand 1.
Moehler, M. et al, 2020. Abstract LBA6 presented at ESMO 2020.

Overall survival

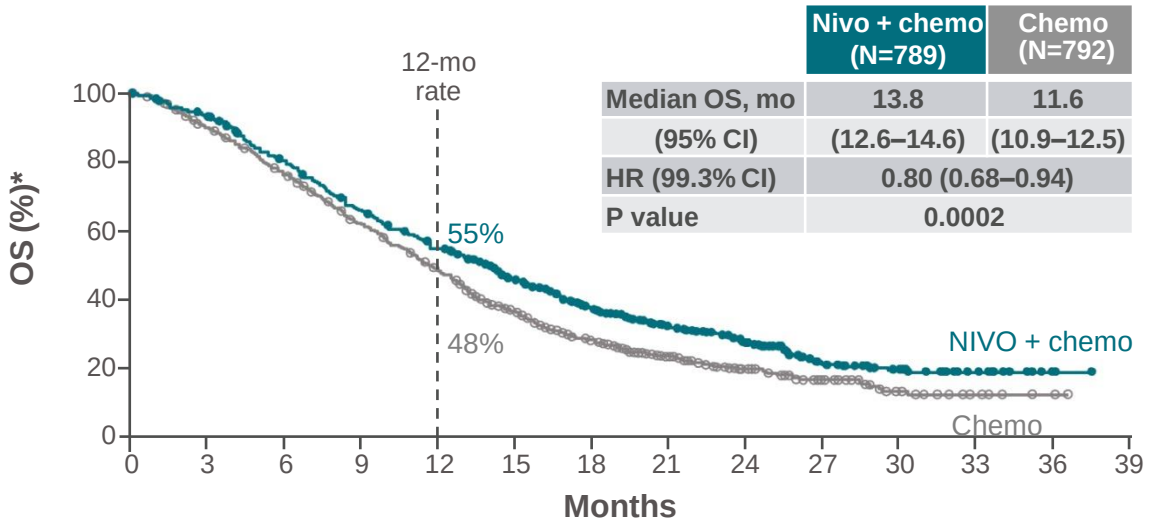
PD-L1 CPS ≥ 1



	Nivo + chemo (N=641)	Chemo (N=655)
Median OS, mo	14.0	11.3
(95% CI)	(12.6–15.0)	(10.6–12.3)
HR (99.3% CI)	0.77 (0.64–0.92)	
P value	0.0001	

No. at risk														
Nivo + chemo	641	595	502	412	344	254	183	118	80	40	28	11	1	0
Chemo	655	575	483	383	292	194	131	77	45	25	10	3	0	0

All randomized



	Nivo + chemo (N=789)	Chemo (N=792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6–14.6)	(10.9–12.5)
HR (99.3% CI)	0.80 (0.68–0.94)	
P value	0.0002	

No. at risk														
Nivo + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

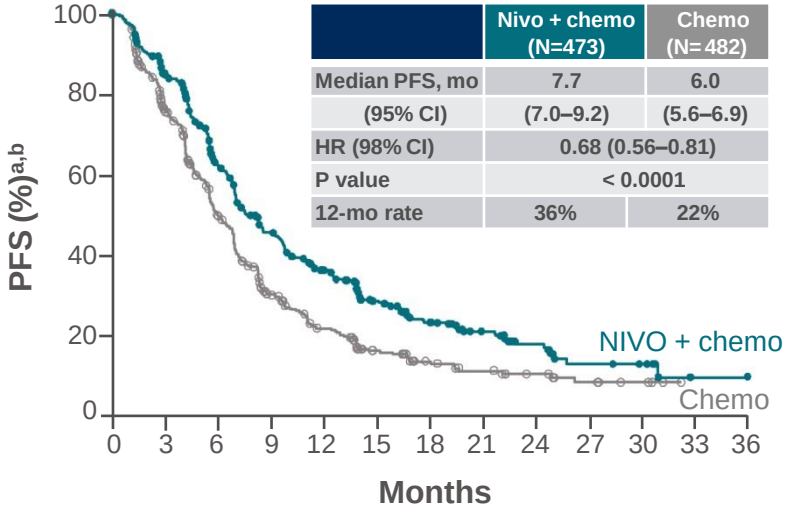
*Minimum follow-up 12.1 months.

- OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with nivolumab + chemotherapy vs chemotherapy

OS: Overall survival. CI: Confidence interval. CPS: Combined positive score. HR: Hazard ratio. PD-L1, programmed death ligand 1.
Moehler, M. et al, 2020. Abstract LBA6 presented at ESMO 2020.

Progression-free survival

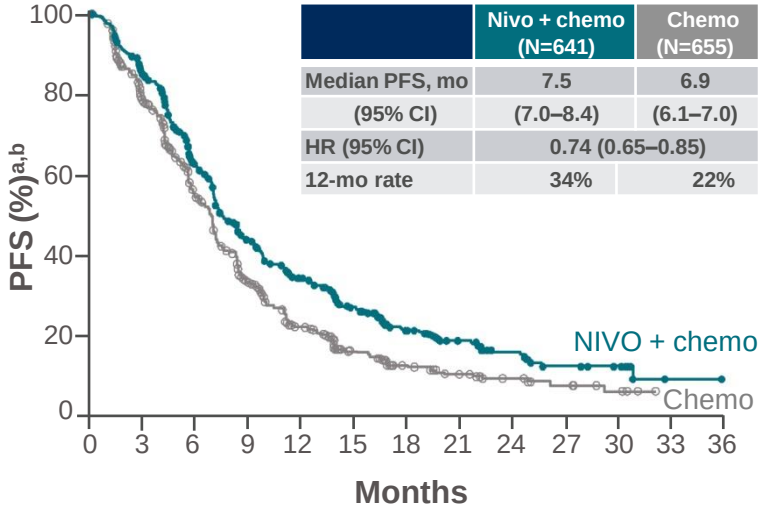
PD-L1 CPS ≥ 5



	Nivo + chemo (N=473)	Chemo (N= 482)
Median PFS, mo	7.7	6.0
(95% CI)	(7.0–9.2)	(5.6–6.9)
HR (98% CI)	0.68 (0.56–0.81)	
P value	< 0.0001	
12-mo rate	36%	22%

No. at risk													
Nivo + chemo	473	384	258	181	132	89	60	39	23	10	8	1	0
Chemo	482	325	200	109	72	41	25	18	12	7	4	0	0

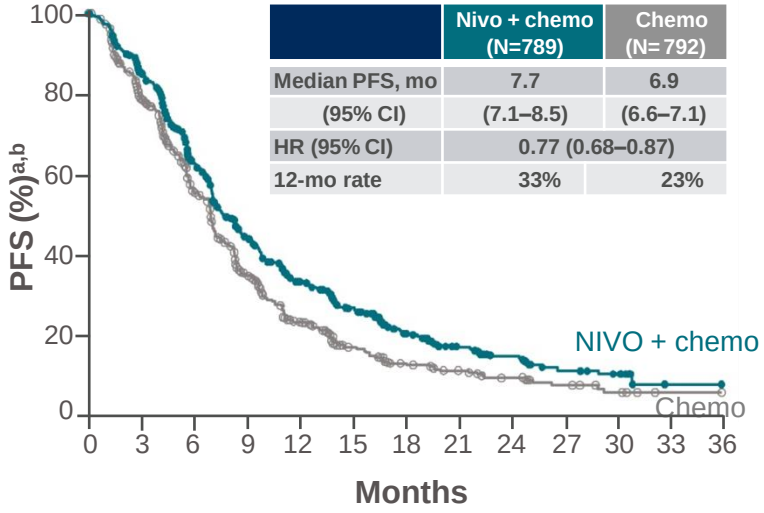
PD-L1 CPS ≥ 1



	Nivo + chemo (N=641)	Chemo (N=655)
Median PFS, mo	7.5	6.9
(95% CI)	(7.0–8.4)	(6.1–7.0)
HR (95% CI)	0.74 (0.65–0.85)	
12-mo rate	34%	22%

No. at risk													
	641	522	351	234	167	113	71	46	27	13	10	1	0
	655	452	291	167	99	53	31	21	13	8	4	0	0

All randomized



	Nivo + chemo (N=789)	Chemo (N= 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1–8.5)	(6.6–7.1)
HR (95% CI)	0.77 (0.68–0.87)	
12-mo rate	33%	23%

No. at risk													
	789	639	429	287	197	136	83	51	31	15	11	1	0
	792	544	351	202	120	65	38	28	18	12	6	1	0

- Superior PFS, 32% reduction in risk of progression or death with nivolumab + chemotherapy vs chemotherapy in patients whose tumors expressed PD-L1 CPS ≥ 5
- PFS benefit with nivolumab + chemotherapy vs chemotherapy in PD-L1 CPS ≥ 1 and all randomized patients

PFS: Progression free survival. CI: Confidence interval. CPS: Combined positive score. HR: Hazard ratio. PD-L1, programmed death ligand 1.
Moehler, M. et al, 2020. Abstract LBA6 presented at ESMO 2020.

Safety and tolerability

Summary of treatment related adverse events (TRAEs)

Patients, N (%)	All treated			
	Nivolumab + chemotherapy (N=782)		Chemotherapy (N=767)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAEs	738 (94)	462 (59)	679 (89)	341 (44)
Serious TRAEs	172 (22)	131 (17)	93 (12)	77 (10)
TRAEs leading to discontinuation	284 (36)	132 (17)	181 (24)	67 (9)
Treatment-related deaths	12 (2)		4 (<1)	

TRAEs with potential immunologic etiology

Select TRAEs, N (%)	All treated			
	Nivolumab + chemotherapy (N=782)		Chemotherapy (N=767)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Endocrine	107 (14)	5 (<1)	3 (<1)	0
Gastrointestinal	262 (34)	43 (5)	207 (27)	25 (3)
Hepatic	203 (26)	29 (4)	134 (17)	16 (2)
Pulmonary	40 (5)	14 (2)	4 (<1)	1 (<1)
Renal	26 (3)	6 (<1)	8 (1)	1 (<1)
Skin	214 (27)	26 (3)	105 (14)	6 (<1)

- Nivolumab plus chemotherapy elicited an expected toxicity profile; no new safety signals reported

TRAE: Treatment related adverse event.
Moehler, M. et al, 2020. Abstract LBA6 presented at ESMO 2020.

Checkmate 649 Conclusions

- Nivolumab is the first PD-1 inhibitor to demonstrate superior OS and PFS in combination with chemotherapy versus chemotherapy alone in previously untreated patients with advanced GC/GEJC/EAC
- Statistically significant and clinically meaningful OS benefit in patients whose tumors expressed PD-L1 CPS ≥ 5 and ≥ 1 and in all randomized patients
- Survival benefit across multiple pre-specified subgroups (assessed in primary population)
- PFS benefit in PD-L1 CPS ≥ 5 (statistically significant), PD-L1 CPS ≥ 1, and all randomized patients
- No new safety signals were identified with nivolumab + chemotherapy
- **Nivolumab + chemotherapy represents a new potential standard first line treatment for patients with advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma**

GC: Gastric cancer. GEJC: Gastroesophageal junction cancer. EAC: Esophageal adenocarcinoma. OS: Overall survival. PFS: Progression free survival. CPS: Combined positive score.
Moehler, M. et al, 2020. Abstract LBA6 presented at ESMO 2020.

ATTRACTION-4

PD-1i plus chemotherapy vs chemotherapy in advanced/ recurrent gastric or gastroesophageal junction cancer: Nivolumab

ATTRACTION-4 Study design

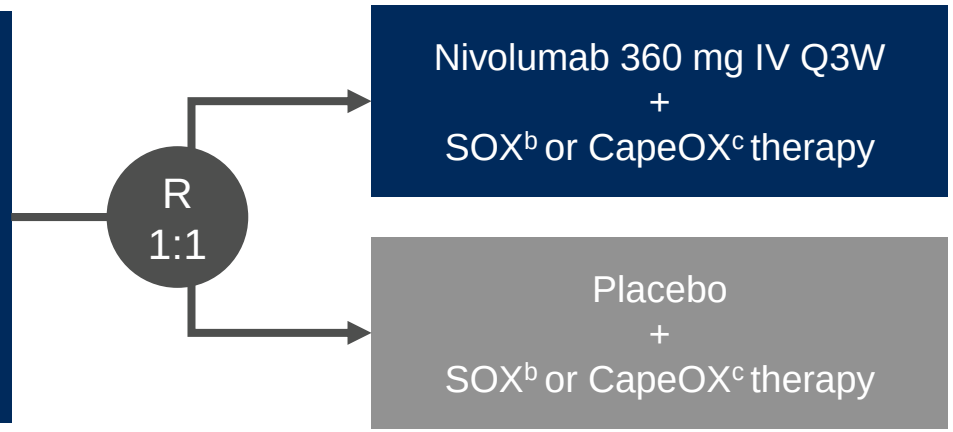
Randomized, multicenter, phase 2/3 study of nivolumab plus chemotherapy in patients with previously untreated advanced or recurrent gastric or gastroesophageal junction cancer

Key eligibility criteria:

- Unresectable advanced or recurrent HER2 (-) G/GEJ cancer
- ECOG PS of 0-1
- Chemo-naive
- Neoadjuvant or adjuvant chemotherapy allowed if completed ≥180 days prior to recurrence

Stratification factors:

- Country
- ECOG PS
- Tumor cell PD-L1 expression
- Disease status



Treatment continued until:

- Progressive disease per RECIST v1.1
- Unacceptable toxicity
- Withdrawal of consent

Co-primary endpoints:

- PFS (central assessment by IRRC) and OS

Other key endpoints:

- PFS (investigator´s assessment)), ORR, DOR, DCR, TTR, BOR, and safety

- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow-up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow-up period was 26.6 months
- A total of 724 patients were randomized between March 2017 and May 2018

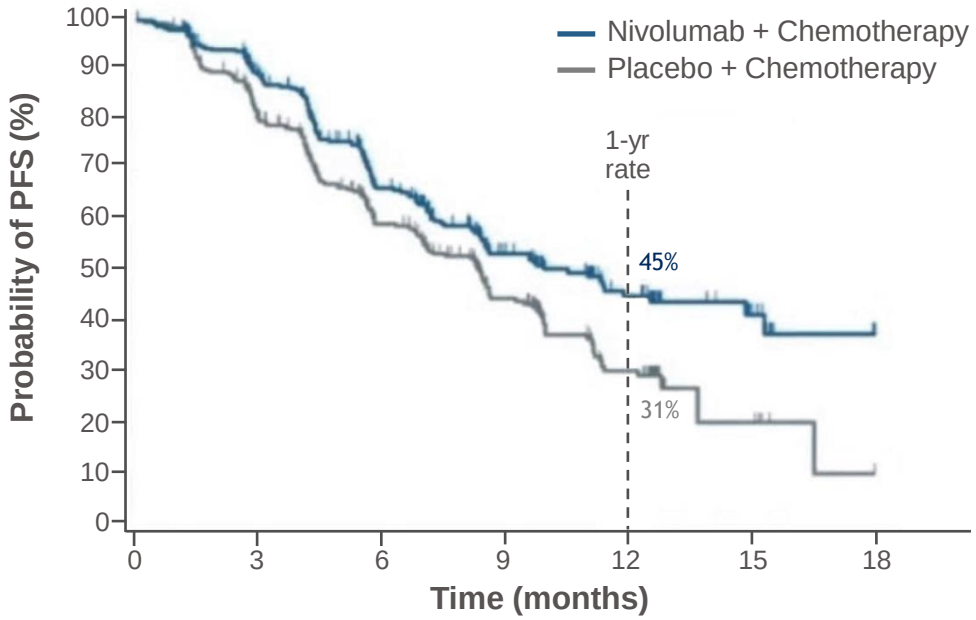
[a]NCT02746796; [b]SOX, S-1 (tegafur-gimeracil-oteracil potassium) 40 mg/m2 orally twice daily (days 1-14) and Oxaliplatin 130 mg/m2 IV (day 1), q3w; [c]CapeOX, Capecitabine 1000 mg/m2 orally twice daily (days 1-14) and Oxaliplatin 130 mg/m2 IV (day 1), Q3W.

RECIST: Response Evaluation Criteria in Solid Tumors. ECOG PS: Eastern Cooperative Oncology Group performance score. IRRC: Independent radiologic review committee. PFS: Progression free survival. OS: Overall survival. DOR: Duration of response. DCR: Disease control rate. TTR: Time to treatment response. BOR: Best overall response. IV: Intravenous. Q3W: Every 3 weeks.

Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

Progression-free survival

Interim analysis



No. at risk							
Nivo + Chemo	362	274	168	94	46	13	0
Placebo + Chemo	362	259	160	80	30	5	0

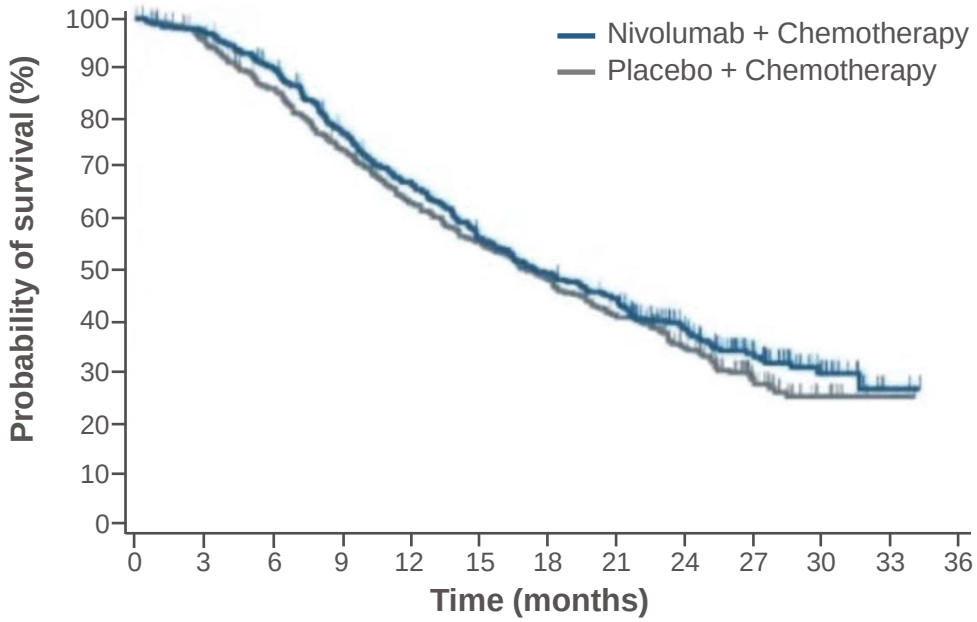
	Nivo + Chemo (N=362)	Placebo + Chemo (N=362)
Median PFS, months (95% CI)	10.45 (8.44-14.75)	8.34 (6.97-9.40)
Hazard ratio (98.51% CI)	0.68 (0.51-0.90)	
P value	0.0007	
1yr PFS rate (%)	45.4	30.6

- Significant improvement in PFS with nivolumab + chemotherapy vs chemotherapy alone

PFS: Progression free survival. CI: Confidence interval.
Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

Overall survival

Final analysis



No. at risk													
Nivo + Chemo	362	364	318	269	232	193	169	150	102	58	23	2	0
Placebo + Chemo	362	342	301	259	219	192	167	141	97	48	16	5	0

	Nivo + Chemo (N=362)	Placebo + Chemo (N=362)
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.90 (0.75-1.08)	
P value	0.257	

- No significant improvement in OS with nivolumab + chemotherapy vs chemotherapy alone

OS: Overall survival. CI: Confidence interval.
Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

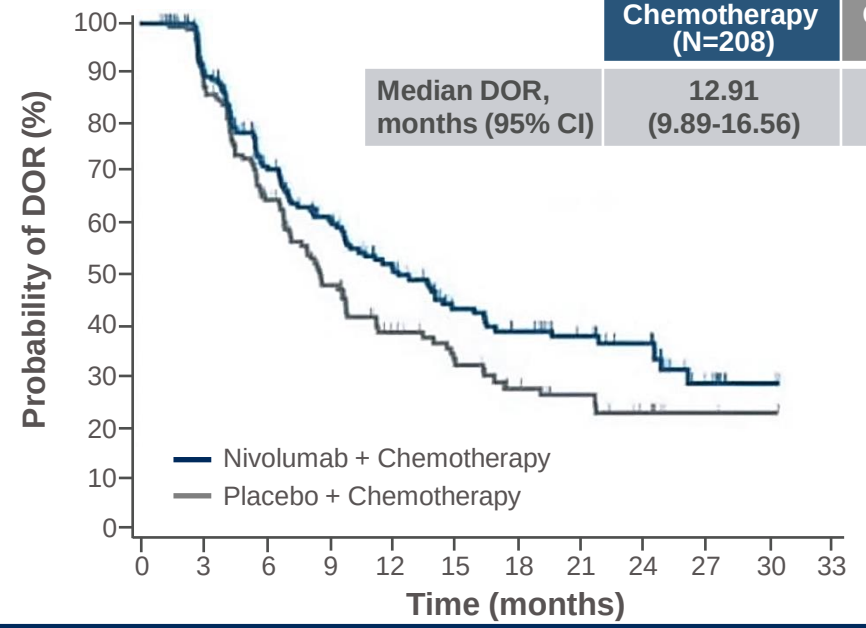
Secondary efficacy endpoints*

Overall response rate (ORR)

	Nivolumab + Chemotherapy (N=362)	Placebo + Chemotherapy (N=362)
ORR, n (%)	208 (57.5)	173 (47.8)
95% CI	52.2-62.6	42.2-53.1
P value	0.0088	
Best overall response, n (%)		
Complete response	70 (19.3)	48 (13.3)
Partial response	138 (38.1)	125 (34.5)
Stable disease	52 (14.4)	75 (20.7)
Progressive disease	25 (6.9)	46 (12.7)
Not evaluable[#]	77 (21.3)	68 (18.8)
DCR, n (%)	260 (71.8)	248 (68.5)
95% CI	66.9-76.4	63.4-73.3
Median TTR (range), months	1.4 (1.0-8-3)	1.4 (1.0-15.3)

Duration of response (DOR)

	Nivolumab + Chemotherapy (N=208)	Placebo + Chemotherapy (N=173)
Median DOR, months (95% CI)	12.91 (9.89-16.56)	8.67 (7.20-11.37)



No. at risk												
Nivolumab + Chemotherapy	208	174	119	90	71	50	43	34	27	10	2	0
Placebo + Chemotherapy	173	139	84	57	40	32	22	16	9	3	2	0

*Data cutoff 31 Jan 2020 at final analysis; [#]Patients without image examination for response evaluation, without change in tumors assessable for response, or without measurable lesions judged by the central review.

OS: Overall survival. CI: Confidence interval. DCR: Disease control rate. DOR: Duration of response, ORR: Overall response rate, TTR: Time to treatment response.

Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

Adverse event summary

Patients, N (%)	Nivolumab + Chemotherapy (N=359)[a]			Placebo + Chemotherapy (N=358)[a]		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
AEs[b]						
Any AEs	358 (99.7)	249 (69.4)	8 (2.2)	357 (99.7)	226 (63.1)	6 (1.7)
Serious AEs	135 (37.6)	103 (28.7)	8 (2.2)	120 (33.5)	89 (24.9)	6 (1.7)
AEs leading to discontinuation	38 (10.6)	19 (5.3)	5 (1.4)	26 (7.3)	12 (3.4)	4 (1.1)
AEs leading to dose delay or reduction	314 (87.5)	190 (52.9)	2 (0.6)	312 (87.2)	170 (47.5)	1 (0.3)
Drug-related AEs[b]						
Any AEs	351 (97.8)	205 (57.1)	3 (0.8)[c]	349 (97.5)	174 (48.6)	2 (0.6)[d]
Serious AEs	88 (24.5)	66 (18.4)	3 (0.8)[c]	51 (14.2)	33 (9.2)	2 (0.6)[d]
AEs leading to discontinuation	22 (6.1)	11 (3.1)	3 (0.8)[c]	17 (4.7)	8 (2.2)	2 (0.6)[d]
AEs leading to dose delay or reduction	307 (85.5)	169 (47.1)	0	291 (81.3)	140 (39.1)	0

[a] Patients who received ≥1 dose of study treatment.
[b] AEs occuring from the date of initiating the study treatment to the earlier date of initiating the subsequent therapy or 28 days after the last dose of the study treatment.
[c] One event each of febrile neutropenia, hepatic failure and sudden death.
[d] One event each of sepsis and haemolytic anaemia.

AE: Adverse event.
Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

Drug-related adverse events

Adverse events with potential immunologic etiology

Selected Drug-related AEs, N (%)[a,b]	Nivolumab + Chemotherapy (N=359)[c]			Placebo + Chemotherapy (N=358)[c]		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
Endocrine	41 (11.4)	8 (2.2)	0	12 (3.4)	0	0
Gastrointestinal	129 (35.9)	21 (5.9)	0	113 (31.6)	19 (5.3)	0
Hepatic	83 (12.1)	14 (3.9)	1 (0.3)[d]	68 (19.0)	12 (3.4)	0
Hypersensitivity/ Infusion reaction	48 (13.4)	12 (3.3)	0	26 (7.3)	4 (1.1)	0
Pulmonary	12 (3.3)	4 (1.1)	0	7 (2.0)	1 (0.3)	0
Renal	9 (2.5)	1 (0.3)	0	4 (1.1)	1 (0.3)	0
Skin	134 (37.3)	14 (3.9)	0	86 (24.0)	4 (1.1)	0

[a] AEs occuring from the date of initiating the study treatment to the earlier date of initiating the subsequent therapy or 28 days after the last dose of the study treatment.
[b] Selected Drug-related AEs are those with potential immunologie etiology that require frequent monitoring/intervention.
[c] Patients who received ≥1 dose of study treatment.
[d] One event of hepatic failure..

AE: Adverse event.
Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

ATTRACTION-4 Conclusions

- Nivolumab plus chemotherapy demonstrated a statistically significant improvement in PFS, but not in OS
- Higher overall response rates and more durable response
- The pre-specified objective of the phase 3 part of ATTRACTION-4 was achieved, showing clinically meaningful efficacy
- Nivolumab plus chemotherapy demonstrated a manageable safety profile
- **Nivolumab plus chemotherapy could be considered a new first-line treatment option in unresectable advanced or recurrent gastric/gastroesophageal cancer**

PFS: Progression free survival. OS: Overall survival.
Boku, N. et al, 2020. Abstract LBA7 presented at ESMO 2020.

KEYNOTE-590

PD-1i plus chemotherapy vs chemotherapy in advanced esophageal or esophagogastric junction cancer: Pembrolizumab

KEYNOTE-590: Study design

Phase 3 study of chemotherapy + pembrolizumab vs chemotherapy + placebo as first-line therapy for patients with advanced esophageal or esophagogastric junction cancer

<u>Key Eligibility Criteria</u>

- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic EGJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable

<u>Stratification Factors</u>

- Asia vs Non-Asia region
- ESCC vs EAC
- ECOG PS 0 vs 1

R (1:1)

Pembrolizumab 200 mg IV Q3W for ≤35 cycles
+
Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤6 cycles

Placebo[a]
+Chemotherapy
5-Fu 800 mg/m² IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤6 cycles

Dual-Primary endpoints: OS and PFS (RECIST v1.1, investigator)
Secondary endpoint: ORR (RECIST v1.1, investigator)

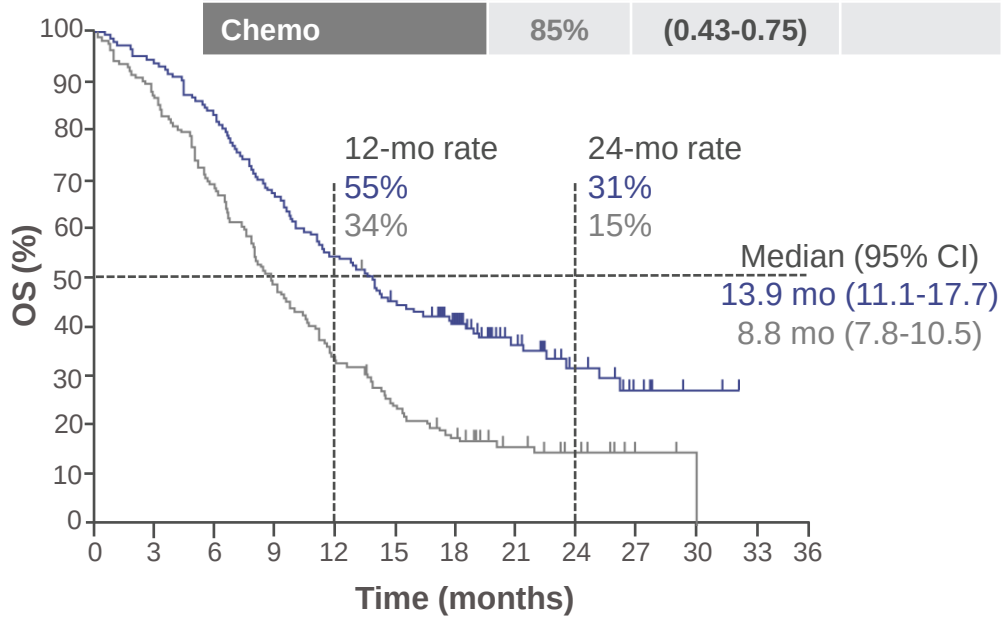
- Tumor response assessed at week 9 then Q9W (RECIST v1.1, investigator)

EAC: Esophageal adenocarcinoma. ESCC: Esophageal squamous cell carcinoma. EGJ: Esophageogastric junction. IV: Intravenous. Q3W: Every 3 weeks. R: Randomized. RECIST: Response Evaluation Criteria in Solid Tumors . OS: Overall survival. PFS: Progression free survival. ORR: Objective response rate. ECOG: Eastern Cooperative Oncology Group.
Kato, K. et al, 2020. **A**bstract LBA8 presented at ESMO 2020.

Overall survival (OS) - ESCC population only

ESCC PD-L1 CPS ≥10

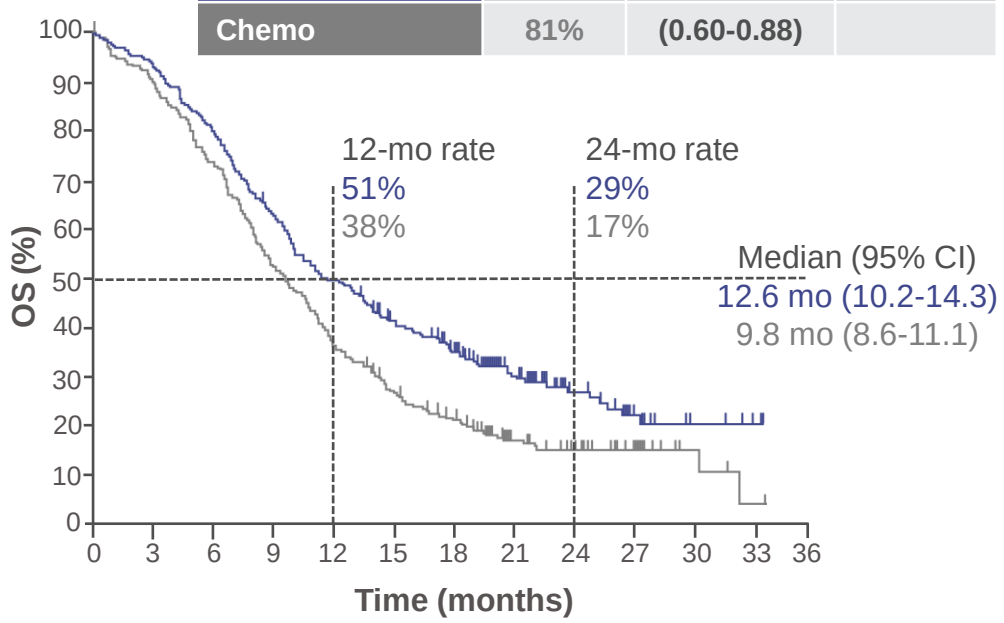
	Events	HR (95% CI)	p
Pembro + Chemo	66%	0.57	<0.0001
Chemo	85%	(0.43-0.75)	



No. at risk													
Pembro + Chemo	143	134	119	96	78	61	51	29	16	7	3	0	0
Chemo	143	124	99	70	48	34	24	15	10	4	1	0	0

All ESCC patients

	Events	HR (95% CI)	p
Pembro + Chemo	69%	0.72	0.0006
Chemo	81%	(0.60-0.88)	



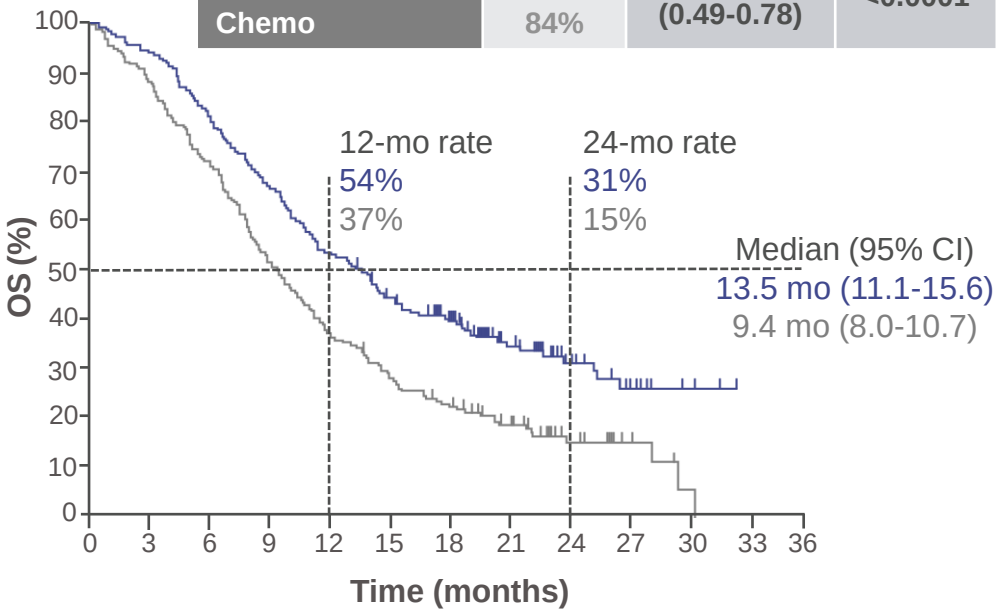
No. at risk													
Pembro + Chemo	274	258	221	175	139	111	89	60	27	14	6	2	0
Chemo	274	247	203	146	103	75	57	34	23	13	4	1	0

ESCC: Esophageal squamous cell carcinoma. CPS: Combined positive score. OS: Overall survival. HR: Hazard ratio.
Kato, K. et al, 2020. **A**bstract LBA8 presented at ESMO 2020.

Overall survival (OS) - Full population (ESCC & EAC)

PD-L1 CPS ≥10

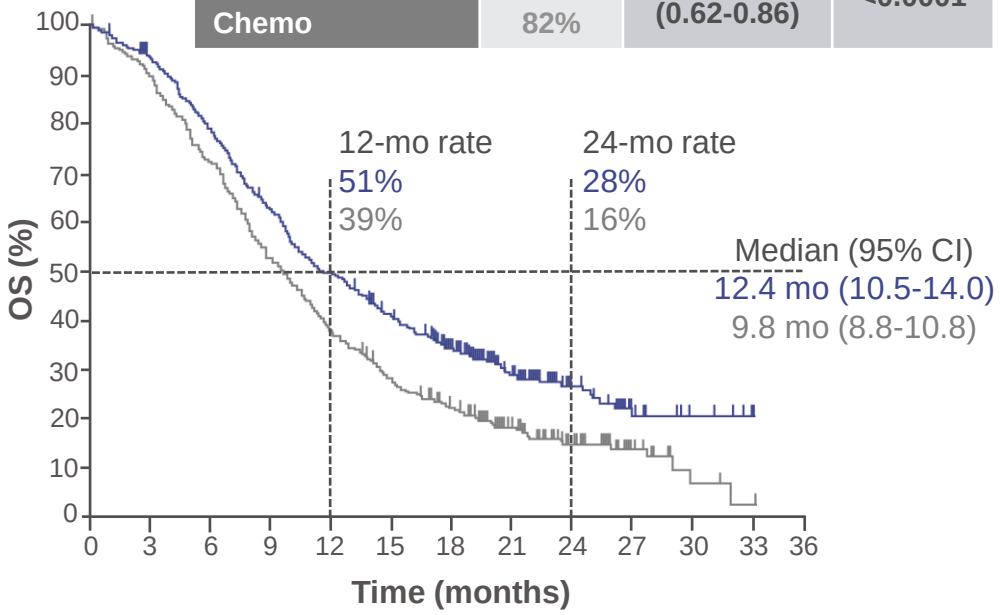
	Events	HR (95% CI)	p
Pembro + Chemo	67%	0.62 (0.49-0.78)	<0.0001
Chemo	84%		



No. at risk													
Pembro + Chemo	186	175	151	125	100	79	66	40	23	10	4	0	0
Chemo	197	174	142	102	73	55	42	28	13	6	1	0	0

All patients

	Events	HR (95% CI)	p
Pembro + Chemo	70%	0.73 (0.62-0.86)	<0.0001
Chemo	82%		



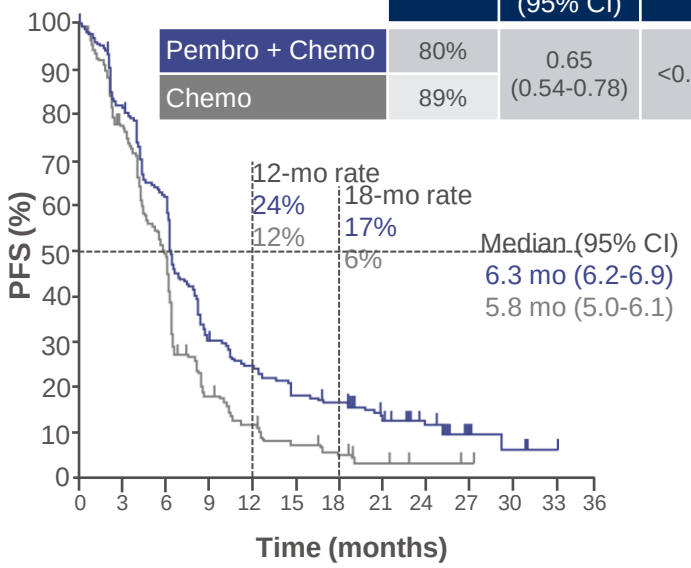
No. at risk													
Pembro + Chemo	373	348	295	235	187	151	118	68	36	17	7	2	0
Chemo	376	338	274	200	147	108	82	51	28	15	4	1	0

CPS: Combined positive score. OS: Overall survival. CI: Confidence interval. HR: Hazard ratio.
Kato, K. et al, 2020. Abstract LBA8 presented at ESMO 2020.

Progression-free survival (PFS)

ESCC, irrespective of CPS

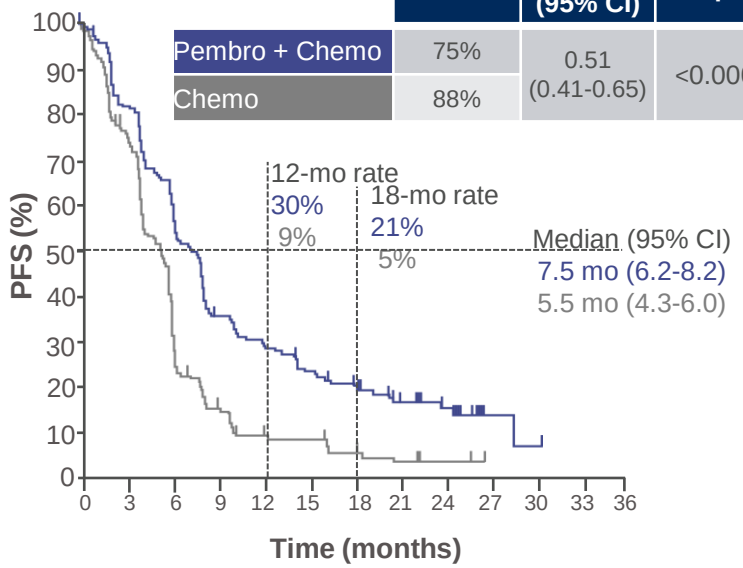
	Events	HR (95% CI)	p
Pembro + Chemo	80%	0.65 (0.54-0.78)	<0.0001
Chemo	89%		



No. at risk													
Pembro + Chemo	274	211	156	71	57	41	35	19	13	3	2	0	0
Chemo	274	205	127	45	26	16	11	5	2	1	0	0	0

PD-L1 CPS ≥10, irrespective of histology

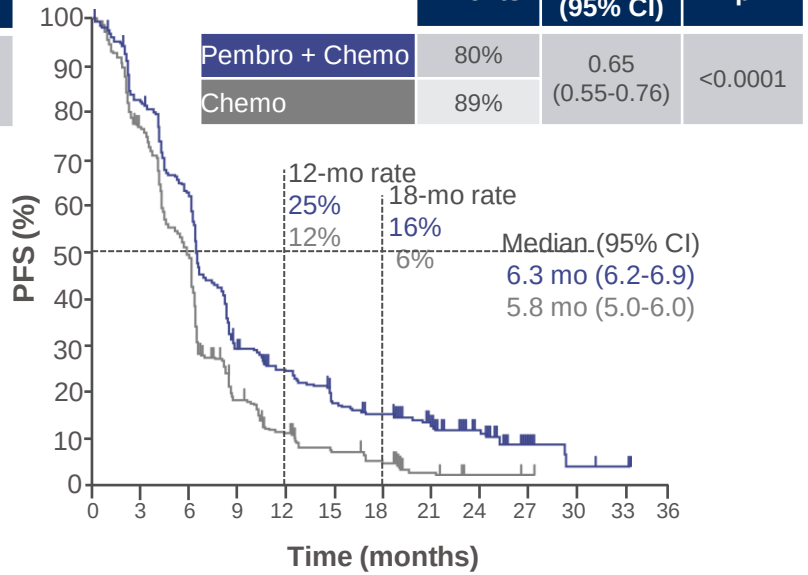
	Events	HR (95% CI)	p
Pembro + Chemo	75%	0.51 (0.41-0.65)	<0.0001
Chemo	88%		



Pembro + Chemo	186	143	109	56	48	36	29	17	12	2	1	0	0
Chemo	197	145	85	26	14	12	7	5	2	1	0	0	0

All Patients

	Events	HR (95% CI)	p
Pembro + Chemo	80%	0.65 (0.55-0.76)	<0.0001
Chemo	89%		

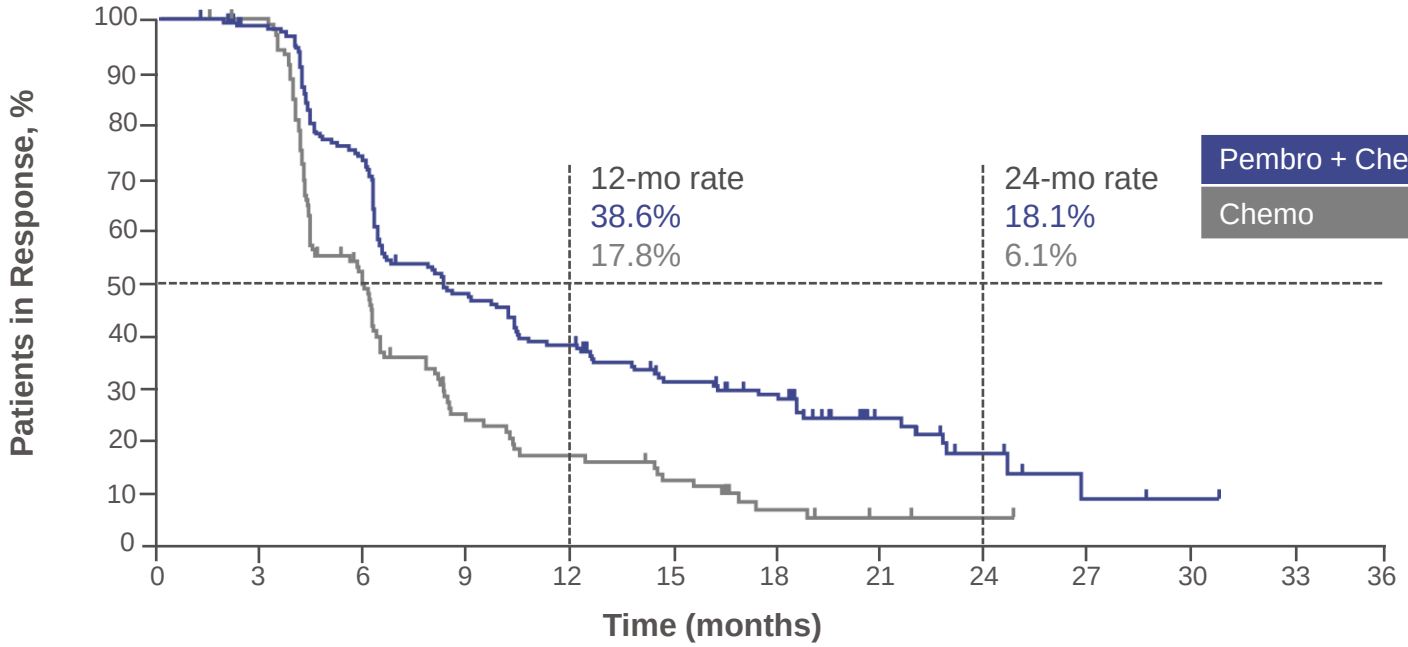


Pembro + Chemo	373	289	210	96	79	55	45	25	17	4	2	0	0
Chemo	376	278	172	62	36	22	14	6	2	1	0	0	0

PFS: Progression free survival. ESCC: Esophageal squamous cell carcinoma. CPS: Combined positive score. OS: Overall survival. CI: Confidence interval. HR: Hazard ratio.
Kato, K. et al, 2020. **A**bstract LBA8 presented at ESMO 2020.

Response rate and duration

In all patients: By investigator according to RECIST v1.1



	ORR, % (95% CI)	% difference[a] P
Pembro + Chemo	45.0 (39.9-50.2)	15.8 <0.0001
Chemo	29.3 (24.7-34.1)	

Median DOR, (range)
8.3 mo (1.2+ to 31.0+)
6.0 mo (1.5+ to 25.0+)

No. at risk													
Pembro + Chemo	168	162	117	75	60	43	35	16	6	2	1	0	0
Chemo	110	106	50	22	16	11	5	2	1	0	0	0	0

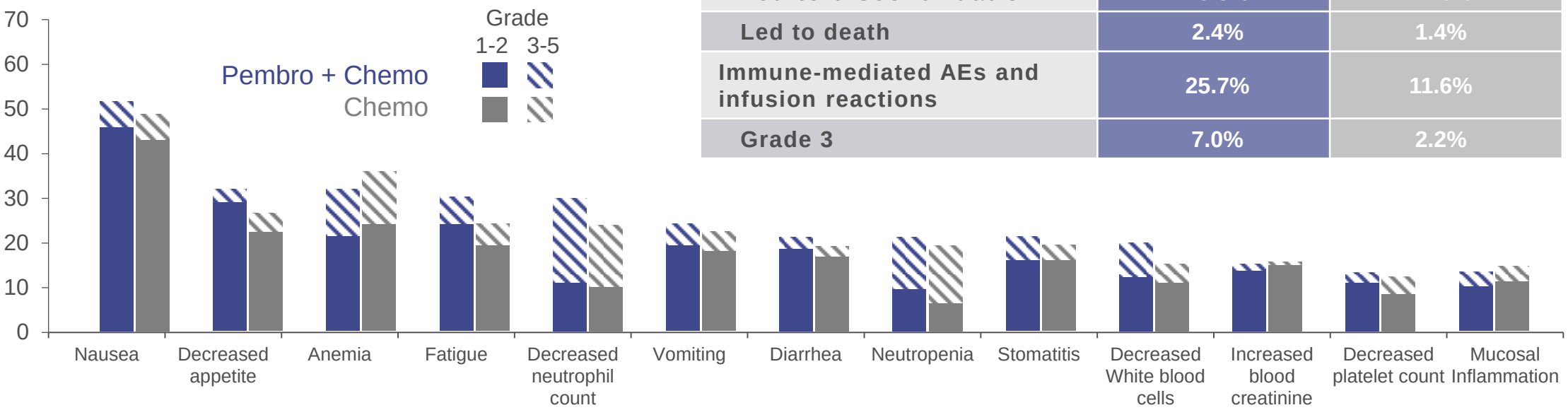
[a]Estimate based on Miettinen & Nurminen method stratified by geographic region. histology. and ECOG performance status; Data cut-off: July 2. 2020

RECIST: Response Evaluation Criteria in Solid Tumors. OOR: Objective response rate. DOR: Duration of response. ECOG: Eastern Cooperative Oncology Group. CI: Confidence interval. HR: Hazard ratio.
Kato, K. et al, 2020. Abstract LBA8 presented at ESMO 2020.

Safety and tolerability

Adverse events in all treated patients

AEs	Pembro + Chemo (N=370)	Chemo (N=370)
Any	100%	99.5%
Treatment-related	98.4%	97.3%
Grade 3	71.9%	67.6%
Led to discontinuation	19.5%	11.6%
Led to death	2.4%	1.4%
Immune-mediated AEs and infusion reactions	25.7%	11.6%
Grade 3	7.0%	2.2%



RECIST: Response Evaluation Criteria in Solid Tumors. OOR: Objective response rate. DOR: Duration of response. ECOG: Eastern Cooperative Oncology Group. CI: Confidence interval. HR: Hazard ratio.
Kato, K. et al, 2020. **A**bstract LBA8 presented at ESMO 2020.

KEYNOTE-590 Conclusions

- **First-line pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma when compared to chemotherapy plus placebo**
  - **Superior OS**: ESCC CPS ≥10 (HR 0.57, P<0.001), ESCC (HR 0.72, P=0.006), CPS ≥10 (HR 0.62, P<0.001), all patients (HR 0.73, P<0.001)
  - **Superior PFS**: ESCC (HR 0.65), CPS ≥10 (HR 0.51), all patients (HR 0.65), all P<0.001
  - **Superior ORR**: All patients (45.0% vs 29.3%, Δ15.8%, P<0.001)
- Comparable safety profile between the two treatment groups
  - No new safety signals detected
- **Pembrolizumab plus chemotherapy should be a new standard-of-care as first-line therapy in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma**

OS: Overall survival. PFS: Progression free survival. ORR: Objective response rate. ESCC: Esophageal squamous cell carcinoma. CPS: Combined positive score. HR: Hazard ratio. EGJ: Esophagogastric junction.
Kato, K. et al, 2020. Abstract LBA8 presented at ESMO 2020.

PD-L1 expression and tislelizumab efficacy in gastroesophageal adenocarcinoma

Novel tumor and immune cell score with VENTANA PD-L1 (SP263) assay and combined positive score (CPS)

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Study background

- Tumor cell (TC) and immune cell (IC) PD-L1 expression may be associated with anti-PD-1 efficacy in gastroesophageal adenocarcinoma (GEA)
- PD-L1 protein expression on TCs and ICs can be assessed via cell counting using Combined Positive Score (CPS) with Dako 22C3 assay
- CPS is the number of PD-L1 staining cells (TCs, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100
- However, the CPS scoring method can be challenging
- A novel combined algorithm, tumor and immune Cell (TIC) score, was developed for the Ventana SP263 assay to assess TC and IC PD-L1 expression based on tumor area
- Associations between CPS and TIC scoring methods, and potential correlations with efficacy, were investigated in patients with GEA from the tislelizumab first-in-human study (NCT02407990)

TC: Tumor cell. IC: Immune cell. PD-L1: programmed death ligand 1. PD-1: programmed cell death protein 1 GEA: Gastroesophageal adenocarcinoma. CPS: Combined positive score.
Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Methods

PD-L1 Assessment:

- PD-L1 expression in tumor samples from GEA cohort of the tislelizumab first-in-human study (BGB-A317-001) were analyzed post-hoc
- Clinical utilization of two PD-L1 assays were evaluated, vCPS (Ventana SP263 assay; N=74) and CPS (Dako 22C3 assay; N=49)

Methodology of PD-L1 expression assessment	Visually estimated Combined Positive Score (vCPS)	Combined Positive Score (CPS)
Assay	VENTANA PD-L1 (SP263) assay on automated VENTANA Benchmark ULTRA® platform	Dako PD-L1 IHC 22C3 assay on Dako Autostainer Link 48
PD-L1 scoring algorithm	$\frac{\text{Percent area occupied by PD-L1 staining cells (tumor cell, immune cell*)}}{\text{Tumor area**}}$	$\frac{\text{Number of PD-L1 staining cells (tumor cell, macrophage, lymphocyte)}}{\text{Total number of viable tumor cells}} \times 100$
Measurement method	Derived by visual estimation of area occupied by PD-L1 staining TC and IC against tumor area	Derived by cell counting

Statistical analysis:

- ORR
- OS and PFS (Brookmeyer and Crowley method with log-log transformation
- Kaplan-Meier curves of PD-L1 subgroups compared log-rank test)

Analytical validation of VENTANA PD-L1 assay in GC and GEJ adenocarcinoma:

- The VENTANA PD-L1 (SP263) assay was validated for use in GC/GEJ adenocarcinoma FFPE samples in a series of studies that addressed assay repeatability, intermediate precision, reader precision, and inter-laboratory reproducibility

* Immune cells include lymphocytes, macrophage, histocytes, reticular dendritic cells, plasma cells, and neutrophils.
** Tumor area is defined as the area covered by tumor cells and tumor associated stroma.
CPS: Combined positive score. IC: Immune cell. IHC: Immunohistochemistry. PD-L1: Programmed death-ligand 1.TC, tumor cell. vCPS: Visually-estimated combined positive score.
Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Baseline characteristics and clinical outcome

- Of 81 patients enrolled in BGB-A317-001 GEA cohort, PD-L1 expression was evaluable by vCPS (by VENTANA PD-L1 SP263) and CPS (by Dako 22C3) in 74 and 49 patients with available FFPE tumors, respectively; 45 were evaluable by both assays

Baseline characteristics and clinical outcome

Characteristic		vCPS Evaluable N = 74	CPS Evaluable N = 49	All GEA Patients N = 81
Age, N (%)	<65 ≥65	45 (60.8) 29 (39.2)	33 (67.3) 16 (32.7)	48 (59) 33 (41)
Sex, N (%)	Male Female	48 (65) 26 (35)	33 (67) 16 (33)	54 (67) 27 (33)
Tumor type, N (%)	GC/GEJ adenocarcinoma EAC	48 (65) 26 (35)	27 (55) 22 (45)	54 (67) 27 (33)
Tumor stage, N (%)	III IV	4 (5.4) 70 (95)	1 (2.0) 48 (98)	5 (6.2) 76 (94)
Response, N (%)	PR SD PD NA	7 (9.5) 14 (19) 43 (58) 1 (1.4)	4 (8.2) 10 (20) 30 (61) 1 (2.0)	8 (9.9) 17 (21) 46 (57) 1 (1.2)
ORR, % (95% CI)		10.9 (4.5, 21.2)	9.1 (2.5, 21.7)	11.3 (5, 21)
Median PFS, months (95% CI)		2.0 (1.7, 2.1)	2.0 (1.5, 2.1)	2.0 (1.8, 2.1)
Median OS, months (95% CI)		5.6 (3.9, 6.7)	5.6 (3.8, 8.6)	5.9 (4.2, 9.1)
Median follow-up, months (95% CI)		14.2 (10.9, 21.2)	NE (13.9, NE)	17.4 (13.9, NE)

CI, confidence interval; CPS, Combined Positive Score; EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJ, gastroesophageal junction; NA, not applicable; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD; stable disease; vCPS, visually-estimated Combined Positive Score.

Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Clinical utility of vCPS and CPS

Response, prevalence, positive predictive value (PPV), and negative predictive value (NPV) for vCPS ≥5% and CPS ≥1

Scoring method	PD-L1	BEP	ORR (%)	PD-L1 Prevalence (%)	Response Odds Ratio	PPV (%)	NPV (%)
vCPS (SP263)	≥5% <5%	38 36	18.2 3.2	51	6.67	15.8	83.3
CPS (22C3)	≥1 <1	22 27	20.0 0	45	∞*	18.2	88.9

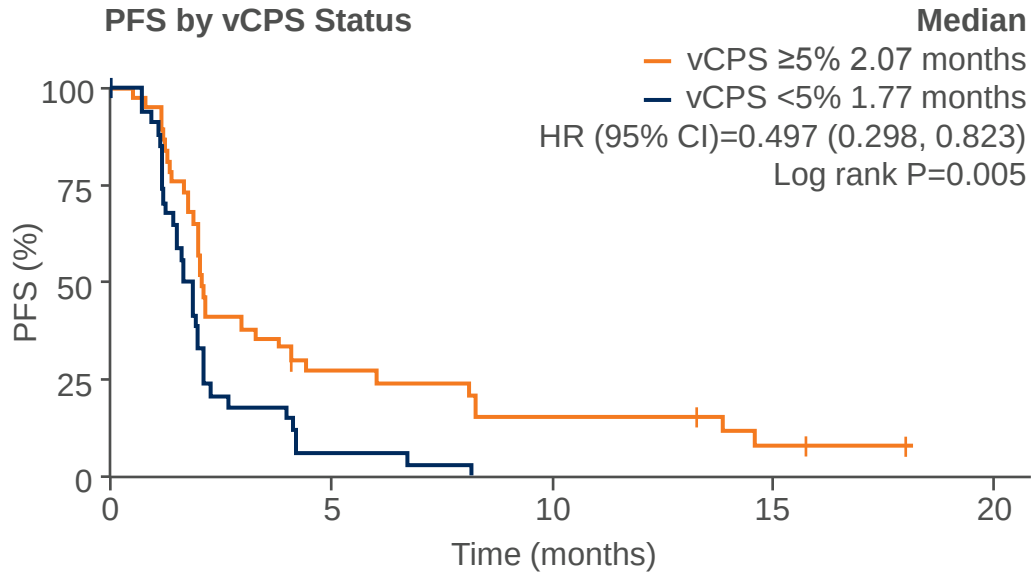
*Odds ratio could not be estimated due to no responders in CPS <1.

- Enriched ORR was observed in patients with vCPS ≥5% tumors versus vCPS <5% tumors (ORR=18.2% vs 3.2%); similar to those using a CPS ≥1 cutoff

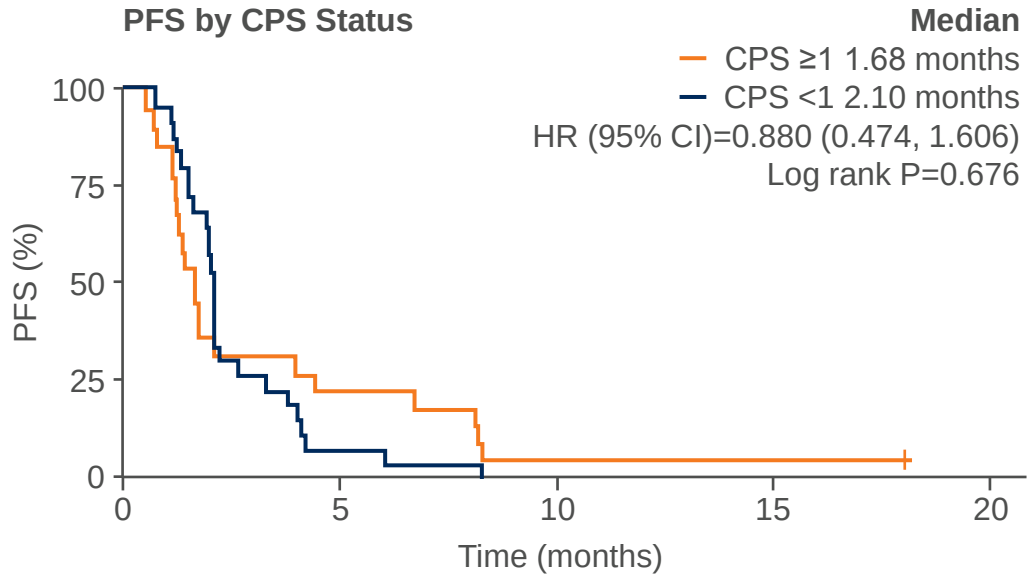
BEP: Biomarker evaluable population. CI: Confidence interval. CPS: Combined positive score. NPV: Negative predictive value. ORR: Objective response rate. PD-L1: Programmed death-ligand 1. PFS. Progression-free survival. PPV: Positive predictive value. vCPS: Visually-estimated combined positive score.
Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Clinical utility of vCPS and CPS

- At a 17.4-month median follow-up, patients with vCPS ≥5% or CPS ≥1 tumors showed survival benefit



No. at risk					
vCPS ≥5%	38	9	5	2	0
vCPS <5%	36	2	0	0	0



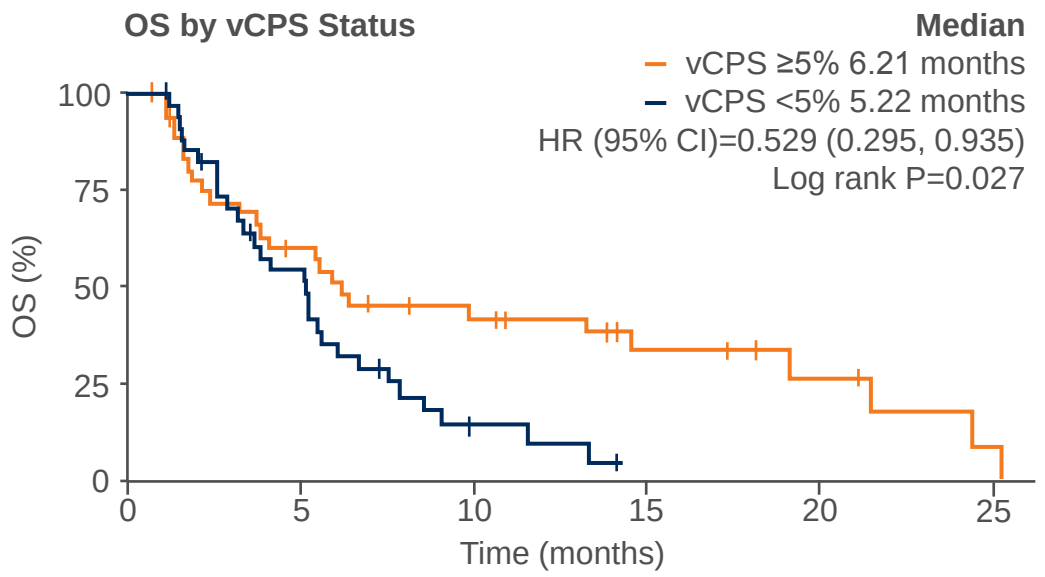
No. at risk					
CPS ≥1	22	5	1	1	0
CPS <1	27	2	0	0	0

CI: Confidence interval. CPS: Combined positive score. PFS. Progression-free survival. PPV: Positive predictive value. vCPS: Visually-estimated combined positive score.. HR: hazard ratio. PFS: progression-free survival. OS: overall survival

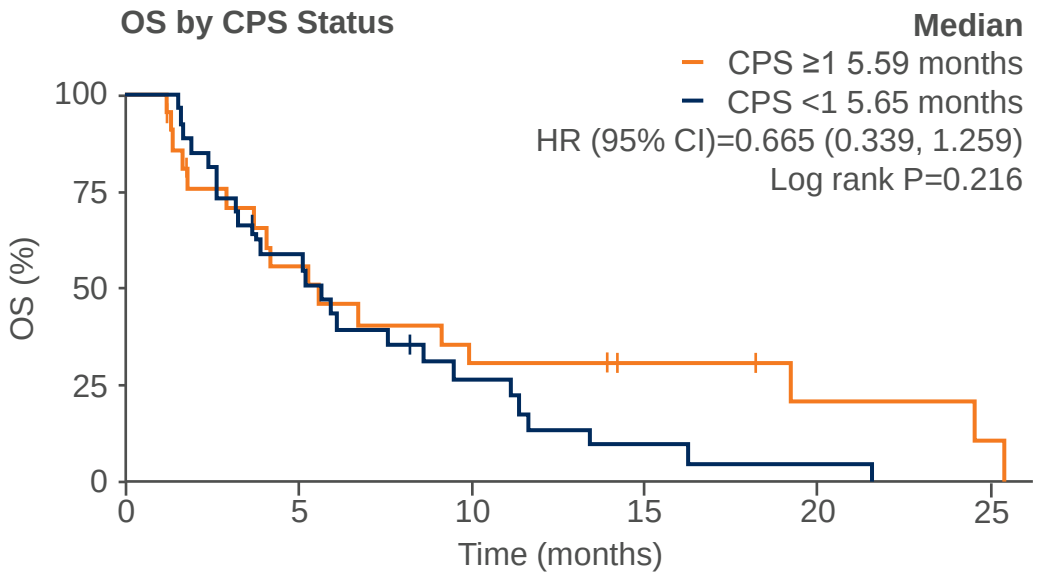
Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Clinical utility of vCPS and CPS

- More favourable PFS and OS were seen in patients with vCPS ≥5% tumors (PFS HR=0.497, OS HR=0.529) and CPS ≥1 tumors (PFS HR=0.880, OS HR=0.665)



No. at risk						
vCPS ≥5%	38	20	13	7	4	1
vCPS <5%	36	17	3	0	0	0



No. at risk						
CPS ≥1	22	11	6	4	2	1
CPS <1	27	15	6	2	1	0

CI: Confidence interval. CPS: Combined positive score. PFS. Progression-free survival. PPV: Positive predictive value. vCPS: Visually-estimated combined positive score.. HR: hazard ratio. PFS: progression-free survival. OS: overall survival

Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Validation

Analytical validation of VENTANA PD-L1 (SP263) assay in GC and GEJ adenocarcinoma

Repeatability and intermediate precision studies

24 GC or GEJ adenocarcinoma cases representing a range of PD-L1 expression levels
- 12 with vCPS ≥5% (including 2 borderline cases)
- 12 with vCPS <5% (including 2 borderline cases)
- One reader evaluated all cases

→ Within-run, between-day repeatability, and intermediate precision (between antibody, detection kit lot, and instrument) for the VENTANA PD-L1 (SP263) assay showed **100% overall percent agreement (OPA) with vCPS in gastric and GEJ adenocarcinoma**

Between-reader and within-reader precision studies

100 GC or GEJ adenocarcinoma cases representing a range of PD-L1 expression levels
- 50 with vCPS ≥5% (including 5 borderline cases)
- 50 with vCPS <5% (including 5 borderline cases)

→ VENTANA PD-L1 (SP263) assay **demonstrated between-reader precision and within-reader precision (OPA) with vCPS of 99.3% and 99%, respectively**

Inter-laboratory reproducibility

28 GC or GEJ adenocarcinoma cases representing a range of PD-L1 expression levels
- 14 with vCPS ≥5% (including 2 borderline cases)
- 14 with vCPS <5% (including 2 borderline cases)

→ Inter-laboratory reproducibility testing, performed across two readers at each of three external laboratories, demonstrated **OPA of 95% between readers and 92.5% between sites**

CPS: Combined positive score. IC: Immune cell. IHC: Immunohistochemistry. PD-L1: Programmed death-ligand 1.TC, tumor cell. vCPS: Visually-estimated combined positive score. TIC: Tumor and immune cell. OPA: Overall percent agreement.
Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

Conclusions

- At evaluated cutoffs, both VENTANA PD-L1 (SP263) and Dako 22C3 CPS assays aided identification of GEA patients with PD-L1 high tumors who were more likely to gain favorable clinical benefit from PD-1 inhibition than those with PD-L1 low tumors
- VENTANA PD-L1 (SP263) assay is a robust and reproducible tool for assessing and quantifying PD-L1 expression in GC and GEJ adenocarcinoma
- **Reproducibility of the VENTANA PD-L1 (SP263) assay with vCPS by differing pathologists, materials, and laboratories points to highly trainable assay nature and consistency in gastric cancer and gastroesophageal junction adenocarcinoma**
- Further clinical validation is underway for TIC ≥5% in patients with gastric and gastroesophageal junction adenocarcinoma from a phase 3 study (NCT03777657)

CPS: Combined positive Score. vCPS: Visually-estimated combined positive score. GEA: Gastro esophageal adenocarcinoma. GEJ: Gastroesophageal junction. PD-L1: Programmed death-ligand 1.

Chao, Y. et al, 2020. Poster 154P presented at ESMO 2020.

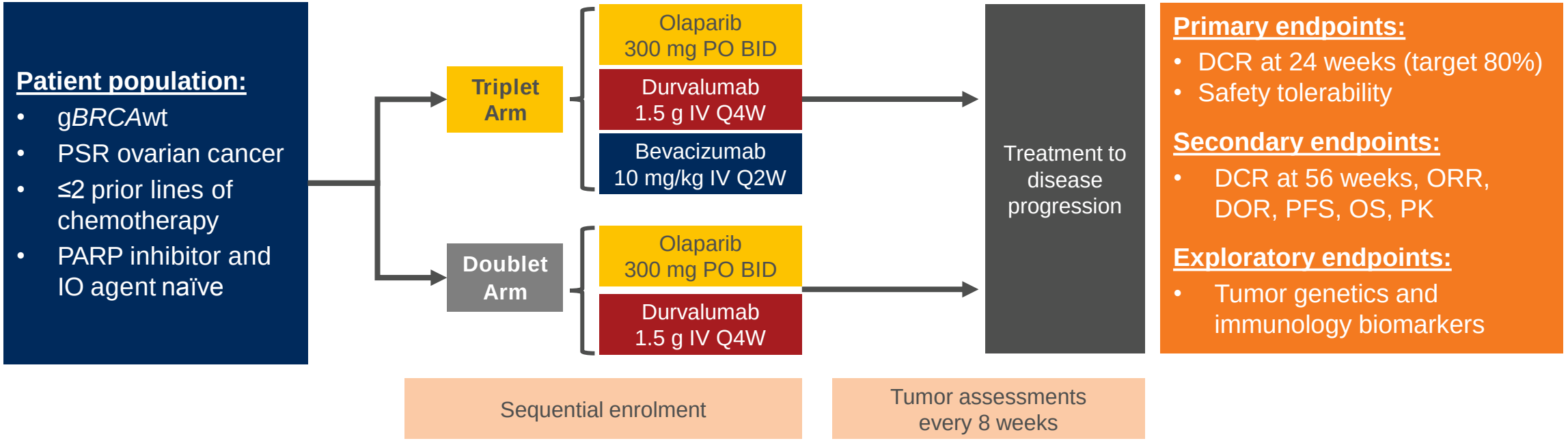
Ovarian cancer

MEDIOLA

PARPi + PD-1i in BRCAmut PSROC: Olaparib + durvalumab

MEDIOLA Study design

Phase 2 study of olaparib + durvalumab (MEDIOLA): Updated results in germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer (OC)

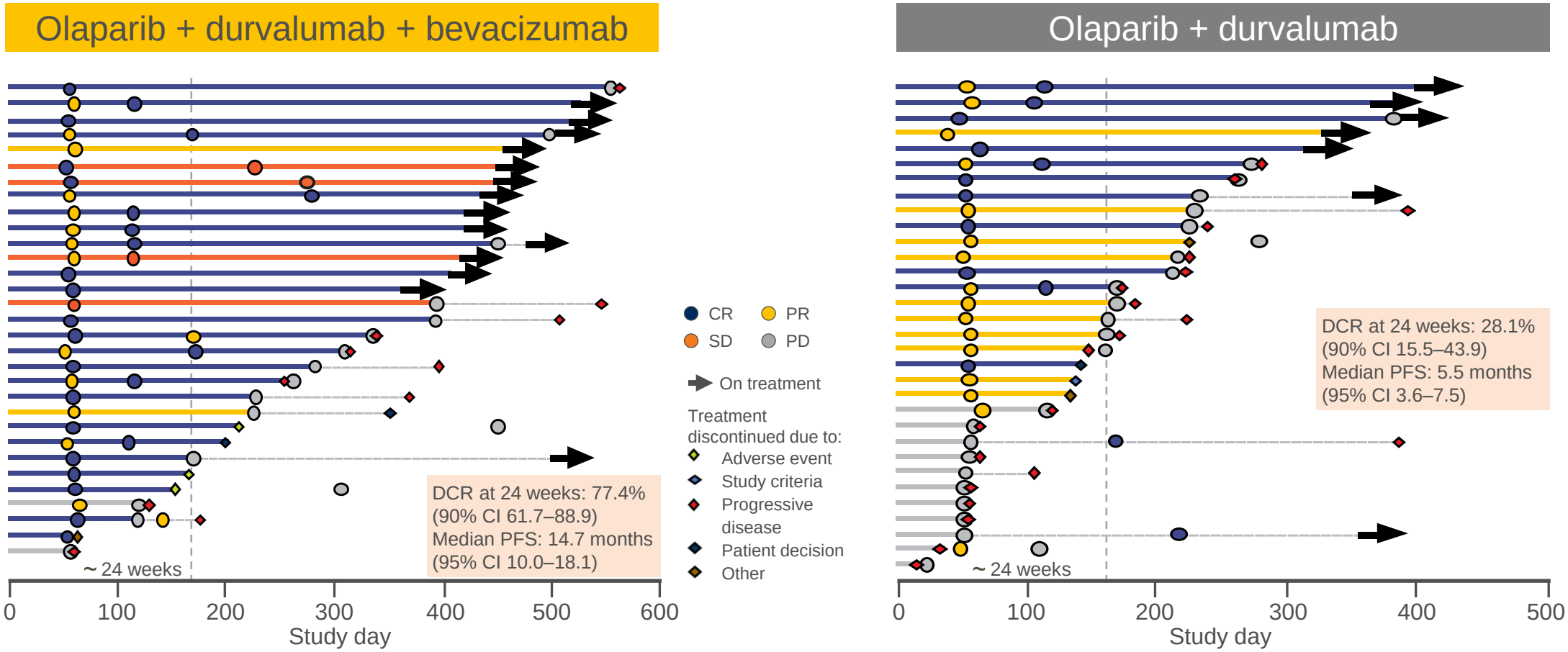


BID: Twice daily. DCR: Disease control rate. DOR: Duration of response. IO: Immuno-oncology. IV: Intravenous; ORR, objective response rate; OS, overall survival; PARP, Poly (ADP-ribose) polymerase; PFS, progression-free survival; PK, pharmacokinetics; PO, per oral; PSR, platinum-sensitive relapsed; q2w, every 2 weeks; q4w, every 4 week

Drew, Y. et al. Abstract 814MO presented at ESMO 2020.

MEDIOLA Results - efficacy

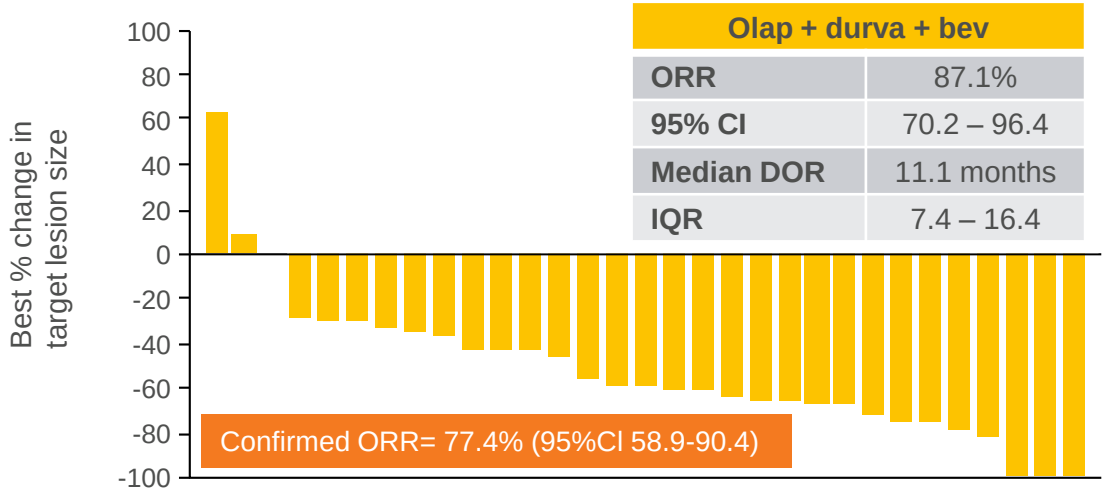
Time to progression or treatment discontinuation

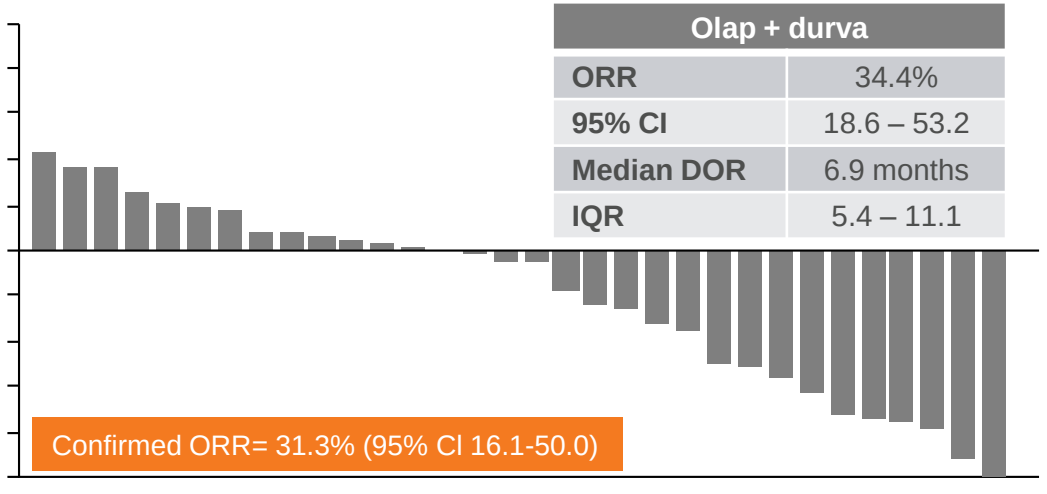


DCR: Disease control rate. PFS: Progression-free survival. CI: Confidence interval.
Drew, Y. et al. Abstract 814MO presented at ESMO 2020.

MEDIOLA Exploratory analysis

Objective response rate (ORR)





	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
Genomic instability status (GIS)* subgroup	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100 (69.2-100)	10/10	50 (18.7-81.3)	5/10
GIS-negative	75 (34.9-96.8)	6/8	16.7 (0.4-64.1)	1/6
GIS-unknown	84.6 (54.6-98.1)	11/13	31.3 (11.0-58.7)	5/16

- Triplet cohort demonstrates GIS-independent, high ORR

Olap: Olaparib. Bev: Bevacizumab. CI: Confidence interval. DCO: Data cut off. DOR: Duration of response. Durva: Durvalumab. IQR, interquartile range; LOH, loss of heterozygosity; olap, olaparib; * GIS as determined by foundation medicine tumour analysis must have genome wide LOH ≥14, a somatic *BRCA1* and/or *BRCA2* mutation, or a mutation in *ATM, BRIP1, PALB2, RAD51C, BARD1, CDK12, CHEK1, CHEK2, FANCL, PPP2R2A, RAD51B, RAD51D or RAD54L* to be considered positive. At the time of the DCO, the prespecified cut-off for genome-wide LOH of 14% was used (Swisher et al. Lancet Oncol 2017; 18:75-87)

Drew, Y. et al. Abstract 814MO presented at ESMO 2020.

MEDIOLA Safety Profiles

Patients with AE*, n (%)	Olap + durva + bev (N=31)	Olap + durva (N=32)
Nausea	22 (71)	28 (88)
Fatigue	16 (52)	16 (50)
Anaemia	15 (48)	13 (41)
Diarrhoea	12 (39)	14 (44)
Constipation	9 (29)	7 (22)
Vomiting	15 (48)	4 (13)
Decreased appetite	11 (35)	9 (28)
Headache	11 (35)	7 (22)
Abdominal pain	8 (26)	6 (19)
Arthralgia	8 (26)	8 (25)
Urinary tract infection	9 (29)	5 (16)
Blood creatinine increased	5 (16)	7 (22)
Hypothyroidism	2 (6)	5 (16)
Dysgeusia	4 (13)	6 (19)
AST increased	5 (16)	2 (6)
Myalgia	3 (10)	7 (22)
Rash	5 (16)	3 (19)
Back pain	3 (10)	6 (19)
Hypertension	8 (26)	1 (3)
Pruritus	2 (6)	5 (16)
Asthenia	1 (3)	7 (22)
Stomatitis	5 (16)	1 (3)
Weight decreased	5 (16)	3 (9)
Proteinuria	7 (23)	0
Epistaxis	6 (19)	0
Dysphonia	5 (16)	0

Patients with AE grade ≥3†, N (%)	Olap + durva + bev (N=31)	Olap + durva (N=32)
Anemia	4 (13)	7 (22)
Hypertension	4 (13)	1 (3)
Lipase increased	2 (6)	2 (6)
Fatigue	2 (6)	1 (3)
White blood cell count decreased	2 (6)	0
Neutropenia	0	2 (6)
AE leading to discontinuation of ≥1 study treatment	5 (16)	2 (16)
	• Anemia • Lethargy • Intestinal perforation • Chronic kidney disease • Proteinuria	• Renal impairment • Lipase increased

* Most common AEs any grade (frequency >15%); †AEs of grade ≥3 occurring in 2 or more patients; AEs per common terminology criteria for adverse events (CTCAE) v4.03
AE: Adverse event. AST: Aspartate transaminase.

Drew, Y. et al. Abstract 814MO presented at ESMO 2020.

Conclusions

- **Triplet combination of olaparib, durvalumab and bevacizumab showed promising efficacy as treatment in the absence of chemotherapy for women with germline BRCA wild type platinum - sensitive relapsed advanced ovarian cancer, with 77% disease control rate at 24 weeks and median PFS of 15 months**
- Exploratory analysis suggests high ORR in triplet cohort not driven by differences in genomic instability status (GIS); ORR was ≥75% in the GIS+, GIS− and GIS unknown subgroups
- Safety profile of combination of olaparib plus durvalumab with/ without bevacizumab was consistent with known safety profiles expected for the single agents
- Combination of olaparib, durvalumab and bevacizumab now being tested as part of first-line maintenance treatment in the Phase 3 study, DUO-O (NCT 03737643)

PFS: Progression free survival. ORR: Objective response rate.

Drew, Y. et al. Abstract 814MO presented at ESMO 2020.

PARP inhibition in ovarian cancer

Pivotal phase 2 trial of pamiparib in advanced ovarian cancer

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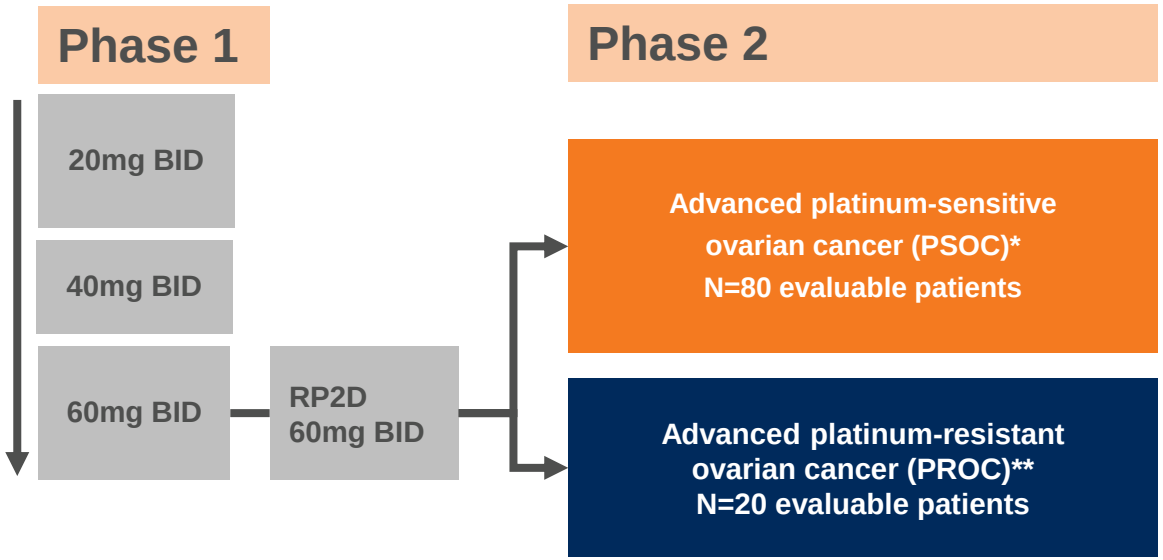
Study design

Phase 1/2 open-label, multicenter study assessing safety and antitumor activity of pamiparib in adults (≥18 years), Chinese patients with advanced ovarian cancer whose disease progressed despite standard therapy, or for which there is no standard therapy



Pamiparib 60 mg administered PO BID on Day 1 of Cycle 1 (21-day cycle) and continuously in all subsequent cycles until disease progression, toxicity, or patient withdrawal

*Defined as disease progression occurring ≥6 months after last platinum treatment

**Defined as disease progression that occurred <6 months after last platinum treatment

Study Population

- **High grade, non-mucinous, epithelial OC** (including fallopian or primary peritoneal cancer) and **ECOG performance status of 0-1**
- **Known deleterious/suspected deleterious gBRCAmut with ≥ 2 lines of standard chemotherapy**, and currently experiencing relapsed disease/discontinued most recent standard treatment due to unacceptable toxicity
- Exclusions: Untreated/active brain metastases or received prior treatment within 14 days of initiating study
- **A protocol amendment (PA)** initiated a more proactive dose modification algorithm and close hematology monitoring; a pre- and post-PA safety analysis was conducted

BID: Twice daily. RP2D: Recommended phase 2 dose. PO: Orally. PROC: Platinum-resistant ovarian cancer. PSOC: Platinum-sensitive ovarian cancer. ECOG: Eastern cooperative oncology group. gBRCAmut: genomic BRCA1/2 mutations. OC: Ovarian cancer.

Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Endpoints and assessments

Primary endpoint

- Objective response rate (ORR) based on independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary endpoints

- Duration of response (DOR) and progression-free survival (PFS) by IRC and investigator review
- Disease control rate and clinical benefit rate by IRC and investigator review
- ORR by investigator review
- Overall survival (OS)
- CA-125 response rate per Gynecologic Cancer Intergroup criteria
- Pamiparib safety/tolerability profile

Assessments

- **Tumor imaging and CA-125 testing**: every 6 weeks after 1st dose of pamiparib for 1st 18 weeks, every 9 weeks for remaining period in 1st year, and every 12 weeks from 2nd year onward
- **Safety and tolerability assessments**: based on monitoring of AEs, as well as on vital signs, electrocardiograms, physical examinations, and clinical laboratory result
- **Statistical Methods**: Antitumor activity per RECIST v1.1 was assessed in all efficacy-evaluable patients
- **Safety and tolerability**: Evaluated in all patients who received ≥1 dose of pamiparib

ORR: Objective response rate. IRC: Independent review committee. RECIST: Response evaluation criteria in solid tumors. DOR: Duration of response. PFS: Progression free survival. OS: Overall survival AE: Adverse event.
Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Results – antitumor activity

Tumor response by patient cohort in the efficacy-evaluable population by IRC and investigator assessment based on RECIST v1.1

		IRC Assessment		Investigator assessment	
		PSOC (N=82)	PROC (N=19)	PSOC (N=82)	PROC (N=19)
Best overall response, N (%)	Compete response (CR)	8 (9.8)	0 (0.0)	5 (6.1)	0 (0.0)
	Partial response (PR)	45 (54.9)	6 (31.6)	46 (56.1)	5 (26.3)
	Stable disease (SD)	25 (30.5)	12 (63.2)	28 (34.1)	10 (52.6)
	Progressive disease (PD)	4 (4.9)	1 (5.3)	3 (3.7)	3 (15.8)
	Not estimable	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Objective response rate (ORR), % (95% CI)		64.6 (53.3-74.9)	31.6 (12.6-56.6)	62.2 (50.8-72.7)	26.3 (9.1-51.2)
Disease control rate (DCR), % (95% CI)		95.1 (88.0-98.7)	94.7 (74.0-99.9)	96.3 (89.7-99.2)	78.9 (54.4-93.9)
Cinical benefit rate (CBR) ≥24 weeks, % (95% CI)		74.4 (63.6-83.4)	52.6 (28.9-75.6)	72.0 (60.9-81.3)	52.6 (28.9-75.6)
Median time to response, months (min, max)		1.7 (1.3, 6.3)	1.4 (1.2, 1.4)	2.7 (1.2, 8.3)	1.3 (1.2, 4.2)

- ORR in PSOC 64.6% by IRC (62.2% by investigator assessment) and 31.6% in PROC (26.3% by investigator assessment)
- ORR and CR rate per RECIST v1.1 similar between IRC and investigator assessment
- CA-125 response rate 79.7% (95% CI, 68.8-88.2) in PSOC patients and 38.1% (95% CI, 18.1-61.6) in PROC patients

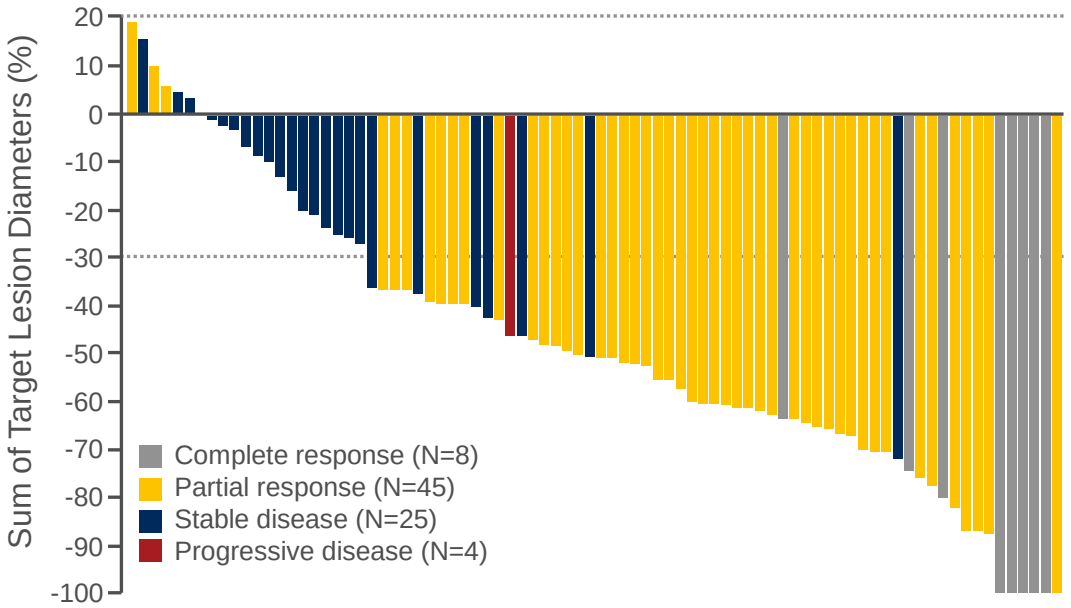
CBR=CR+PR+SD ≥24 weeks; DCR=CR+PR+SD; ORR=CR+PR
IRC: Independent review committee. RECIST: Response evaluation criteria in solid tumors. CI: Confidence interval. PROC: Platinum resistant ovarian cancer. PSOC: Platinum-sensitive ovarian cancer. RECIST: Response evaluation criteria in solid tumors.
Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Results - reduction in target lesions from baseline

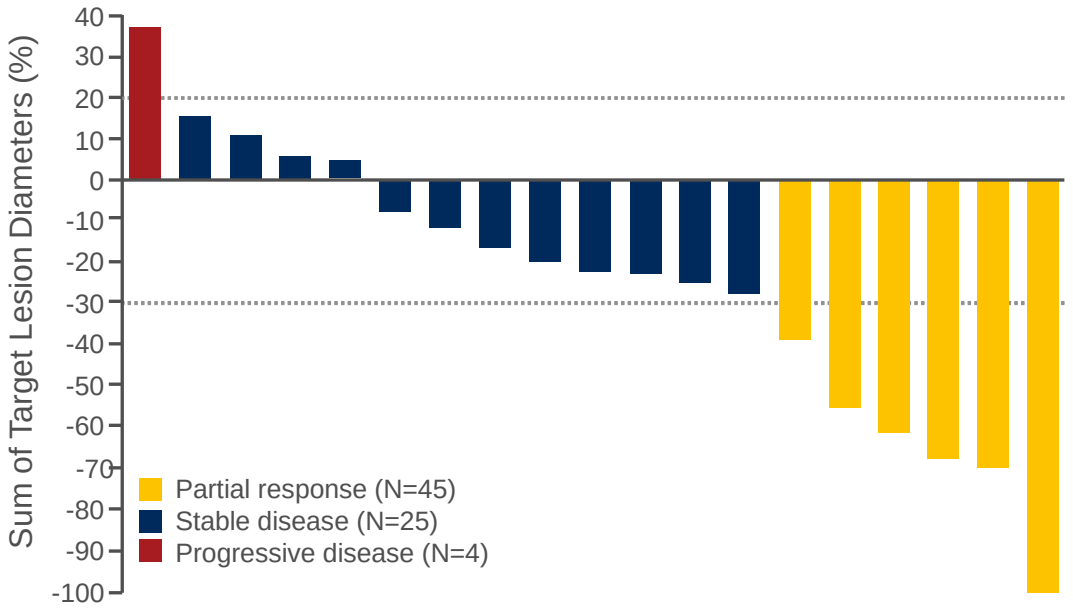
Best change in sum of target lesion diameters by confirmed best overall response of the efficacy-evaluable population* per RECIST v1.1

- In both cohorts, most patients had a reduction in target lesions from baseline

A. PSOC (Cohort 1)



B.. PROC (Cohort 2)



*Patients were considered efficacy-evaluable if they had measurable disease at baseline per RECIST v1.1 and had ≥1 postbaseline tumor assessment, unless treatment had been discontinued due to clinical progression or death prior to tumor assessment.

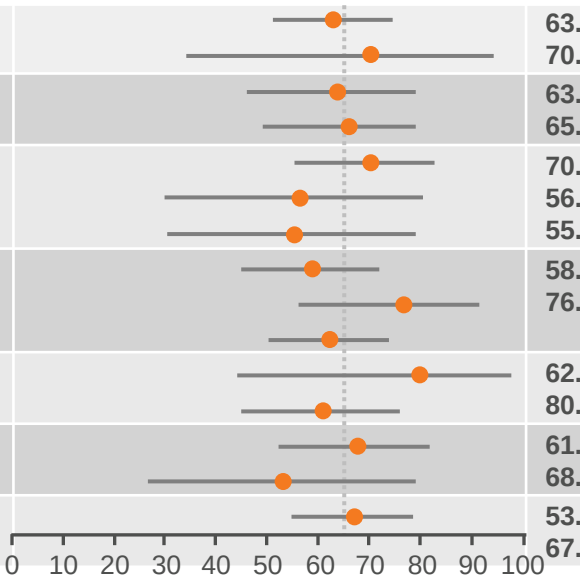
RECIST: Response evaluation criteria in solid tumors. PROC: Platinum resistant ovarian cancer. PSOC: Platinum-sensitive ovarian cancer.
Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Results – ORR in PSOC patients

IRC assessed objective response rates (RECIST v1.1) by baseline characteristics in PSOC patients

- Primary endpoint of ORR in PSOC patients was generally consistent across all subgroups

		Response/Patients (N)	ORR (95% CI)
Age	<65 years	46/72	63.9 (51.7, 74.9)
	≥65 years	7/10	70.0 (34.8, 93.3)
ECOG performance status	0	23/36	63.9 (46.2, 79.2)
	1	30/46	65.2 (49.8, 78.6)
Prior systemic chemotherapy lines	2	34/48	70.8 (55.9, 83.0)
	3	9/16	56.3 (29.9, 80.2)
	≥4	10/18	55.6 (30.8, 78.5)
Time to progression to last platinum-based therapy	6-12 months	33/56	58.9 (45.0, 71.9)
	≥12 months	20/26	76.9 (56.4, 91.0)
BRCA mutation type	*BRCA1*	45/72	62.5 (50.3, 73.6)
	BRCA2	8/10	80.0 (44.4, 97.5)
Target lesion diameter per IRC at study entry	<50 mm	25/41	61.0 (44.5, 75.8)
	≥50 mm	28/41	68.3 (51.9, 81.9)
CA-125 atstudy entry	<70 kU/L	8/15	53.3 (26.6, 78.7)
	≥70 kU/L	45/67	67.2 (54.6, 78.2)



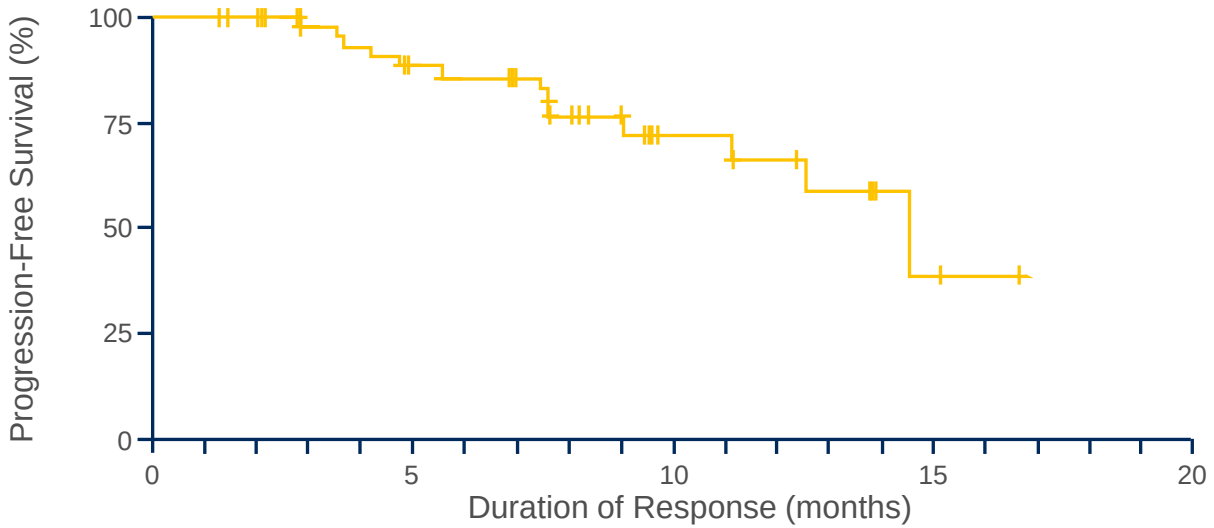
Data are presented as ORR (range); the dotted line corresponds to 65% ORR.
BRCA: breast cancer susceptibility gene. CI: confidence interval. ECOG: Eastern Cooperative Oncology Group. IRC: independent review committee. ORR: objective response rate.
PSOC: platinum-sensitive ovarian cancer. RECIST: Response Evaluation Criteria in Solid Tumors.
Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Results - duration of response and progression-free survival in PSOC patients

Duration of response and progression free survival in PSOC patients by IRC assessment per RECIST v1.1

- Median duration of response was 14.5 months (95% CI, 11.1-NE)

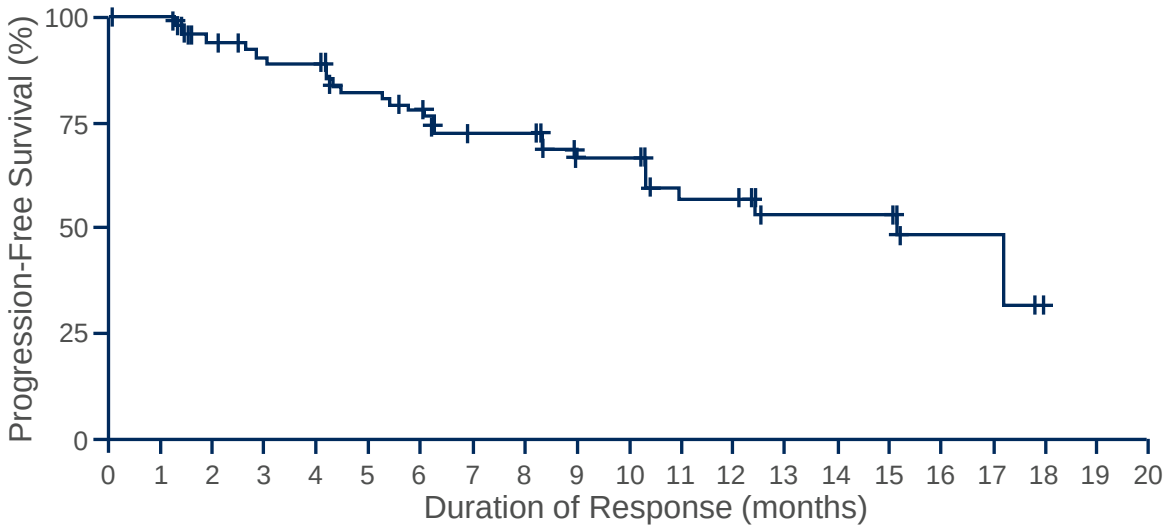
Duration of Response in Efficacy-Evaluable Population



No. at risk (N)					
PSOC	53	34	12	2	0

- Median progression-free survival was 15.2 months (95% CI, 10.35-NE)

Progression-Free Survival in Safety Population

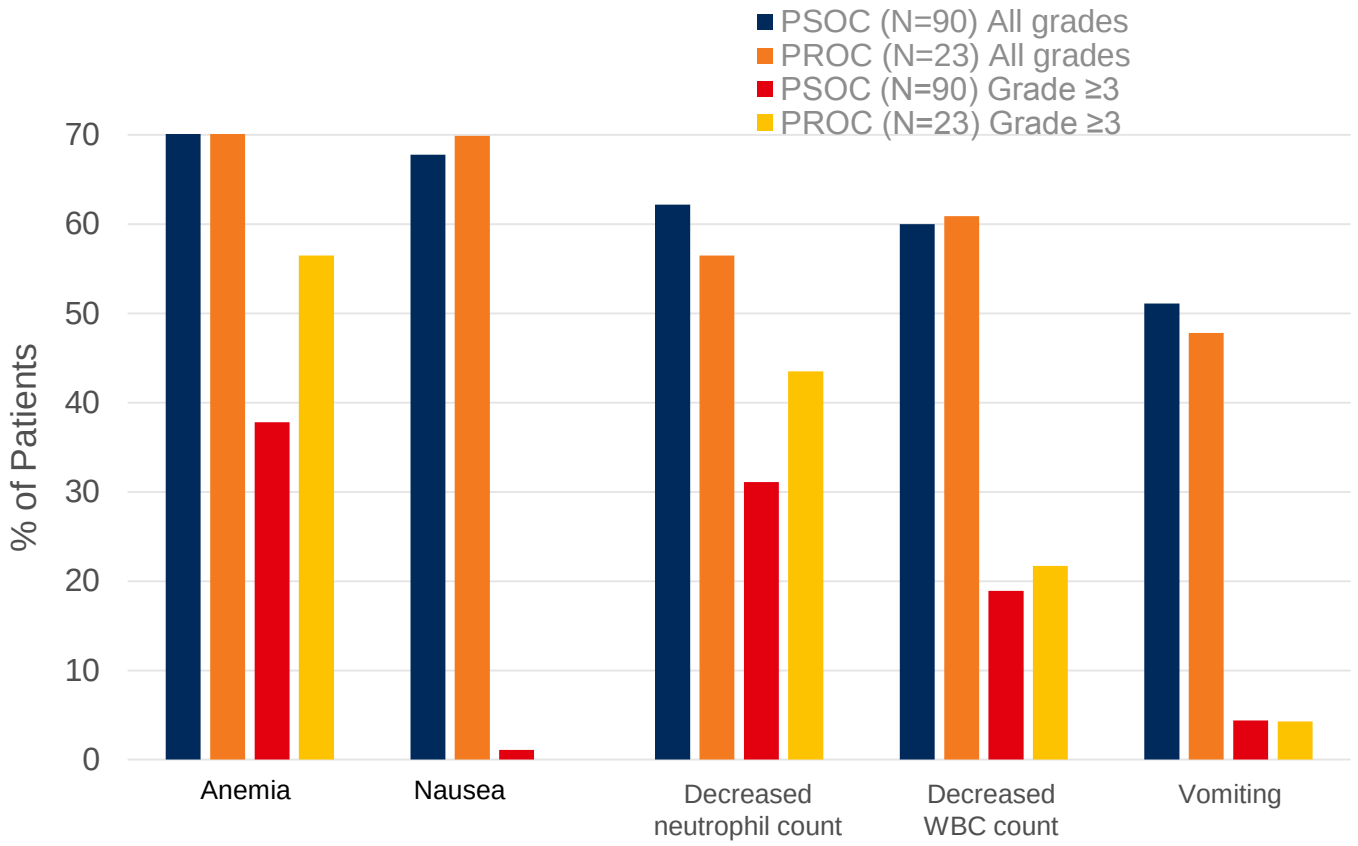


No. at risk (N)																				
PSOC	90	88	78	72	72	62	57	41	41	32	31	22	22	12	12	12	3	3	1	0	0

IRC: Independent review committee. RECIST: Response evaluation criteria in solid tumors. CI: Confidence interval. PSOC: Platinum-sensitive ovarian cancer. NE: not evaluable.
Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Results – safety and tolerability

Summary of most common TEAEs



- Median treatment duration 8.3 months (range, 0.1-19.3 months) in PSOC patients and 4.1 months (range, 0.1-19.9 months) in PROC patients
- Across both PSOC and PROC cohorts, the most frequently reported AEs of any grade were GI disorders and hematologic toxicities
- In the post-protocol amendment (PA) subgroup, the percentage of patients who experienced grade ≥3 hematologic AEs was lower vs the pre-PA subgroup
- No patient in the post-PA subgroup experienced a hematologic AE that led to treatment discontinuation

WBC: White blood cell. PROC: Platinum resistant ovarian cancer. PSOC: Platinum-sensitive ovarian cancer. GI: Gastrointestinal. PA: Protocol amendment. AE: Adverse event. TEAE: treatment-emergent adverse events

Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

Conclusions

- **Statistically and clinically meaningful and durable response observed in patients with PSOC**
- **Clinically meaningful and durable response observed in patients with PROC**

- Pamiparib 60 mg PO BID demonstrated a generally tolerated and acceptable safety profile
- Overall safety profile generally consistent between patients with PSOC and PROC
- Similar to other PARP inhibitors, hematologic toxicities were the most significant safety events observed
- Hematological toxicities were manageable and could be better managed with a more proactive modification plan and closer hematologic monitoring
- No myelodysplastic syndrome reported
- No significant complications (e.g. grade ≥3 hemorrhage, fever, or infection) potentially related to hematologic toxicity reported

PROC: Platinum-resistant ovarian cancer. PSOC: Platinum-sensitive ovarian cancer. BID: Twice daily. PO: Orally
Wu, X. Et al, 2020. Poster 820P presented at ESMO 2020

NORA

PARPi maintainance in OC: Niraparib

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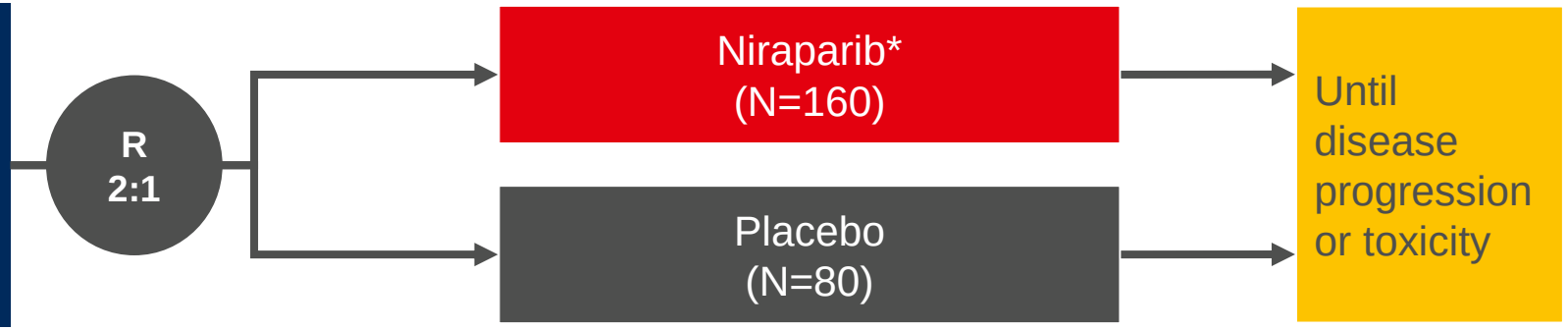
NORA Study design

Individualized starting dose of niraparib in Chinese patients with platinum-sensitive recurrent ovarian cancer (PSROC): A randomized, double-blind, placebo-controlled, phase 3 trial

Main inclusion criteria

- Platinum-sensitive, recurrent OC
- High-grade serous or high grade predominantly serous histology or known to have g*BRCA*mut
- Completed at least 2 previous lines of platinum-containing therapy
- Partial or complete response to the last platinum-based chemotherapy



Stratification factors

- g*BRCA* mutation: Yes or No
- Response to last chemotherapy: complete or partial response
- Time to progression after penultimate platinum-based regimen: 6-12 vs >12 months

*** Individual dosing - adopted in protocol amendment**

- Body weight ≥77 kg and platelets ≥150,000/μL started with 300 mg QD
- Body weight <77 kg and/or platelets <150,000/μL started with 200 mg QD

Primary endpoint

- Progression-free survival (PFS) by BICR

  Primary analysis of PFS in ITT population
  Statistical assumption: PFS hazard ratio of 0.54, two-sided type I error of .05, power >90%

Secondary endpoint

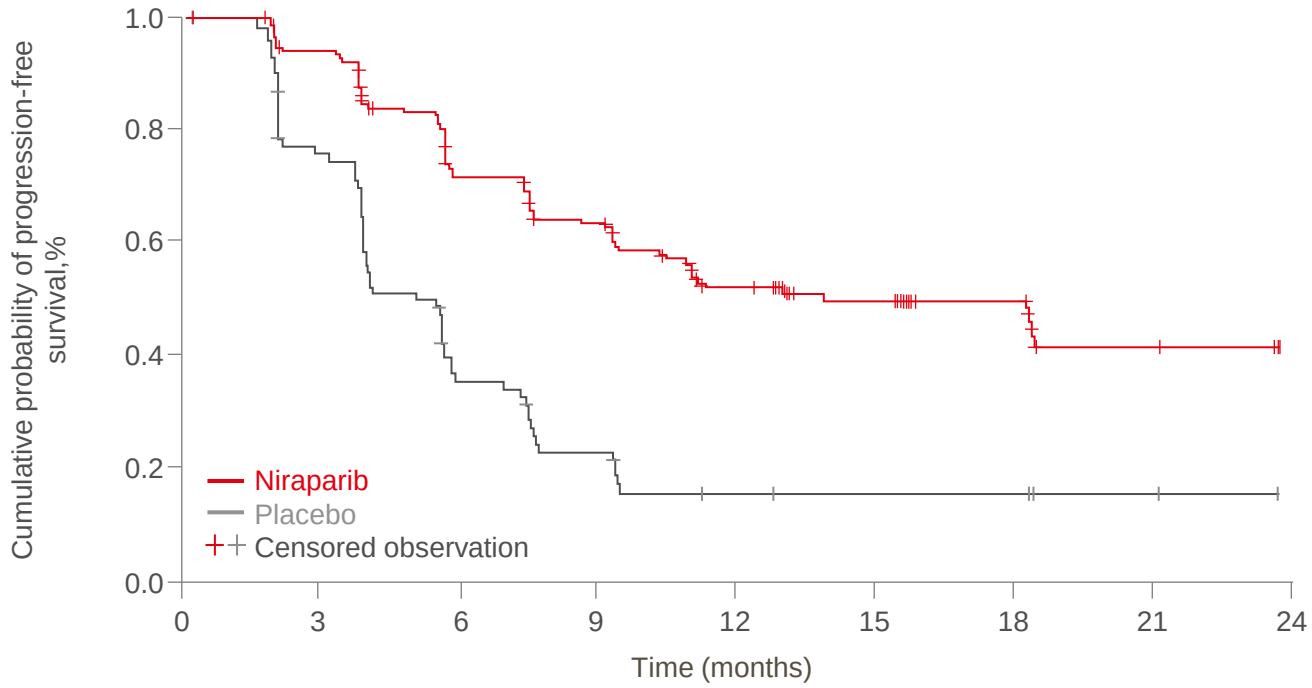
- Safety
- Chemotherapy-free interval (CFI)
- Time to first subsequent therapy (TFST)
- Overall survival (OS)

ITT: Intention to treat. PFS: Progression free survival.CR: Complete response. PR: Partial response. BICR: Blinded independent central review. QD: Once daily. ISD: PFS: Progression free survival. OC: Ovarian cancer. ISD: Individualized starting dose. R: Randomize

Wu, X. et al, 2020. LBA29 presented at ESMO 2020

NORA Primary endpoint

PFS (BICR) in ITT population



Niraparib	177	160	116	100	70	43	25	8	0
Placebo	88	63	28	18	11	8	8	2	0

68% reduction of hazard for relapse or death with niraparib

	Niraparib (N=177)	Placebo (N=88)
Median PFS		
Months (95% CI)	18.3 (10.9–NE)	5.4 (3.7–5.7)
Hazard ratio (95% CI)	0.32 (0.23-0.45)	
p-value[1]	<0.0001	

[1] p-value is from stratified log-rank test.

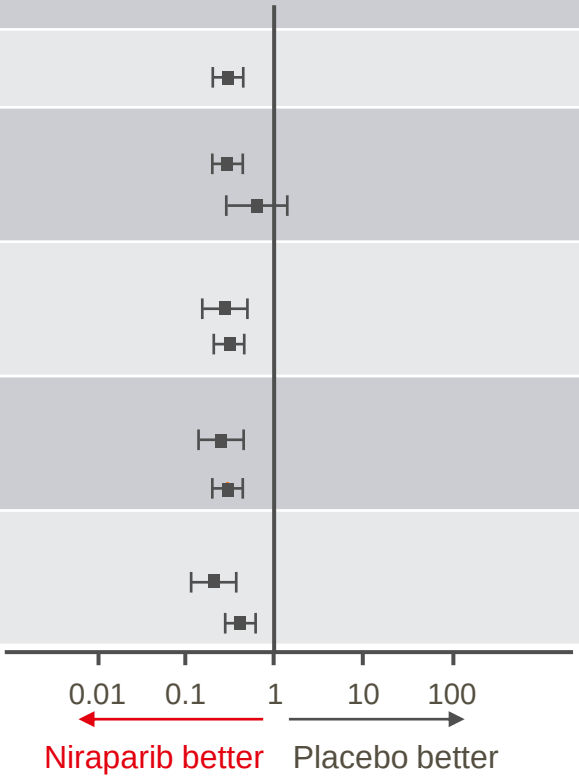
Niraparib resulted in significantly longer mPFS than placebo in ITT population of all-comer patients

ITT, intention to treat; **BICR**: blinded independent central review; **CI**, confidence interval; **NE**, not estimable; **PFS**, progression-free survival

Individualized starting dose of niraparib in chinese patients with platinum-sensitive recurrent ovarian cancer (PSROC): A randomized, double-blind, placebo-controlled, phase 3 trial (NORA).
X. Wu et al. ESMO 2020, abstract LBA29

PFS (BICR) in pre-specified subgroups

	Niraparib Events / N	Placebo Events / N	Hazard Ratio (95% CI)
Subgroup			
Overall	80/177	66/88	0.32 (0.23,0.46)
Age, year			
18-64	63/152	57/76	0.30 (0.21,0.44)
≥65	17/25	9/12	0.65 (0.29,1.46)
Time to progression after penultimate therapy, months			
6-12	29/56	25/28	0.31 (0.17,0.55)
≥12	51/121	41/60	0.33 (0.22,0.51)
Best response to platinum			
Complete response	28/86	32/47	0.26 (0.15,0.46)
Partial response	52/90	34/41	0.33 (0.21,0.52)
Germline BRCA mutation status			
Positive	24/64	28/35	0.22 (0.12,0.39
Negative	56/112	38/53	0.40 (0.26,0.61)

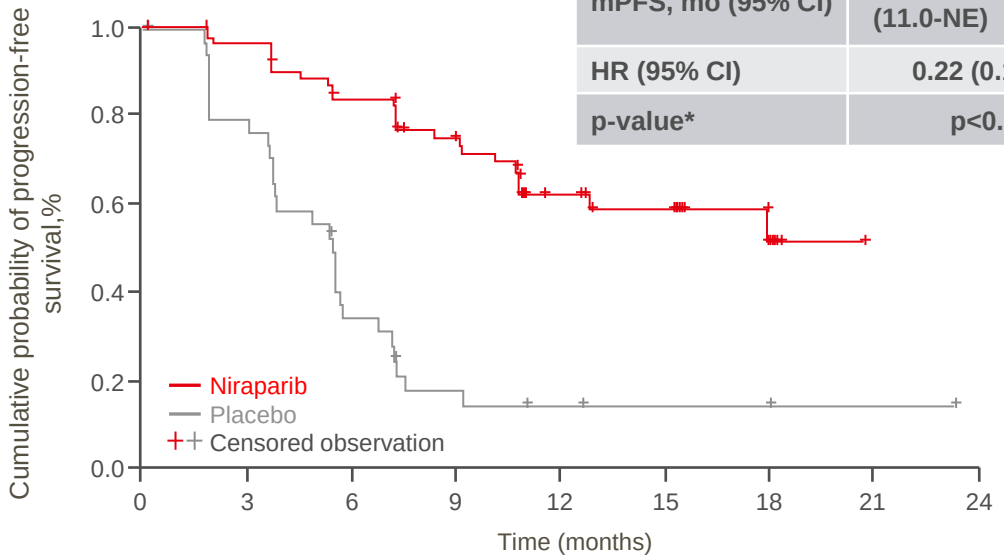


PFS: Progression free survival. BICR: Blinded independent central review. CI: Confidence interval.
Wu, X. et al, 2020. LBA29 presented at ESMO 2020

PFS (BICR) in biomarker subgroups

g*BRCA*mut subgroups

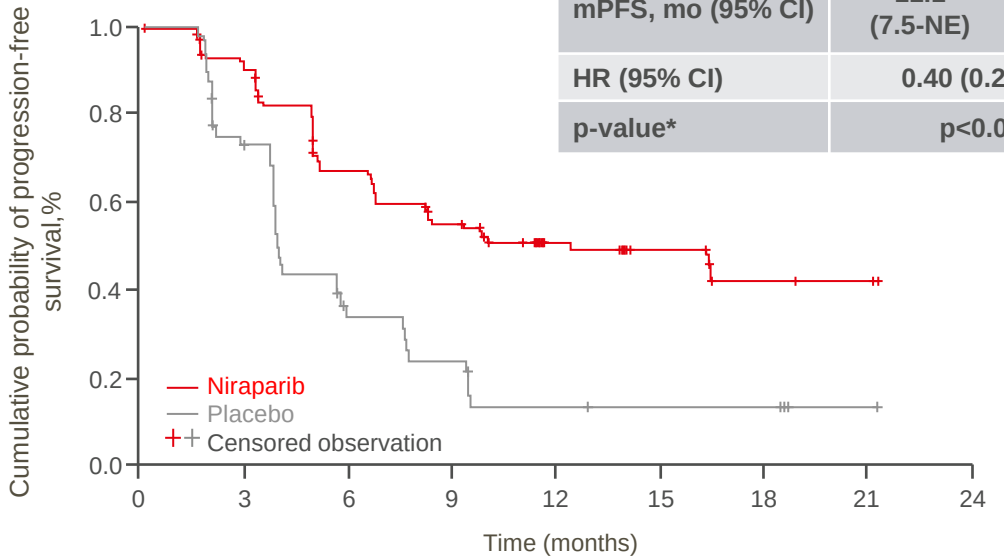
	Niraparib (N=65)	Placebo (N=35)
mPFS, mo (95% CI)	NR (11.0-NE)	5.5 (3.7-6.9)
HR (95% CI)	0.22 (0.12-0.39)	
p-value*	p<0.0001	



Niraparib	65	61	51	43	29	18	9	1	0
Placebo	35	27	11	5	3	2	2	1	0

Non-g*BRCA*mut subgroups

	Niraparib (N=112)	Placebo (N=53)
mPFS, mo (95% CI)	11.1 (7.5-NE)	3.9 (3.7-6.9)
HR (95% CI)	0.40 (0.26-0.61)	
p-value*	p<0.0001	



Niraparib	112	99	65	57	41	25	16	7	0
Placebo	53	36	17	13	8	6	6	1	0

* p-value is from stratified log-rank test, descriptive only

- Niraparib provided clinical benefit regardless of g*BRCA* mutation status

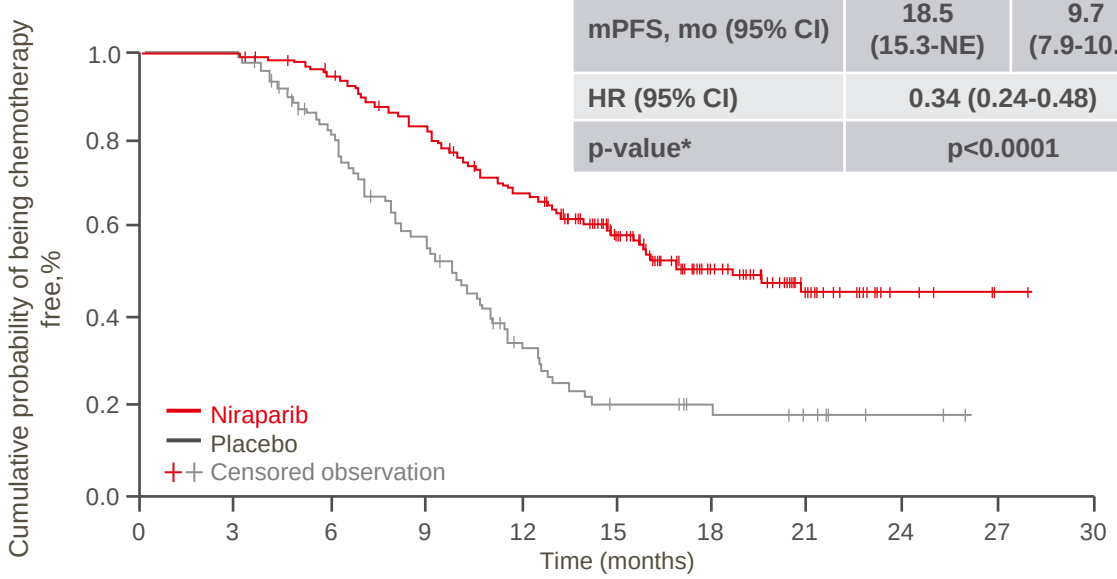
PFS: Progression free survival. mPFS: medianPFS. NR: Not reached. HR: Hazard ratio. CI: Confidence interval

Wu, X. et al, 2020. LBA29 presented at ESMO 2020

Secondary efficacy endpoints: CFI and TFST

Chemo-free interval (CFI)

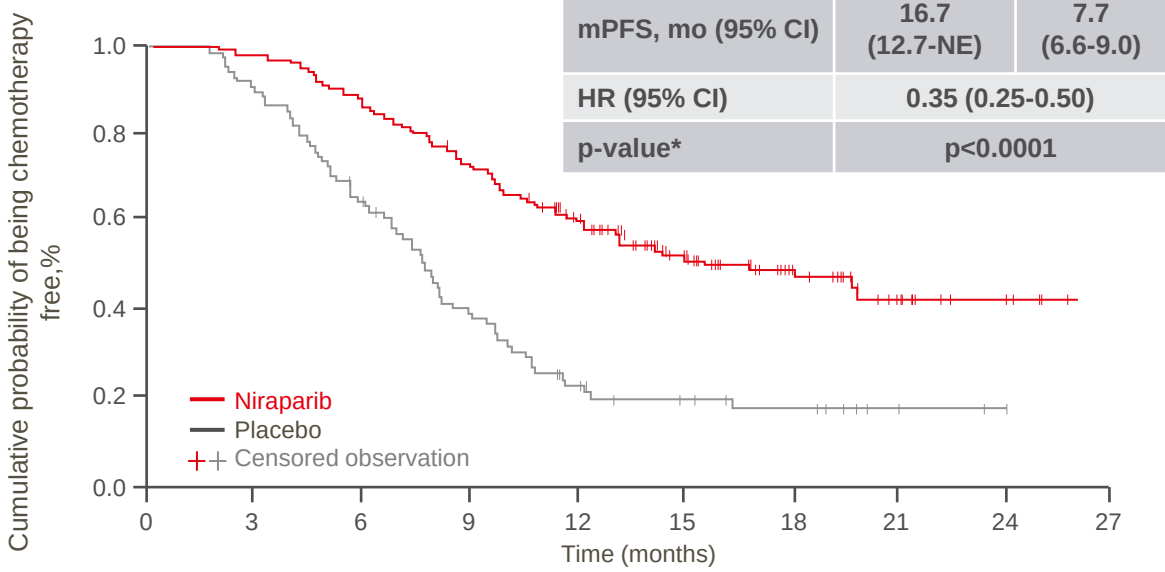
	Niraparib (N=177)	Placebo (N=88)
mPFS, mo (95% CI)	18.5 (15.3-NE)	9.7 (7.9-10.8)
HR (95% CI)	0.34 (0.24-0.48)	
p-value*	p<0.0001	



Niraparib	177	177	163	141	113	72	42	15	4	1	0
Placebo	88	87	65	40	21	12	8	6	2	0	

Time to first subsequent therapy (TFST)

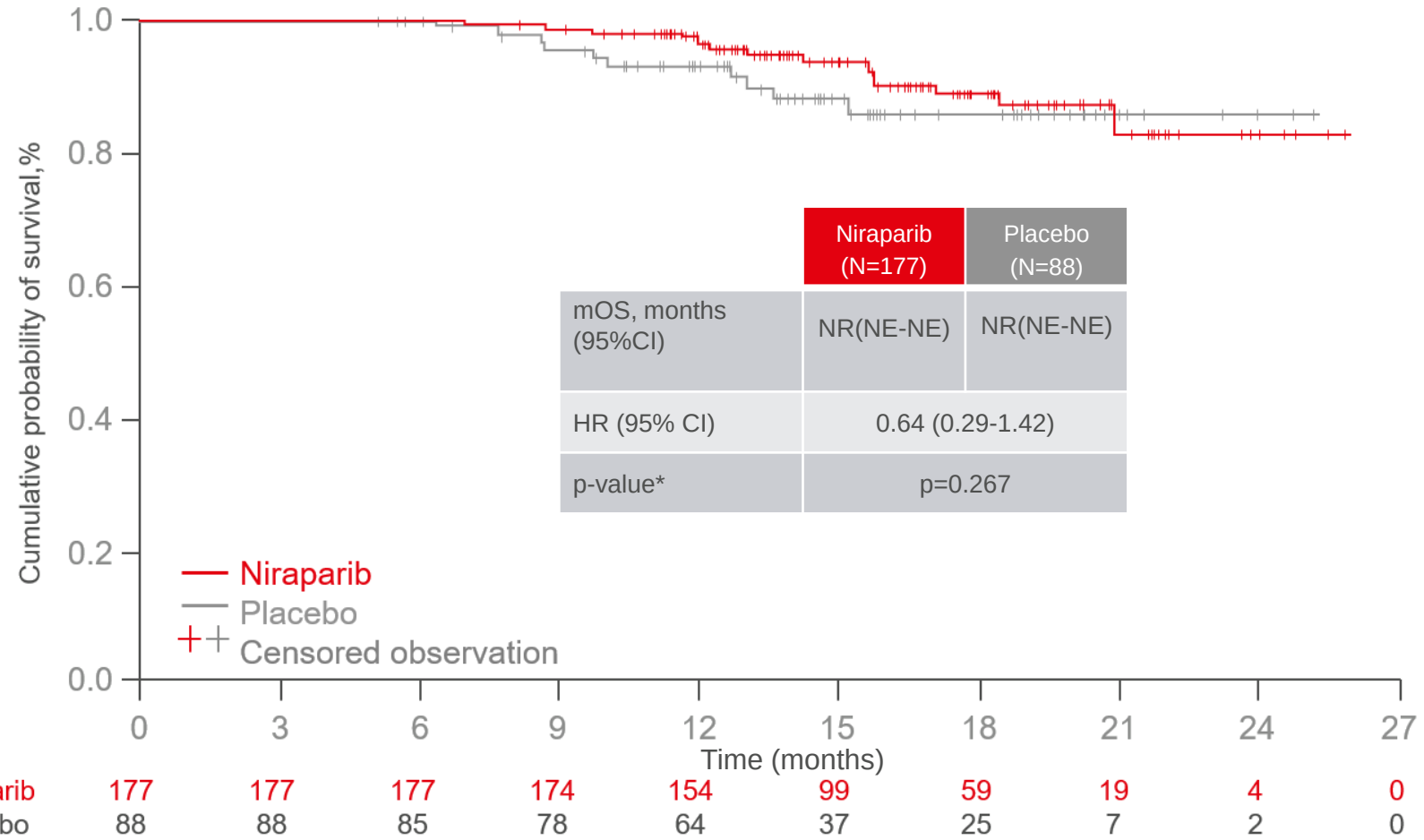
	Niraparib (N=117)	Placebo (N=88)
mPFS, mo (95% CI)	16.7 (12.7-NE)	7.7 (6.6-9.0)
HR (95% CI)	0.35 (0.25-0.50)	
p-value*	p<0.0001	



Niraparib	177	173	152	126	100	56	30	11	2	0
Placebo	88	80	54	32	15	11	8	2	0	

OS: Overall survival. NR: Not reached. HR: Hazard ratio. CI: Confidence interval. NE: Not estimable.
Wu, X. et al, 2020. LBA29 presented at ESMO 2020

Secondary efficacy endpoint: OS



	Niraparib (N=177)	Placebo (N=88)
mOS, months (95%CI)	NR(NE-NE)	NR(NE-NE)
HR (95% CI)	0.64 (0.29-1.42)	
p-value*	p=0.267	

	Niraparib (N=177)	Placebo (N=88)
Events, n (%)	**16 (9.0)**	**10 (11.4)**
Censored, n (%)	**161 (91.0)**	**78 (88.6)**

OS data were immature

OS: Overall survival. NR: Not reached. HR: Hazard ratio. CI: Confidence interval

Wu, X. et al, 2020. LBA29 presented at ESMO 2020

Safety and tolerability

Summary of adverse events

Treatment emergent adverse events (TEAE) N (%)	Niraparib (N=177)	Placebo (N=88)
Any TEAE	177 (100)	84 (95.5)
≥Grade 3	90 (50.8)	17(19.3)
Any treatment-related TEAE	176 (99.4)	77 (87.5)
≥Grade 3	79 (44.6)	10 (11.4)
Any serious TEAE	31(17.5)	10 (11.4)
Any related serious TEAEs	23 (13)	4 (4.5)
Any TEAEs leading to dose reduction	106 (59.9)	12 (13.6)
Any TEAEs leading to treatment discontinuation	7 (4)	5 (5.7)
Any TEAEs leading to death*	0	1 (1.1)

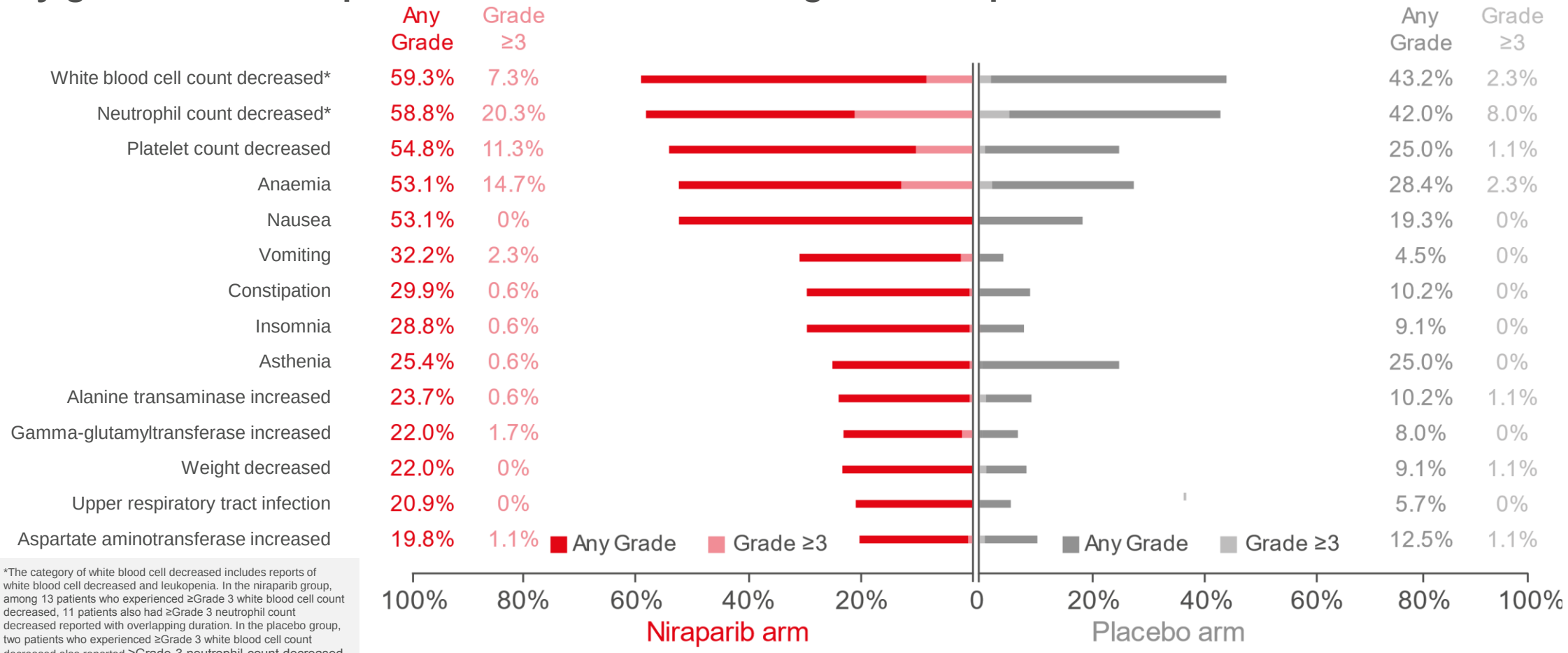
* The death case in placebo arm was a patient with secondary primary cancer (gastric cancer), which was considered as unrelated death. After the primary data cut-off, one case of treatment-related, fatal acute leukaemia (classification undefined) was reported in the niraparib group.

- Niraparib generally well tolerated, no new safety signals observed
- Most AEs managed with dose modification
- TEAEs leading to discontinuation low (4%)

TEAE: Treatment emergent adverse event. AE: Adverse event.
Wu, X. et al, 2020. LBA29 presented at ESMO 2020

Summary of adverse events

Any grade in >10% of patients in either arm and/or grade ≥3 in patients overall



*The category of white blood cell decreased includes reports of white blood cell decreased and leukopenia. In the niraparib group, among 13 patients who experienced ≥Grade 3 white blood cell count decreased, 11 patients also had ≥Grade 3 neutrophil count decreased reported with overlapping duration. In the placebo group, two patients who experienced ≥Grade 3 white blood cell count decreased also reported ≥Grade 3 neutrophil count decreased with overlapping duration.

TEAE: Treatment emergent adverse event.

Wu, X. et al, 2020. LBA29 presented at ESMO 2020

NORA Conclusions

- First fully powered phase 3 randomized clinical trial evaluating a PARP inhibitor in Chinese patients with OC
- Primary endpoint met, demonstrating that platinum-based chemotherapy and niraparib administered with an ISD regimen significantly improves CR and PR in patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
  - PFS in overall population: HR 0.32 ($p<0.0001$)
  - PFS in *gBRCAmut* subgroup: HR 0.22 ($p<0.0001$)
  - PFS in non-gBRCAmut subgroup: HR 0.40 ($p<0.0001$)
- Prospective evaluation of ISD in NORA validated the NOVA retrospective analysis. ISD of Niraparib demonstrated consistent PFS benefit vs NOVA* with improved safety profile, especially hematological toxicities
- **ISD of niraparib is safe and should be considered standard clinical practice for maintenance for patients with OC**

*NOVA trial: 300mg niraparib

PFS: Progression free survival. OC: Ovarian cancer. ISD: Individualized starting dose. CR: Complete response. PR: Partial response
Wu, X. et al, 2020. LBA29 presented at ESMO 2020

Other solid tumors

LEAP-005

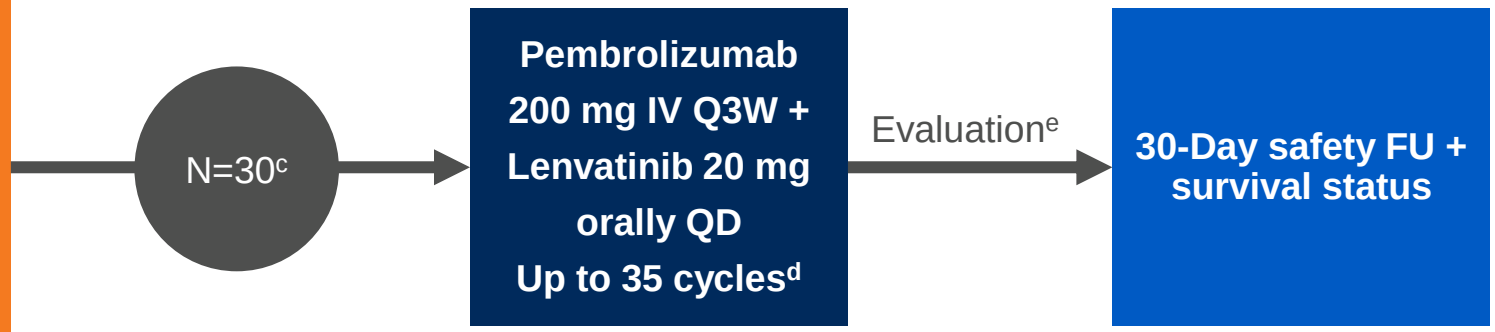
PARPi + PD-1i in previously treated advanced solid tumors: Lenvatinib plus pembrolizumab

LEAP-005 Study design

Phase 2 study of lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors

Key Inclusion/Exclusion

- ≥18 years of age
- Histologically/cytologically advanced solid tumor[a]
  - Triple negative breast (2L/3L)
  - Ovarian (4L)
  - Gastric (3L)
  - Colorectal (non/MSI H/pMMR) (3L)
  - Biliary tract (2L)
  - Glioblastoma multiforme (2L)
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1
- Tissue for PD-L1 assessment[b]



Primary endpoints: ORR (RECIST v1.1 or RANO, BICR)[f], safety/tolerability
Key secondary endpoints: DCR, DOR, PFS (RECIST v1.1 or RANO, BICR)[f]

Response assessed Q9W[g] until week 54; then Q12W until week 102; then Q24W thereafter

[a]Numbers in parentheses indicate line of therapy. [b]PD-L1 status assessed centrally using PD L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria , CA, USA). [c]Initial planned enrollment per cohort. [d]With investigator and sponsor approval, patients with disease progression before completing 35 cycles could remain on treatment if they were experiencing clinical benefit without intolerable toxicity; patients experiencing clinical benefit could continue lenvatinib treatment beyond 35 cycles. [e]In interim analysis, if adequate ORR determined, cohort expansion to 100 patients [f]Response assessed per RECIST v1.1, RANO (for glioblastoma), or iRECIST . [g]For glioblastoma cohort, response was assessed Q6W until week 18, then Q9W until week 54.

RECIST: Response Evaluation Criteria in Solid Tumours. RANO: Response assessment in neuro-oncology criteria. ECOG: Eastern Cooperative Oncology Group. PS: performance status. IV: Intravenous. BICR: Blinded independent central review. FU: follow-up. PD-L1: programmed death ligand 1. ORR: objective response rate. DCR: disease control rate. DOR: duration of response. PFS: progression-free survival

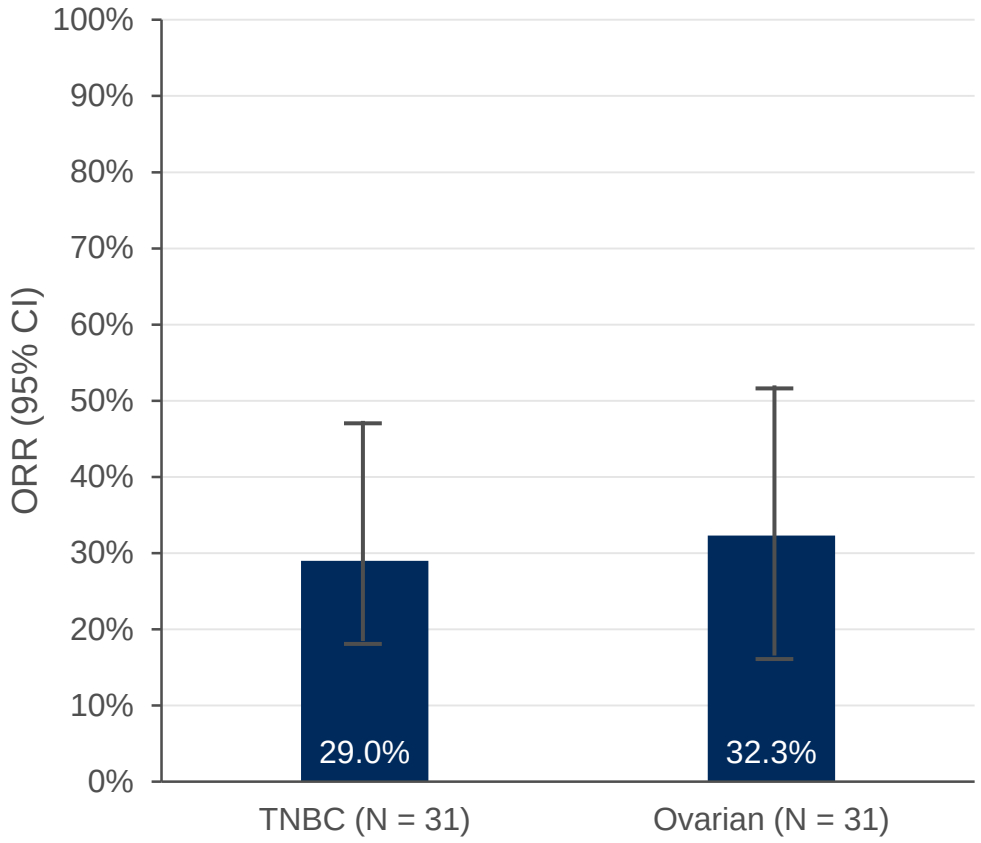
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Antitumor activity: Women's cancers

Confirmed objective responses, RECIST v1.1 by BICR

	2L/3L TNBC (N=31)	4L Ovarian (N=31)
ORR, % (95% CI)	29.0 (14.2-48.0)	32.3 (16.7-51.4)
DCR,[a] % (95% CI)	58.1 (39.1-75.5)	74.2 (55.4-88.1)
Best overall response, N (%)		
CR	1 (3)	1 (3)
PR	8 (26)	9 (29)
SD	9 (29)	13 (42)
Non-CR/Non-PD	0	1 (3)
PD	8 (26)	5 (16)
Non-evaluable[b]	1 (3)	0
No assessment[c]	4 (13)	2 (6)
DOR,	NR	NR
median (range), mo	(0.0+ to 8.4+)	(1.5+ to 7.9+)

Objective response rate



[a]Defined as best overall response of CR, PR or SD. [b]Patient had post-baseline imaging and best overall response was determined to be nonevaluable per RECIST v1.1. [c]Patient had no post-baseline imaging. Data cutoff date: April 10, 2020.

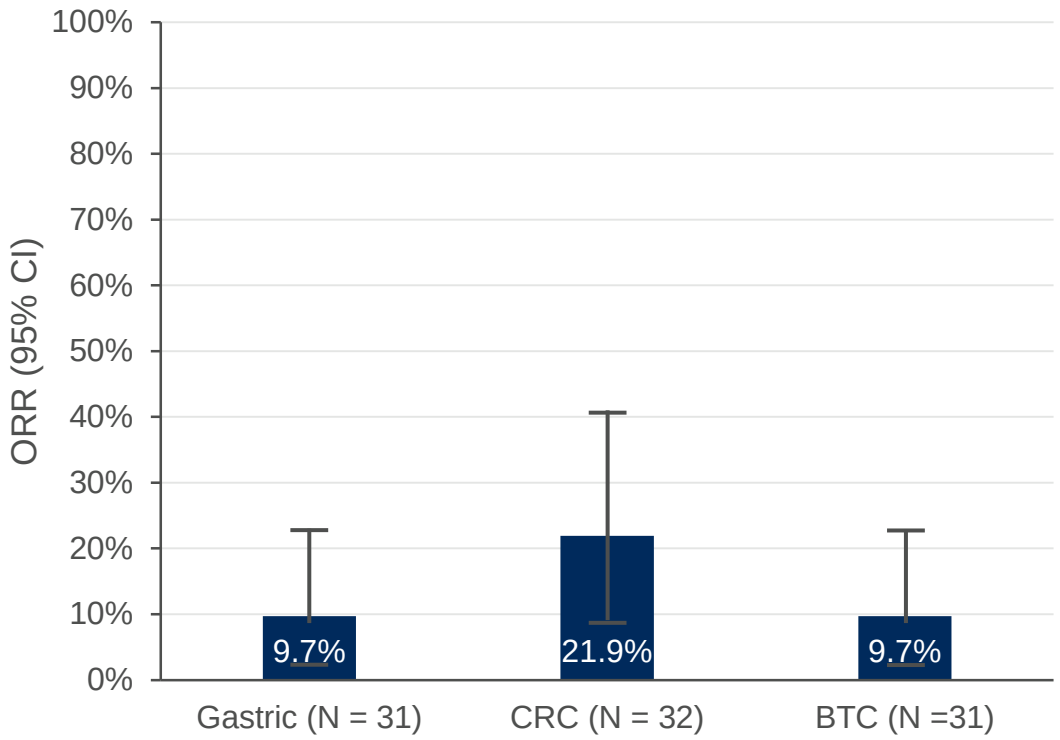
RECIST: Response Evaluation Criteria in Solid Tumours. BICR: Blinded independent central review. TNBC: Triple negative breat cancer. ORR: Objective response rate. NR: Not reached.
CR: Complete response. PR: Partial response. PD: Progressive disease. DOR: Duration of response.
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Antitumor activity: GI cancers

Confirmed objective responses, RECIST v1.1 by BICR

	3L Gastric (N=31)	3L CRC (N=32)	2L BTC (N=31)
ORR, % (95% CI)	9.7 (2.0-25.8)	21.9 (9.3-40.0)	9.7 (2.0-25.8)
DCR,[a] % (95% CI)	48.4 (30.2-66.9)	46.9 (29.1-65.3)	67.7 (48.6-83.3)
Best overall response, n (%)			
CR	1 (3)	0	0
PR	2 (6)	7 (22)	3 (10)
SD	12 (39)	8 (25)	18 (58)
Non-CR/Non-PD	0	0	0
PD	11 (35)	12 (38)	7 (23)
Non-evaluable[b]	0	1 (3)	2 (6)
No assessment[c]	5 (16)	4 (13)	1 (3)
DOR,	NR	NR	5.3
median (range), mo	(2.1+ to 2.3+)	(2.1+ to 10.4+)	(2.1+ to 6.2)

Objective response rate



[a]Defined as best overall response of CR, PR or SD. [b]Patient had post-baseline imaging and the best overall response was determined to be nonevaluable per RECIST v1.1. [c]Patienthad no post-baseline imaging. Data cutoff date: April 10, 2020.

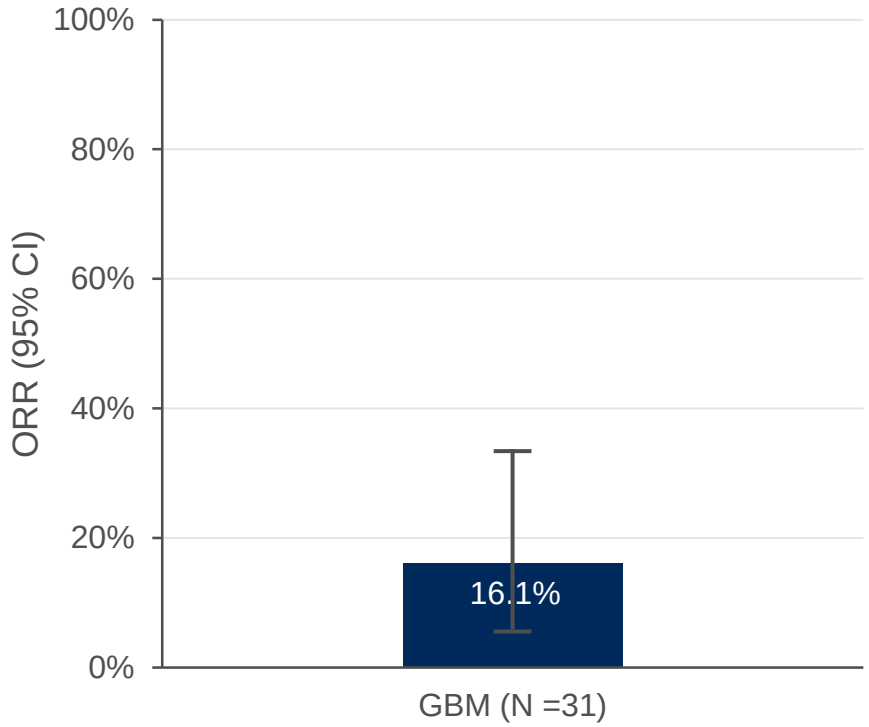
RECIST: Response Evaluation Criteria in Solid Tumours. BICR: Blinded independent central review. CRC: Colorectal cancer. BTC: Biliary tract cancer. ORR: Objective response rate. DCR: disease control rate. NR: Not reached. CR: Complete response. PR: Partial response. PD: Progressive disease. SD: stable disease. DOR: Duration of response. GI: gastrointestinal cancer
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Antitumor activity: Glioblastoma

Confirmed objective responses, RANO by BICR

	2L GBM (N=31)
ORR, % (95% CI)	16.1 (5.5-33.7)
DCR,[a] % (95% CI)	58.1 (39.1-75.5)
Best overall response, n (%)	
CR	0
PR	5 (16)
SD	13 (42)
Non-CR/Non-PD	0
PD	11 (35)
Non-evaluable[b]	1 (3)
No assessment[c]	1 (3)
DOR,	3.2
median (range), mo	(2.5 to 4.9+)

Objective response rate



[a]Defined as best overall response of CR, PR or SD. [b]Patient had post-baseline imaging and the best overall response was determined to be nonevaluable per RECIST v1.1. [c]Patienthad no post-baseline imaging. Data cutoff date: April 10, 2020.

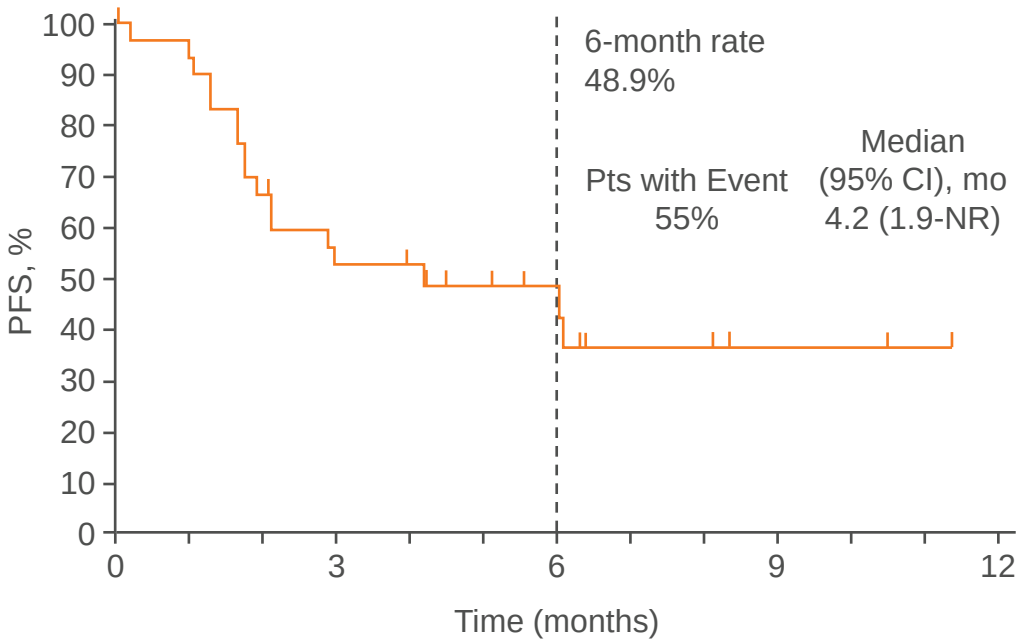
RANO: Response assessment in neuro-oncology. BICR: Blinded independent central review. ORR: Objective response rate. DCR: disease control rate. CR: Complete response. PR: Partial response. PD: Progressive disease. SD: stable disease. DOR: Duration of response. GBM: glioblastoma

Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Progression-free survival: Women's cancers

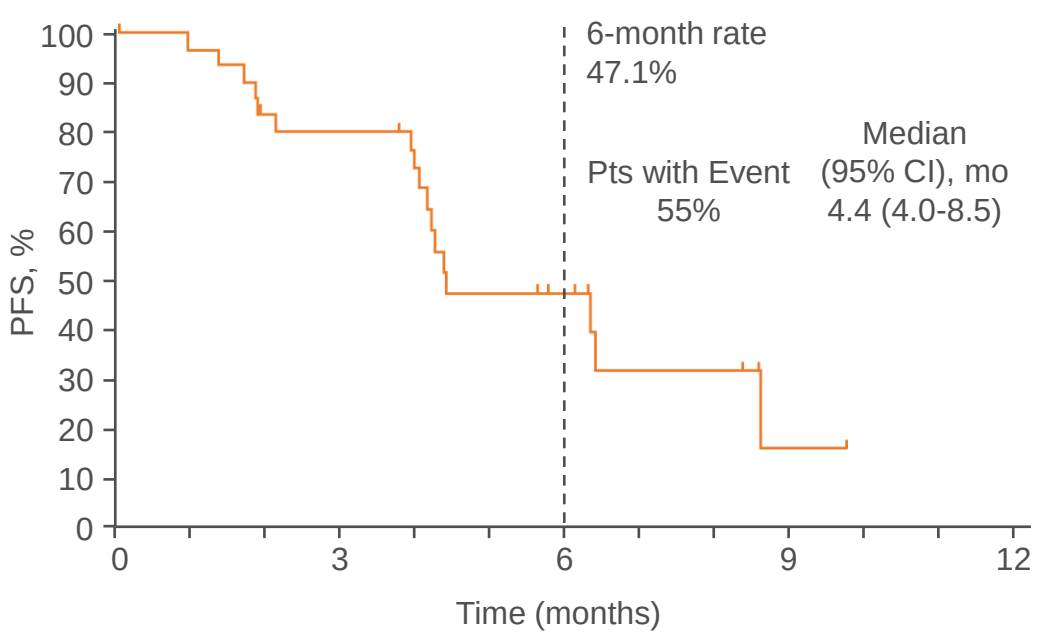
RECIST v1.1 by BICR

2L/3L TNBC Cohort



No. at risk				
31	15	8	2	0

4L Ovarian Cohort



No. at risk				
31	23	9	1	0

RECIST: Response Evaluation Criteria in Solid Tumors. BICR: Blinded independent central review. TNBC: Triple negative breast cancer. PFS: Progression free survival. CI: Confidence interval. NR: Not reached.

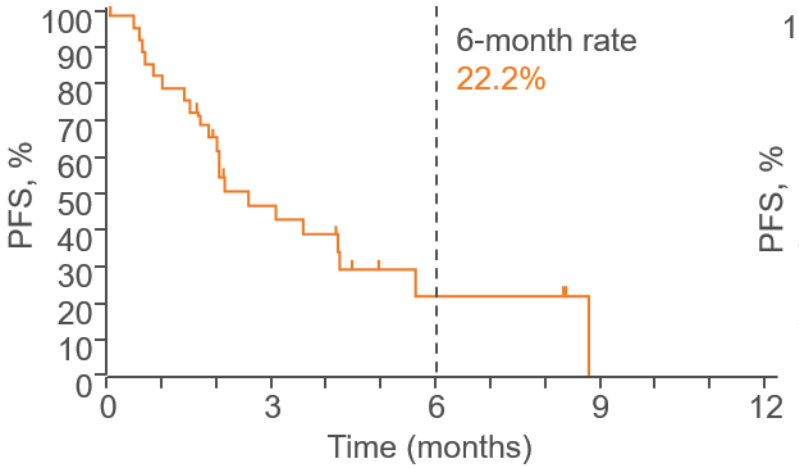
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Progression-free survival: GI cancers

RECIST v1.1 by BICR

3L Gastric

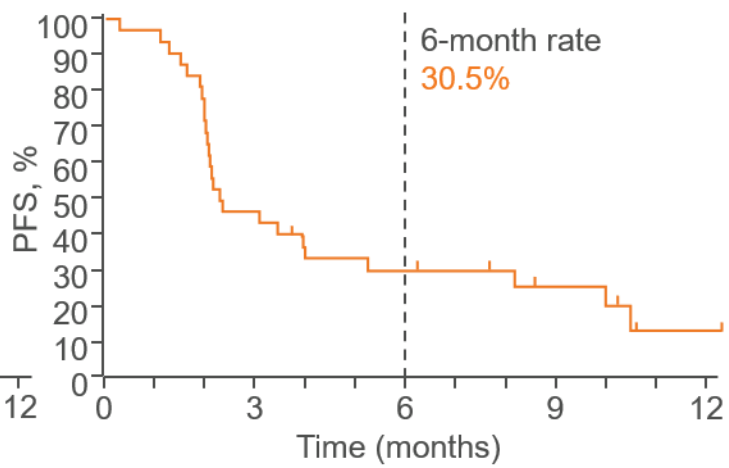
Pts with Event	Median (95% CI), mo
68%	2.5 (1.8−4.2)



No. at risk				
31	12	3	0	0

3L CRC

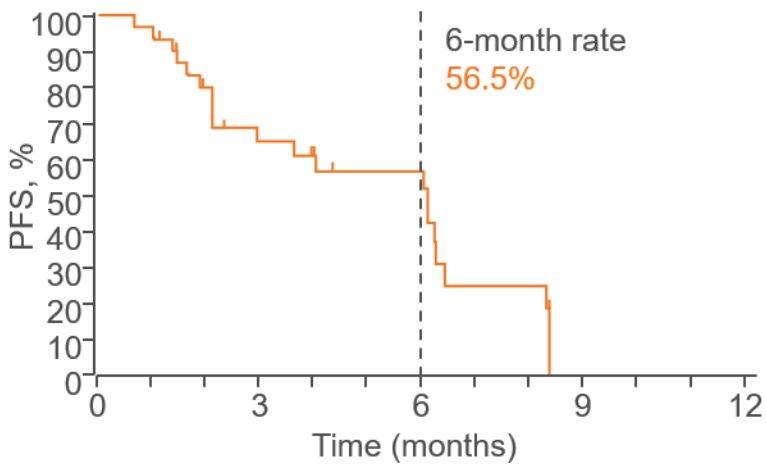
Pts with Event	Median (95% CI), mo
78%	2.3 (2.0−5.2)



No. at risk				
32	15	9	5	1

2L BTC

Pts with Event	Median (95% CI), mo
65%	6.1 (2.1−6.4)



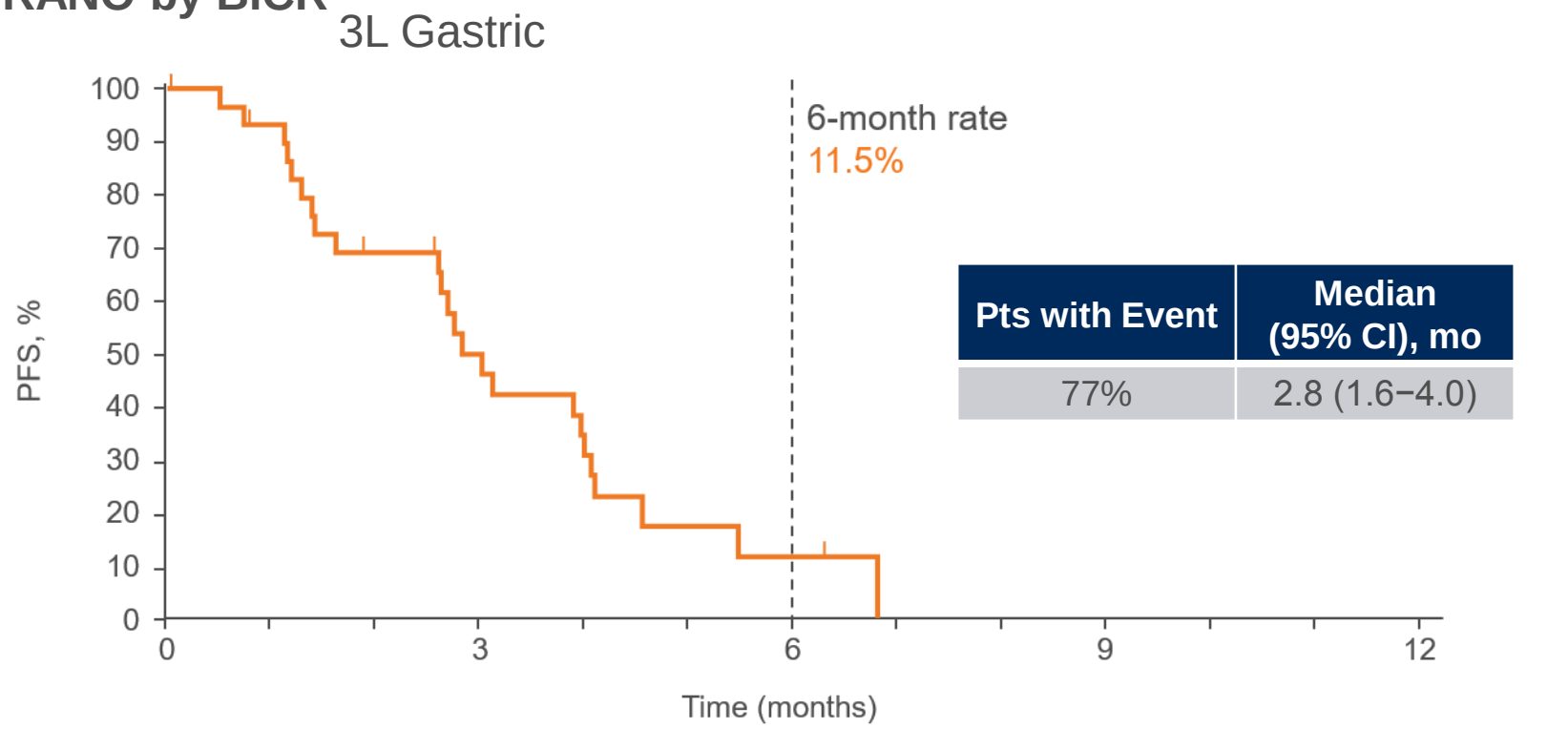
No. at risk				
31	16	12	0	0

RECIST: Response Evaluation Criteria in Solid Tumors. BICR: Blinded independent central review. PFS: Progression free survival. CI: Confidence interval. CRC: Colorectal cancer. BTC: Biliary tract cancer. GI: gastrointestinal

Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Progression-free survival: Glioblastoma

RANO by BICR



Pts with Event	Median (95% CI), mo
77%	2.8 (1.6−4.0)

No. at risk				
31	13	2	0	0

RANO: Response assessment in neuro-oncology. BICR: Blinded independent central review. PFS: Progression-free survival. CI: Confidence interval. GBM: Glioblastoma.
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Safety and tolerability

Summary of safety data

N (%)	2L/3L TNBC (N=31)	4L Ovarian (N=31)	3L Gastric (N=31)	3L CRC (N=32)	2L BTC (N=31)	2L GBM (N=31)
Treatment-related AEs	30 (97)	29 (94)	28 (90)	32 (100)	30 (97)	29 (94)
Grade 3-5	17 (55)	21 (68)	13 (42)	16 (50)	15 (48)	11 (35)
Led to death	1 (3)[a]	1 (3)[a]	1 (3)[a]	1 (3)[a]	0 (0)	1 (3)[a]
Lead to discontinuation	3 (10)	4 (13)	2 (6)	3 (9)	2 (6)	2 (6)
Lenvatinib[b]	24 (77)	28 (90)	18 (58)	24 (75)	23 (74)	23 (74)
Immune-mediated Aes	15 (48)	15 (48)	8 (26)	14 (44)	14 (45)	9 (29)
Grade 3-5	1 (3)	1 (3)	1 (3)	2 (6)	2 (6)	1 (3)
Infusion reactions	1 (3)	1 (3)	0	0	1 (3)	0
Grade 3-5	0	1 (3)	0	0	0	0

- One or more TRAE in most patients in each cohort
- Grade 3-5 TRAEs in ~50% of patients in each cohort (although 68% in ovarian and 35% in GBM)

[a]Treatment related AEs leading to death (n = 1 each): TNBC, subarachnoid hemorrhage; Ovarian, hypovolemic shock; Gastric, hemorrhage; CRC, intestinal perforation; GBM, pneumonitis. [b]Clinically significant treatment related AEs for lenvatinib. Data cutoff date: April 10, 2020.

AE: Adverse event. TNBC: Triple negative breast cancer. CRC: Colorectal cancer. BTC: Biliary tract cancer. GBM: Glioblastoma. TRAE: treatment-related adverse event.
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

Safety and tolerability

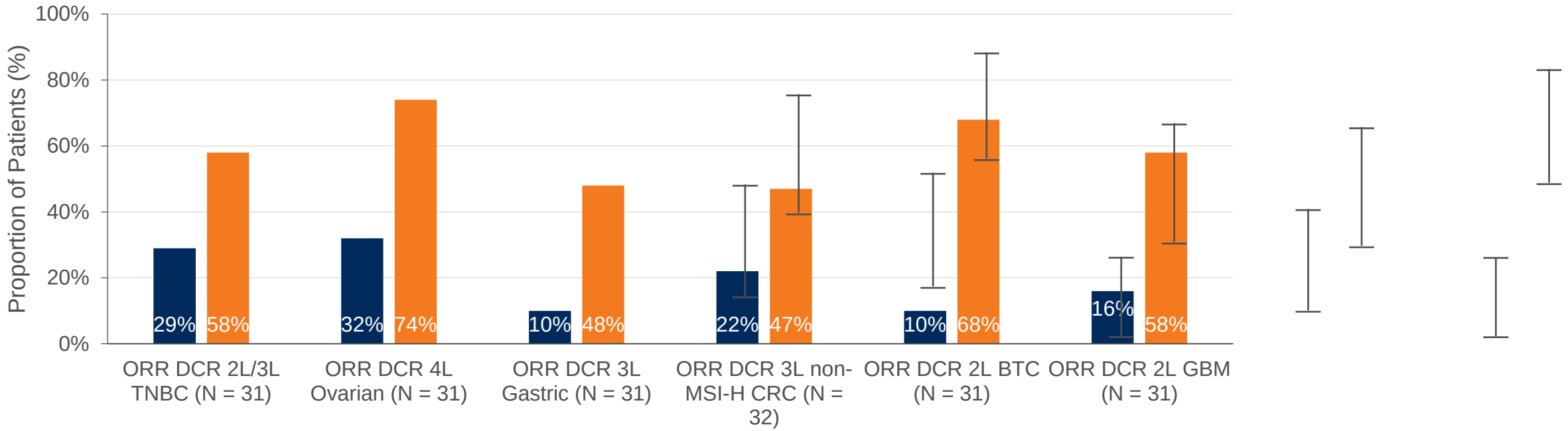
Treatment related AEs occurring in ≥20% of overall study population

N (%)	2L/3L TNBC (N=31)	4L Ovarian (N=31)	3L Gastric (N=31)	3L CRC (N=32)	2L BTC (N=31)	2L GBM (N=31)
Hypertension	13 (42)	17 (55)	6 (19)	14 (45)	13 (42)	10 (32)
Fatigue	9 (29)	13 (42)	8 (26)	9 (29)	10 (32)	6 (19)
Diarrhea	7 (23)	12 (39)	8 (26)	9 (29)	10 (32)	4 (13)
Decreased appetite	8 (26)	12 (39)	6 (19)	10 (32)	7 (23)	4 (13)
Hypothyroidism	8 (26)	13 (42)	5 (16)	9 (29)	9 (29)	8 (26)
Nausea	8 (26)	8 (26)	6 (19)	6 (19)	10 (32)	3 (10)

AE: Adverse event. TNBC: Triple negative breast cancer. CRC: Colorectal cancer. BTC: Biliary tract cancer. GBM: Glioblastoma.
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

LEAP-005 Conclusions

In this interim analysis, prespecified futility efficacy criteria for cohort expansion were met or exceeded and toxicity was manageable in all cohorts



- LEAP-005 will continue to assess the efficacy and safety of lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors in expanded cohorts of 100 patients each

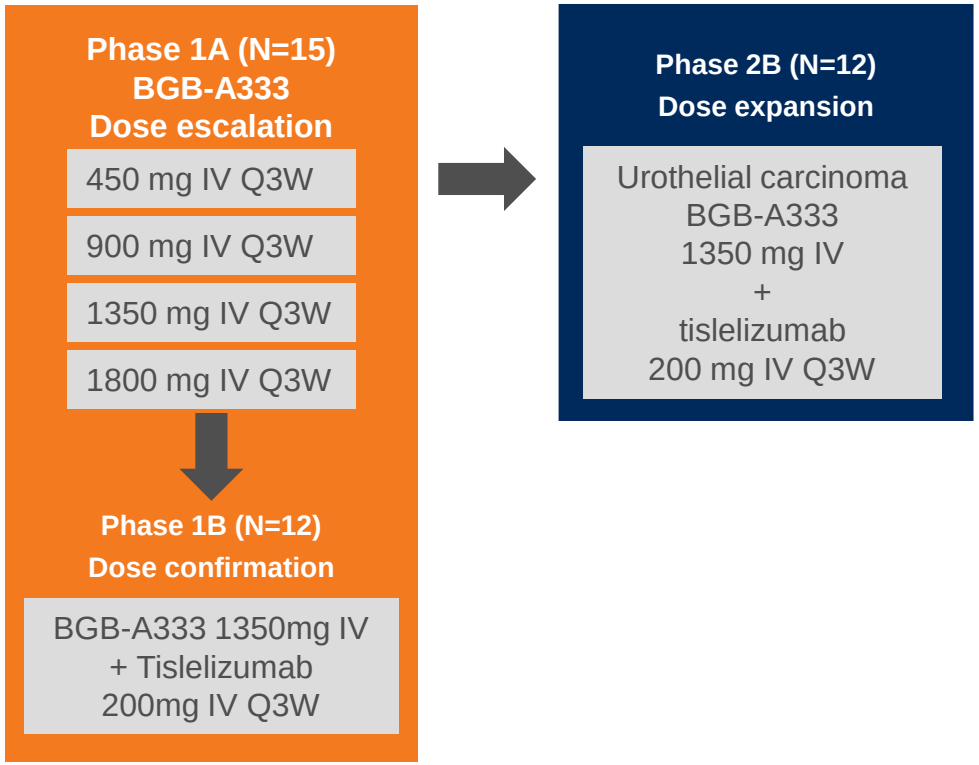
ORR: Objective response rate. DCR: Disease control rate. CRC: Colorectal cancer. BTC: Biliary tract cancer. GBM: Glioblastoma.
Lwin, Z. Et al, 2020. Abstract LBA41 presented at ESMO 2020.

PD-L1i plus PD-1i in urothelial carcinoma

BGB-A333 + Tislelizumab

Study design

Phase 1/2 study of BGB-A333, an anti-PD-L1 monoclonal antibody, in combination with anti-PD-1 antibody tislelizumab in patients with urothelial carcinoma (BGB-900-101)

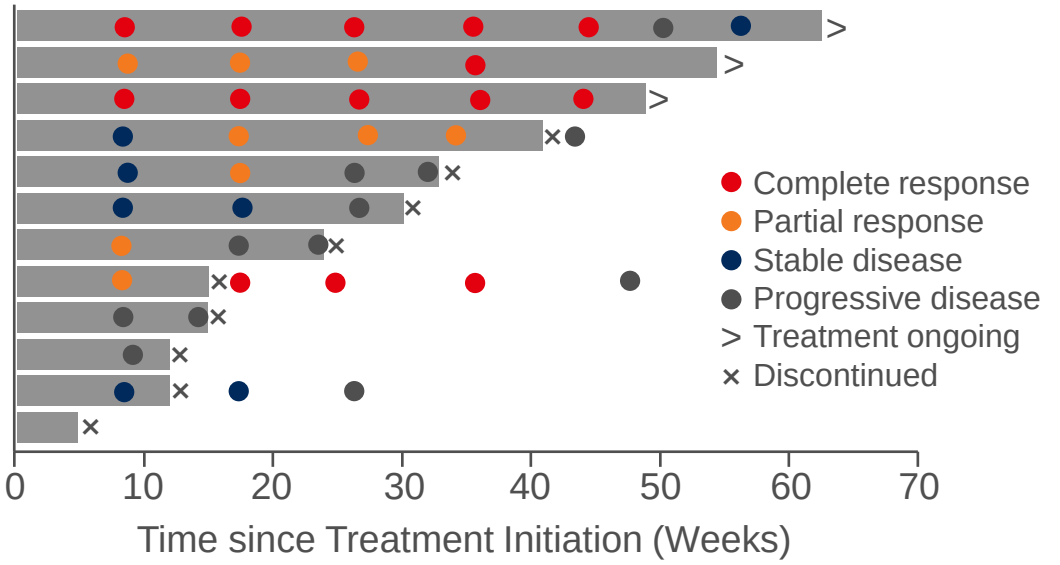


- Simultaneous PD-L1 and PD-1 blockade hypothesized to produce synergistic antitumor effects due to potential distinct modes of action
- Patients in Phase 2B with locally advanced or metastatic UC who had progressed after ≥1 platinum-containing previous regimen received BGB-A333 (anti-PD-L1) 1350mg IV Q3W + tislelizumab (anti-PD-1) 200mg IV Q3W
- As of 26th July 2020 (data cutoff), 12 patients (median age 69.5 years, 92% male) were enrolled in phase 2B
  - Median duration of treatment was 6.2 months
  - Ten patients (83%) had 1 prior systemic therapy
  - Median study follow-up was 10 months

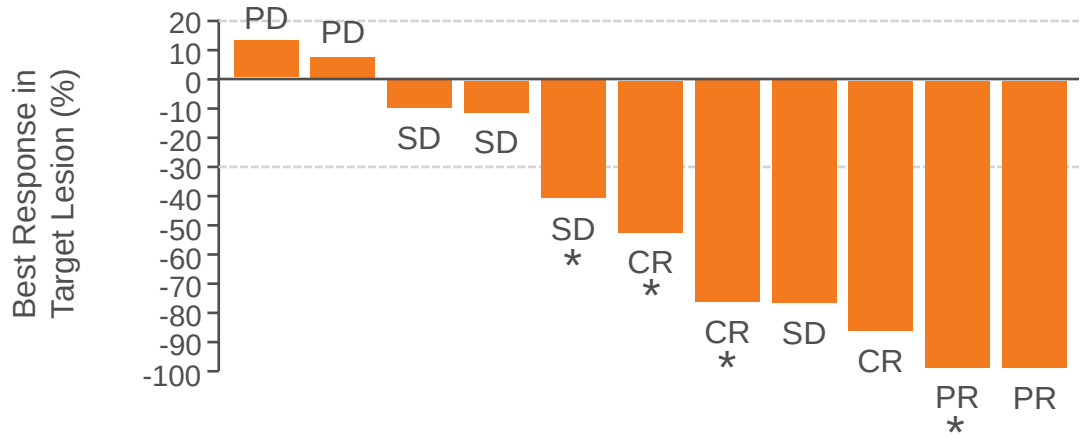
Data cutoff: 26 July 2020. IV: Intravenous. Q3W: Every 3 weeks. UC: Urothelial carcinoma.
Martin-Liberal, J. et al,.2020. Mini oral 535MO presented at ESMO 2020.

Results - efficacy

Combination treatment associated with durable clinical response[a]



Median DOR 9.1 months (95% CI: 6.0-9.6)



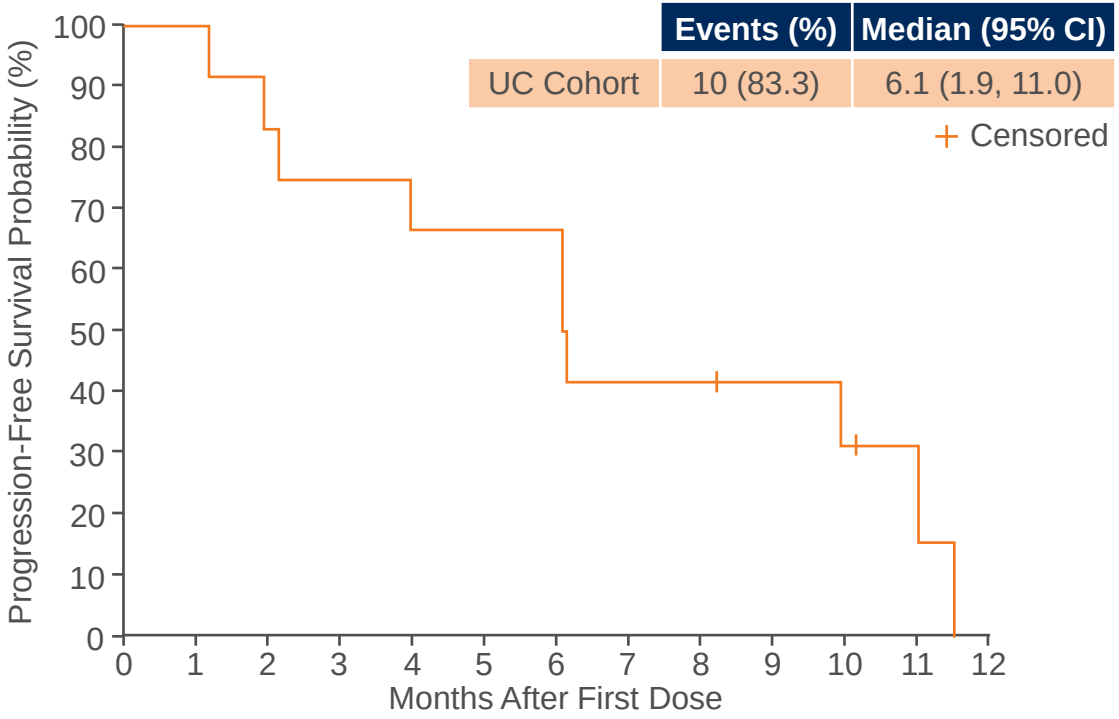
Confirmed responses	PD-L1 high[b] (N=6)	PD-L1 low[b] (N=6)	Total (N=12)
CR	2	1	3
PR	2	0	2
SD	2	2	4
PD	0	2	2
NE	0	1	1
ORR, % (95%CI)	67 (22.3, 95.70	17 (0.42, 64.1)	42 (15.2, 72.3)
DCR, % (95%CI)	100 (54.1, 100.0)	50 (11.8, 88.2)	75 (42.8, 94.5)

[a]Radiologic assessments were performed every 9 weeks in the first year and every 12 weeks thereafter; reported responses were investigator-assessed per RECIST v1.1.
[b]PD-L1 high defined as ≥25% of tumor or immune cells with PD-L1 staining using the VENTANA SP263 assay. PD-L1 low, <25%.
DOR: Duration of response. CR: Complete response. PR: Partial response. SD: Stable disease. PD: Progressive disease NE: Not evaluable. ORR: Objective response rate. DCR: Disease control rate. CI: Confidence interval.
Martin-Liberal, J. et al,.2020. Mini oral 535MO presented at ESMO 2020.

Results - efficacy

PFS, overall

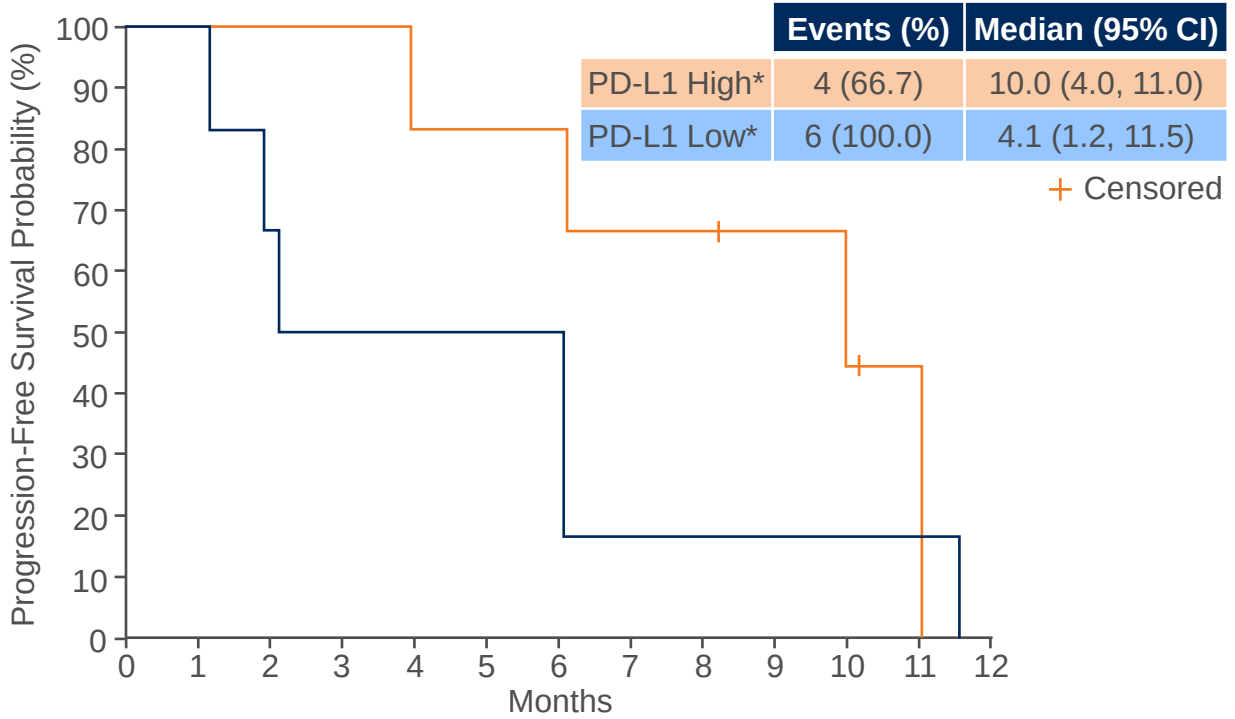
- Median PFS 6.1 months overall



Patients at Risk (N)													
UC Cohort	12	12	10	9	8	8	8	5	5	4	3	2	0

PFS, by PD-L1 expression status

- Median PFS 10.0 months in PD-L1 high population
- Median PFS 4.1 months in PD-L1 low population



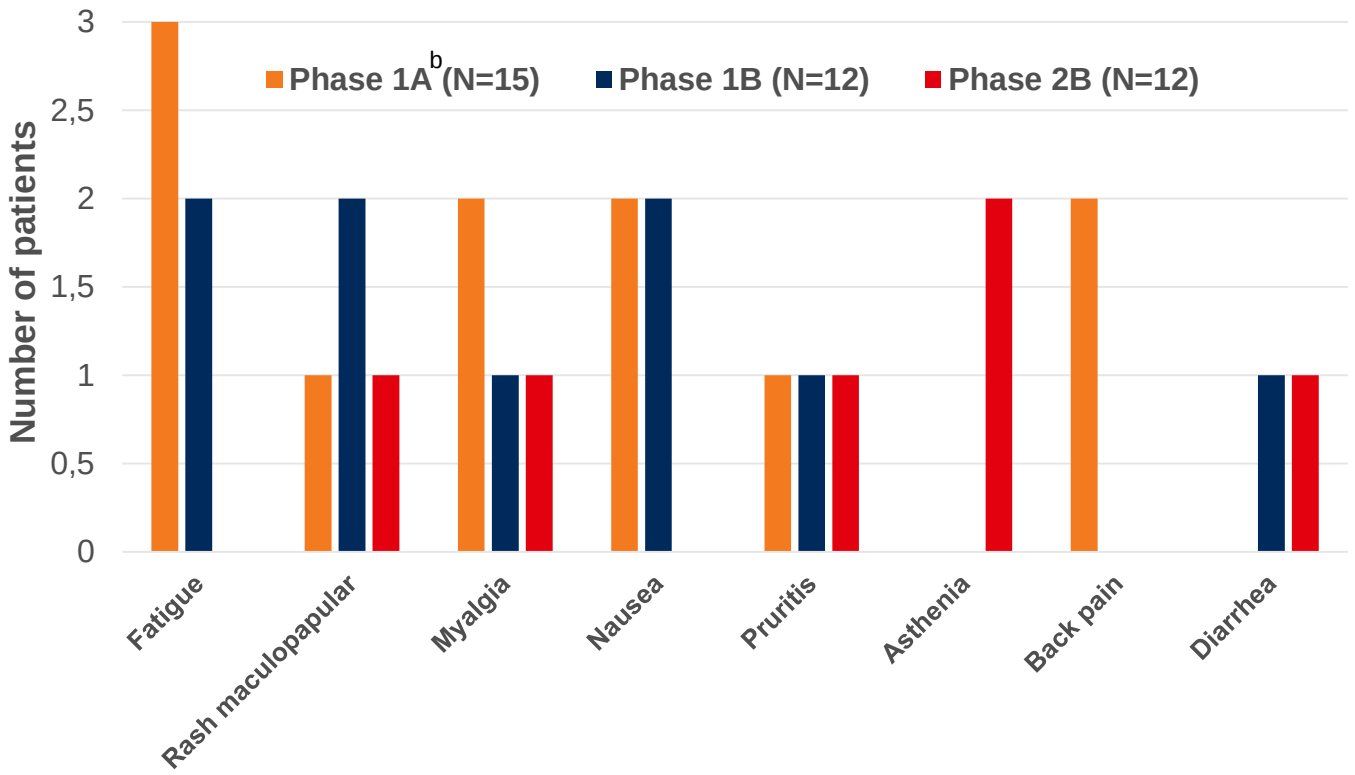
Patients at Risk (N)													
PD-L1 High	6	6	6	6	5	5	5	4	4	3	2	1	0
PD-L1 Low	6	6	4	3	3	3	3	1	1	1	1	1	0

*PD-L1 high defined as ≥25% of tumor or immune cells with PD-L1 staining using the VENTANA SP263 assay. PD-L1 low, <25%.
CI: Confidence interval. PFS: Progression free survival. PD-L1: programmed death ligand 1
Martin-Liberal, J. et al,.2020. Mini oral 535MO presented at ESMO 2020.

Results – safety and tolerability

BGB-A33 + tislelizumab safety profile[a]

Any grade TRAEs occurring in ≥2 patients



- Fatigue was the most commonly reported TRAE across the study
- AE profile consistent with profiles observed during dose escalation and dose confirmation across multiple tumor types
- No patients in phase 2B had a fatal TRAE
- Two patients in phase 2B experienced 4 immune-related AEs (grade 3 endocrine disorders, grade 3 hypophysitis, grade 2 musculoskeletal and connective tissue disorder, grade 2 myositis)

[a]Adverse events were monitored throughout the study per the National Cancer Institute-Common Terminology Criteria for Adverse events v4.03
[b]Patients in phase 1A received single-agent BGB-A333
Data cutoff: 26 July 2020. TRAE: Treatment related adverse event. AE: Adverse event.
Martin-Liberal, J. et al,.2020. Mini oral 535MO presented at ESMO 2020.

Conclusions

- Preliminary antitumor activity observed in patients with locally advanced/ metastatic UC receiving BGB-A333 in combination with tislelizumab
  - Confirmed ORR 42% (5/12 patients), with 3 patients achieving complete responses and 2 achieving partial response
  - Responses were durable (median DOR 9.1 months)
  - Both ORR and PFS consistent with better efficacy in PD-L1 high population vs PD-L1 low population
- BGB-A333 in combination with tislelizumab generally well tolerated in patients with locally advanced/ metastatic UC (N=12)
  - Reported TRAEs generally of mild or moderate severity
- **These data provide insights into combining tislelizumab, a clinical stage anti-PD-1 antibody, with anti-PD-1 antibodies**

UC: Urothelial carcinoma. ORR: Objective response rate. PFS: Progression free survival. DOR: Duration of response. PD-L1: programmed death ligand 1. PD-1: programmed cell death protein 1. TRAE: treatment-related adverse events

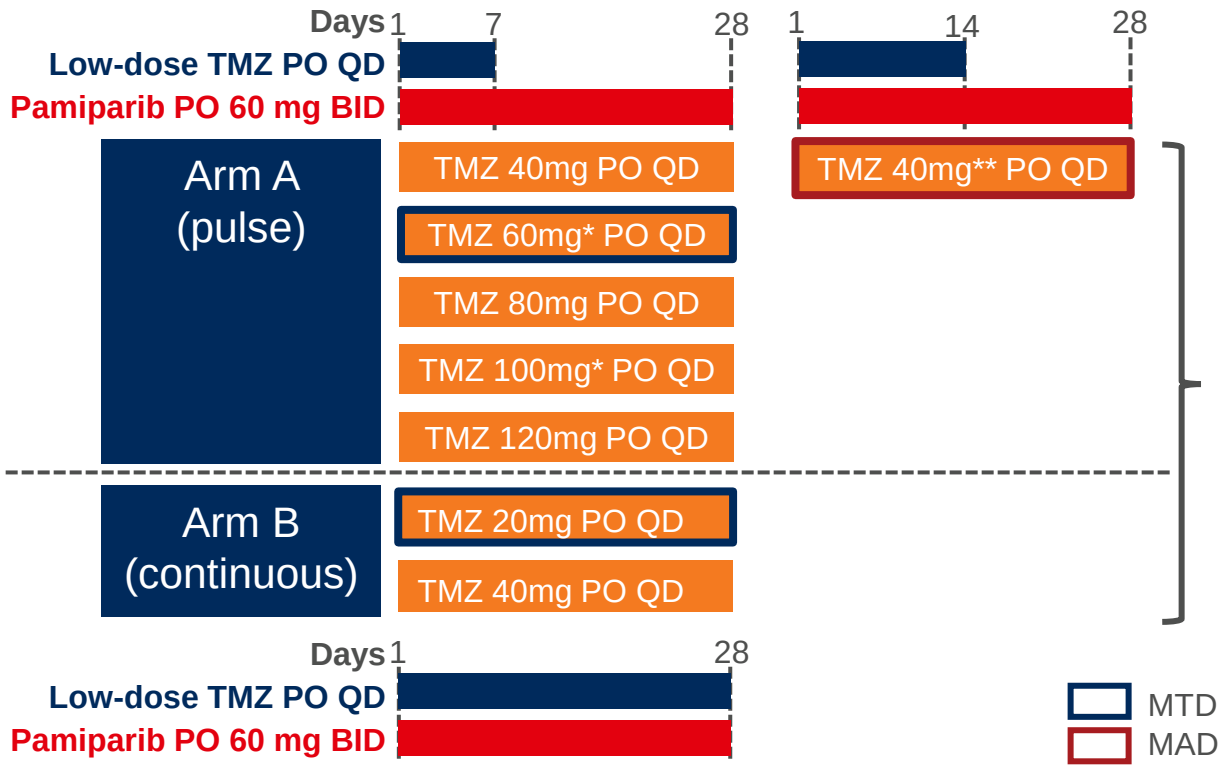
Martin-Liberal, J. et al,.2020. Mini oral 535MO presented at ESMO 2020.

PARP inhibiton + temozolamide

In biomarker-positive patients with locally advanced or metastatic solid tumors

Study design

Clinical benefit in biomarker-positive patients with locally advanced or metastatic solid tumors treated with the PARP1/2 inhibitor pamiparib in combination with low-dose (LD) temozolomide (TMZ)



MTD
MAD

* Intermediate cohorts
** Intermediate schedule

TMZ per label dosing: 75 mg/m^2 (continuous): 150 and 200 mg/m^2 (pulse) BSA equivalent assumes and average BSA=1.73 m^2

RP2D=60 mg pamiparib D1-28 + 60 mg TMZ D1-7

TMZ (dose equivalents)	
Flate dose	BSA equivalent
20mg	11.5mg/m^2
40mg	23mg/m^2
80mg	46mg/m^2
120mg	69mg/m^2

- The study (BGB-290-103) enrolled a total of 114 patients in a dose-escalation and dose-expansion
- Majority of patients were white (75%) and heavily pretreated (median 3 prior therapies, range 1-10)
- Median study follow-up time of 8.4 months (range 0.3-30.0)

Cohort 1: OVCA HRD+ | Cohort 2: TNBC HRD+ | Cohort 3: mCRPC HRD+ | Cohort 4: ES-SCLC | Cohort 5: GC/GEJ

Data cutoff date: April 2020
BID: twice daily. BSA: body surface area. ES-SCLC: extensive-stage small cell lung cancer. GC: gastric cancer. GEJ: gastroesophageal junction. HRD: homologus recombination deficiency. MAD: maximum administered dose. mCRPC: metastatic castration-resistant prostate cancer. MTD: maximum tolerated dose. OVCA: ovarian cancer TMZ: Temozolomide. PO: Orally. QD: once daily. RP2D: recommended phase 2 dose. TNBC: triple-negative breast cancer
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Retrospective biomarker analysis

- Samples from dose-escalation and dose-expansion patients were included in the analysis
- Myriad myChoice HRD test performed in archival tissue sample obtained at baseline
  - Genomic instability score (GIS, formerly HRD score) based on large-scale transitions, telomeric allelic imbalance, and loss of heterozygosity
  - GIS+ defined as GIS score ≥33
- ctDNA NGS DNA-Seq performed in blood samples obtained at baseline
  - Focus on 16 core DNA damage response (DDR) genes:

    ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHECK2, CDK12, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L
  - DDR+ defined as ≥1 mutation in one of 16 DDR genes
- Correlation of DDR/GIS status with overall response rate (ORR) and disease control rate (DCR)

ctDNA: circulating tumor DNA. GIS: Genomic instability score. HRD: homologous recombination deficiency. NGS DNA-seq: next generation DNA sequencing. DDR: DNA damage response. ORR: Overall response rate. DCR: Disease control rate.
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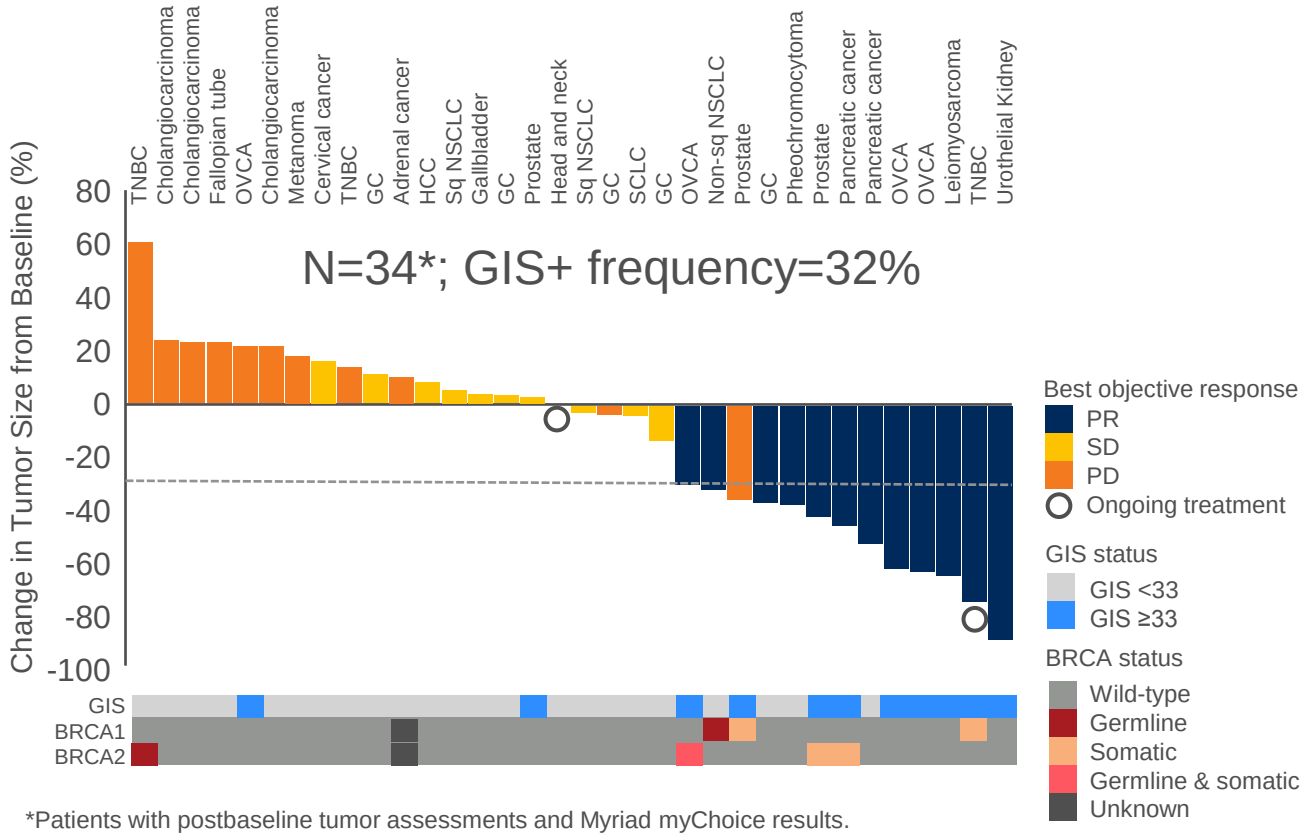
Results - efficacy

- **GIS+ patients had better ORR and DCR than GIS- patients, irrespective of *BRCA* mutation status**



*Patients with postbaseline tumor assessments and Myriad myChoice results.
**The gBRCA1 mutation reported for the nonsquamous NSCLC patient was non-pathogenic.

GIS (formerly HRD score) measures LST+TAI+LOH; GIS+ = GIS score ≥33

ORR			
	BRCA1/2mut (N=7)	***BRCA1/2wt*** (N=27)	**Total** (N=34)
GIS+	**100%** (5/5) (90% CI, 0.55-1.00)	**66.7%** (4/6) (90% CI, 0.27-0.94)	**81.8%** (9/11) (90% CI, 0.53-0.97)
GIS-	50.0% (1/2) (90% CI, 0.03-0.97)	9.5% (2/21) 90% CI, 0.02-0.27)	13.0% (3/23) (90% CI, 0.04-0.30)

DCR			
	BRCA1/2mut (N=7)	***BRCA1/2wt*** (N=27)	**Total** (N=34)
GIS+	**100%** (5/5) (90 CI, 0.55-1.00)	**83.3%** (5/6) (90% CI, 0.42-0.99)	**90.9%** (10/11) (90% CI, 0.64-1.00)
GIS-	50% (1/2) (90%CI, 0.03-0.97)	57.1% (12/21) (90% CI, 0.37-0.75)	56.5% (13/23) (90% CI, 0.38-0.74)

BRCA: Breast cancer gene. DCR: Disease control rate. GC: Gastric cancer. GIS: Geneomic instability score: HCC: Hepatocellular carcinoma. HRD: Homologous recombination deficeincy. LST: Large scale transitions. LOH: Loss of heterozygosity. Mut: mutation. NSCLC: Non small cell lung cancer. ORR: Objective response rate. OVCA: Ovarian cancer. PD: Progressive disease. PR: Partial response. SCLC: Small cell lung cancer. SD: Stable disease. Sq.: Squamous. TAI: telomeric allelic imbalance. TNBC: triple-negative breast cancer

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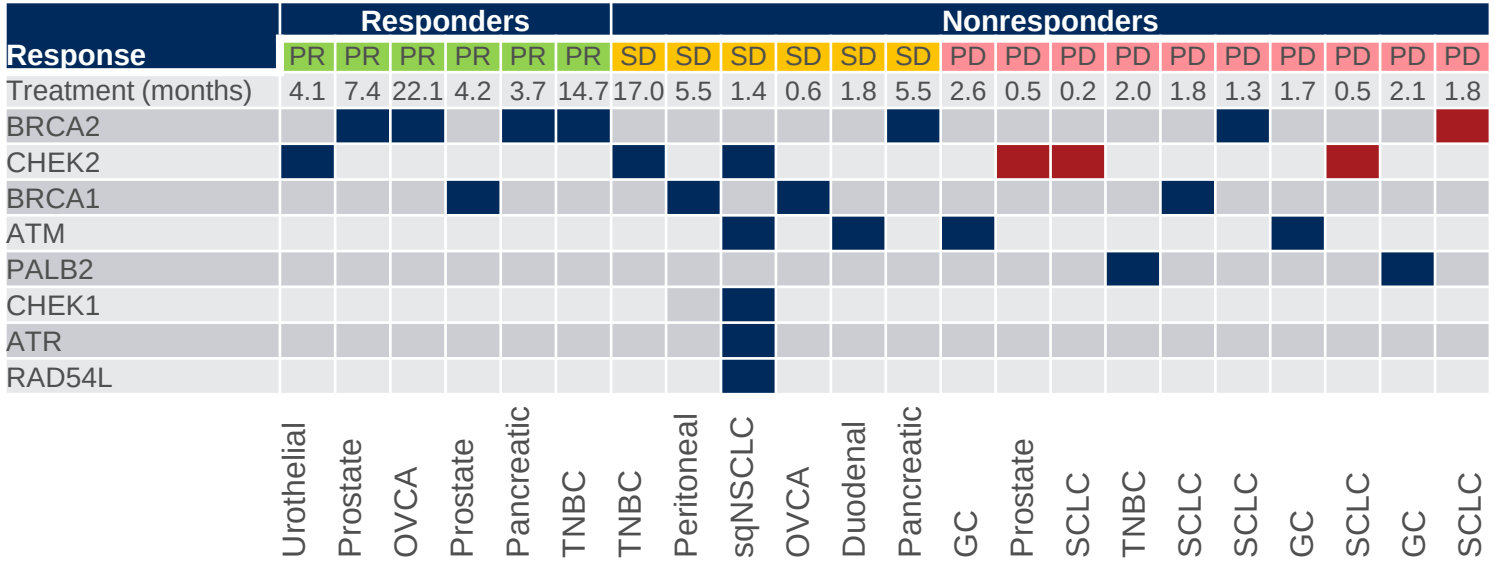
Results

- **DDR+ patients had better ORR than DDR- patients, but responses were associated with *BRCA* mutations**

N=86*; DDR+ frequency=26%



*Patients with postbaseline tumor assessments and ctDNA data.

DDR panel: ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, CDK12, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L

DDR+ = ≥1 mutation in one of 16 DDR genes

5 patients were GIS+ and DDR+

ORR

	BRCA1/2mut (N=14)	*BRCA1/2wt* (N=72)	Total (N=86)
DDR+	**38.5%** (5/13) (90% CI, 0.17-0.65)	**11.1%** (1/9) (90% CI, 0.06-0.43)	**27.3%** (6/22) (90% CI, 0.12-0.47)
DDR-	100% (1/1) (90% CI, 0.05-1.00)	12.7% (8/63) (90% CI, 0.06-0.22)	14.1 (9/64) (90% CI, 0.08-0.23)

DCR

	BRCA1/2mut (N=14)	*BRCA1/2wt* (N=72)	Total (N=86)
DDR+	**61.5%** (8/13) (90% CI, 0.35-0.83	**44.4%** (4/9) (90% CI, 0.17-0.75)	**54.5%** (12/22) (90% CI, 0.35-0.73)
DDR-	100.0% (1/1) (90% CI, 0.05-1.00)	65.1% (41/63) (90% CI, 0.54-0.75)	65.6% (42/64) (90% CI, 0.55-0.76)

BRCA: Breast cancer gene. CNV: copy number variants. ctDNA: circulating tumor DNA. DCR: Disease control rate. DDR: DNA damage response. GC: Gastric cancer. GIS: Geneomic instability score. mut: mutation. ORR: Objective response rate. OVCA: Ovarian cancer. PD: Progressive disease. PR: Partial response. SCLC: Small cell lung cancer. SD: Stable disease. SNV: single nucleotide variants. TNBC: triple-negative breast cancer. Wt: wild-type.

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Conclusions

- In this limited subset of patients treated with pamiparib in combination with different doses of low dose (LD) temozolomide (TMZ), **GIS+ patients derived superior benefit, irrespective of *BRCA1/2* mutation status, compared with DDR+, GIS- and DDR- patients**
- Responses in the DDR+ subpopulation were primarily associated with *BRCA1/2* mutations
- GIS status, a global measure of genomic instability, appears to be a robust biomarker for prediction of response to pamiparib + LD TMZ
- As demonstrated previously, DDR mutations other than *BRCA1/2* have limited utility in predicting response to PARP inhibitors
- A new cohort (cohort 6) is currently evaluating antitumor activity of Pamiparib + LD TMZ in patients with GIS+ NSCLC, head and neck, esophageal, and soft tissue sarcoma tumors

LD: Low dose. TMZ: Temozolamide. GIS: Genomic instability score. BRCA: breast cancer gene. DDR: DNA damage response. NSCLC: non-small cell lung cancer. RP2D: recommended phase 2 dose

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Abbreviations

AE: Adverse event
BID: Twice daily
CI: Confidence interval
CR: Complete response
DCR: Disease control rate
DDR: DNA damage response
DOR: Duration of response
ECOG: Eastern Cooperative Oncology Group
GIS: Genomic instability score
HR: Hazard ratio
IRC: Independent review committee
IRC: Independent Review Committee
LD: Low dose
NSCLC: Non-small cell lung cancer
nsq-NSCLC: non-squamous non-small cell lung cancer
ORR: Objective response rate
OS: Overall survival
PARP: Poly (ADP-ribose) polymerase
PD: Progressive disease
PD-1: Programmed cell death protein-1
PD-L1: Programmed death-ligand 1
PFS: Progression free survival
PO: Orally
PR: Partial response
Q3W: Every 3 weeks
QoL: Quality of life
R: Randomized
RECIST: Response Evaluation Criteria in Solid Tumors
SAE: Severe adverse event
TEAE: Treatment emergent adverse event
TMZ: Temozolamide
TRAE: Treatment related adverse event

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Solid tumors:
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Focus on GI and ovarian cancers

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