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Congress Report ESMO 2020

A GLOBAL DIGEST ON APPROACHES IN ADVANCED SOLID TUMORS

Report from the ESMO Congress, 19th – 21st September 2020, virtual congress

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Preface

Dear Colleagues,

Notable advances that have been achieved in the treatment of solid tumors were discussed at the virtual ESMO Congress 2020, among them remarkable results obtained in the field of gastroesophageal tumors. For patients with metastatic gastric and esophageal cancer, the long-term outcomes have remained poor, and several clinical trials over the last few years assessing PD-(L)1 inhibition have shown modest to negative results. However, the role of immune checkpoint inhibition in the treatment of these difficult-to-treat tumors came of age in September 2020 with an entire Presidential Symposium at virtual ESMO 2020 dedicated to likely practice-changing phase III trials both in the metastatic and, for the first time, in the adjuvant setting for operable disease.

Compared to chemotherapy alone, combinations of the PD-1 inhibitor nivolumab with chemotherapy gave rise to improved outcomes in the CheckMate 649 and ATTRACTION-4 studies that were conducted in the first-line setting. Overall survival was prolonged for the first time in a phase III trial beyond the 1-year boundary in patients with advanced gastric cancer who traditionally had a life expectancy of less than one year when treated with conventional chemotherapy. Similarly, the KEYNOTE-590 trial evaluating pembrolizumab plus chemotherapy in esophageal cancer revealed meaningful benefits with respect to several endpoints. These regimens will most likely provide new first-line standard of care in the future. Also, the adjuvant use of nivolumab post trimodality therapy for stage II/III esophageal/gastroesophageal junction cancers was successfully explored in the CheckMate 577 study, which revealed a doubling in disease-free survival compared to placebo. This trial is noteworthy not only by the fact that it is the first study ever to show a benefit of a novel treatment in early-stage esophagogastric cancers; also, after melanoma, it is the first trial to demonstrate the benefits of a PD-1 inhibitor in the adjuvant setting for any solid tumor and signals the start of a new era of immunotherapeutic use in early-stage malignancies.

Novel combination approaches are being investigated in a wide range of solid tumors including gastrointestinal cancers, gynecological cancers, breast cancer, lung cancer, renal cell carcinoma and urothelial carcinoma, among others. Studies reported at ESMO 2020 assessed combinations of immune checkpoint inhibitors with multikinase inhibitors. Innovation and refinement are also taking place in the context of PARP inhibition, which constitutes a mainstay of treatment of patients with ovarian cancer. In this indication, the combined administration of PARP inhibition, immunotherapy and anti-angiogenesis has shown promise as a chemotherapy-free option in the MEDIOLA trial. Pivotal phase II results have been generated for the investigational PARP inhibitor pamiparib that is also being assessed combined with temozolomide in various locally advanced or metastatic cancers.

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Progress is undoubtedly being made across the full spectrum of malignancies with an improved understanding of the dynamic changes in the immune microenvironment and the evolution of the immune system as it seeks to keep up with an ever-changing tumor. This needs to be regarded as an integral area of research if we are to continue the impressive advances over the next decade.

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Milestones of PD-1 inhibition in gastric and esophageal cancer

Gastric cancer, gastroesophageal junction (GEJ) adenocarcinoma, and esophageal adenocarcinoma are substantial causes of cancer-related mortality worldwide and have poor 5-year overall survival (OS) when diagnosed at an advanced stage [1, 2]. Median OS with standard first-line chemotherapy for advanced or metastatic, *HER2*-negative gastric and GEJ cancer is less than 1 year [3-6].

Several clinical trials investigating anti-PD-(L)1 monotherapy for gastric and GEJ cancer have yielded negative results. However, in 2017, nivolumab was shown to improve survival in patients with gastric and GEJ cancer included in the randomized, double-blind, placebo-controlled, phase III ATTRACTION-2 trial after at least two previous treatment lines [7]. The non-randomized phase II KEYNOTE-059 study demonstrated activity of pembrolizumab in the same setting [8]. Pembrolizumab monotherapy also proved beneficial in pretreated patients with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus in the KEYNOTE-180 [9, 10] and KEYNOTE-181 [11] trials. Based on these studies, pembrolizumab was approved in the setting of recurrent, locally advanced or metastatic esophageal squamous cell carcinoma with combined positive score (CPS) ≥ 10 after ≥ 1 treatment line by the US Food and Drug Administration in 2019 [12]. Large phase III studies evaluating the benefits of nivolumab or

pembrolizumab in combination with first-line chemotherapy for advanced gastric cancer, GEJ cancer and esophageal cancer were presented at ESMO 2020.

Phase III part of ATTRACTION-4

The randomized, multicenter, phase II/III ATTRACTION-4 study assessed nivolumab plus chemotherapy as first-line treatment in patients with *HER2*-negative, advanced gastric or gastroesophageal junction cancer. After the phase II part of the trial had shown encouraging results [13], Boku et al. reported the primary findings of the double-blind, randomized, controlled phase III part of ATTRACTION-4 at the ESMO 2020 Congress [14]. At 130 centers in Japan, Korean and Taiwan, patients received S-1 plus oxaliplatin or capecitabine plus oxaliplatin with either nivolumab 360 mg every 3 weeks (Q3W) or placebo until progression. Each arm contained 362 patients. Progression-free survival (PFS) and OS were defined as the coprimary endpoints.

For PFS, the nivolumab-based therapy proved superior compared to placebo plus chemotherapy, with a median of 10.45 vs. 8.34 months (HR, 0.68; p = 0.0007). At 1 year, 45.4 % vs. 30.6 % of patients were alive and progression-free. All of the subgroups benefited from the addition of the immune checkpoint inhibitor; this was also true regardless of PD-L1 expression (≥ 1 % vs. < 1 %). However, OS did not improve in a significant manner according to the final analysis. Median OS was 17.45 vs. 17.15 months (HR, 0.90; p = 0.257).

A greater proportion of patients treated in the experimental arm responded to the therapy (57.5 % vs. 47.8 %; p = 0.0088; **Table 1**). Duration of response was longer with nivolumab plus chemotherapy than with chemotherapy alone (12.91 vs. 8.67 months). The combination showed a manageable safety profile. AEs leading to discontinuation or dose delay/reductions occurred with comparable frequency across the two arms.

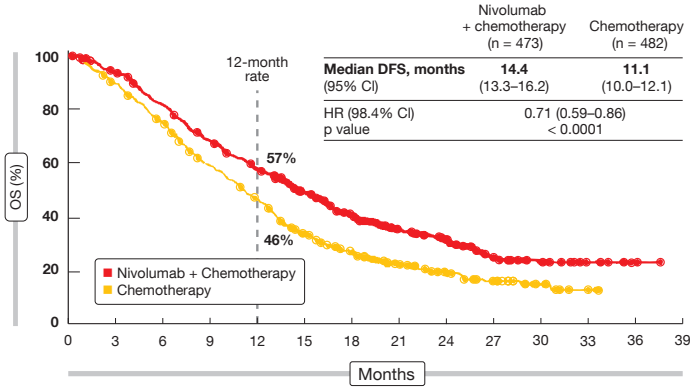

Figure 1: Primary endpoint of CheckMate 649: overall survival benefit with nivolumab plus chemotherapy *versus* chemotherapy in the CPS ≥ 5 population

As the authors noted in their summary, the objective of the phase III part of ATTRACTION-4 was met, demonstrating clinically meaningful efficacy as per protocol the trial was to be deemed positive if at least one of the primary endpoints were met. Nivolumab plus chemotherapy could be considered a new first-line treatment option in patients with unresectable advanced or recurrent gastric or GEJ cancer.

CheckMate 649: insights based on almost 1,600 patients

The largest randomized, global phase III study investigating PD-1-inhibitor–based therapies in the first-line setting for patients with advanced gastric cancer, GEJ cancer, and esophageal adenocarcinoma is CheckMate 649. Möhler et al. reported the first results for the comparison between chemoimmunotherapy vs. chemotherapy at ESMO 2020 [15]. Approximately 790 patients with unresectable, advanced or metastatic *HER2*-negative tumors were randomized into each arm. Chemoimmunotherapy consisted of nivolumab 360 mg plus XELOX Q3W or nivolumab 240 mg plus FOLFOX Q2W, while the patients in the control arm received XELOX Q3W or FOLFOX Q2W alone.

OS testing was conducted hierarchically based on the observation that in gastric, GEJ and esophageal cancers, PD-L1 expression by CPS at a cutoff ≥ 5 shows better enrichment for the efficacy of checkpoint inhibitors than tumor cell PD-L1 expression [16]. The statistical plan specified that if OS in the PD-L1 CPS ≥ 5 population proved significantly superior, OS in the PD-L1 CPS ≥ 1 group was tested, followed by OS in all randomized patients. The PD-L1 CPS ≥ 5 population comprised 473 and 482 individuals in the experimental and control arms, respectively. For the PD-L1 CPS ≥ 1 group, this was 641 and 655, respectively. Results for the third arm of the CheckMate 649 study that assessed dual checkpoint inhibition with nivolumab plus ipilimumab followed by nivolumab monotherapy were not presented at this time.

Improvements in various groups

Overall survival and PFS in the CPS ≥ 5 population were defined as the dual primary endpoints. Indeed, the addition of nivolumab brought about a statistically significant and clinically relevant OS advantage in this group (14.4 vs. 11.1 months; HR, 0.71; p < 0,0001; **Figure 1**), as well as in the population with CPS ≥ 1 (14.0 vs. 11.3 months; HR, 0.77; p = 0.0001) and in all randomized patients (13.8 vs. 11.6 months; HR, 0.80; p = 0.0002). The OS findings consistently favored nivolumab plus chemotherapy

TABLE 1:
Responses achieved in ATTRACTION-4 with nivolumab plus chemotherapy compared to chemotherapy alone

Response, n (%)	Nivolumab + chemotherapy (n = 362)	Placebo + chemotherapy (n = 362)
Overall response rate	208 (57.5)	173 (47.8)
Best overall response		
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)
Disease control rate	260 (71.8)	248 (68.5)

TABLE 2:
KEYNOTE-590: 24-month overall survival rates in the total group and dependent on PD-L1 expression and histology (esophageal squamous-cell carcinoma)

	24-month OS rates (%)			
Subgroup	Pembrolizumab + chemotherapy	Chemo-therapy	HR	p value
All patients	28	16	0.73	< 0.0001
Patients with PD-L1 CPS ≥ 10	31	15	0.62	< 0.0001
Patients with ESCC	29	17	0.72	0.0006
Patients with ESCC and PD-L1 CPS ≥ 10	31	15	0.57	< 0.0001

across multiple subgroups. Likewise, PFS was significantly longer in the patients with CPS ≥ 5 who received nivolumab plus chemotherapy (7.7 vs. 6.0 months; HR, 0.68; p < 0.0001). Superiority of the experimental regimen with regard to PFS was also observed for the CPS ≥ 1 group (7.5 vs. 6.9 months; HR, 0.74) and the total randomized population (7.7 vs. 6.9 months; HR, 0.77). A significantly larger proportion of nivolumab-treated patients developed responses (60 % vs. 45 %; p < 0.0001), which were also more durable (9.5 vs. 7.0 months).

No new safety signals became apparent and the safety profile for the combination was consistent with the profiles of the individual agents. The most common any-grade treatment-related AEs (TRAEs) across both arms included nausea, diarrhea, and peripheral neuropathy. TRAEs occurred with similar incidence in the CPS ≥ 5 population and in all patients treated across both arms; this also applied to select TRAEs of potential immunologic etiology. Here, grade 3/4 events were seen in ≤ 5 % of patients. In their conclusion, the authors emphasized that nivolumab is the first PD-1 inhibitor to demonstrate superior OS and PFS in combination with chemotherapy compared to chemotherapy alone in previously untreated patients with advanced cancers of the stomach, GEJ and esophagus. The combination thus represents a new potential first-line standard in this setting.

KEYNOTE-590: benefits of pembrolizumab

In patients with esophageal cancer, the randomized, double-blind, placebo-controlled, phase III KEYNOTE-590 study assessed pembrolizumab 200 mg Q3W for a maximum of 35 cycles plus 5-FU and cisplatin (n = 373) compared to placebo plus chemotherapy (n = 376) as first-line treatment [17]. The population included had locally advanced, unresectable or metastatic esophageal adenocarcinoma, squamous-cell carcinoma, or advanced/metastatic esophagogastric junction (EGJ) Siewert type 1 adenocarcinoma. Esophageal squamous-cell carcinoma (ESCC) was present in approximately 73 % in both arms. Among the patients with adenocarcinoma, roughly equal proportions had been diagnosed with esophageal or EGJ disease. Approximately half of all study participants in both arms showed PD-L1 CPS ≥ 10.

Indeed, first-line pembrolizumab plus chemotherapy provided statistically significant and clinically meaningful benefits in terms of several endpoints. Median OS was 12.4 vs. 9.8 months (HR, 0.73; p < 0.0001) in the total cohort, with a risk reduction of 27 %. Patients with PD-L1 CPS ≥ 10 experienced a 38 % reduction in their mortality risk (13.5 vs. 9.4 months; HR, 0.62; p < 0.0001). For the group with ESCC, OS was 12.6 vs. 9.8 months (HR, 0.72; p = 0.0006), and for those with ESCC and PD-L1 CPS ≥ 10, 13.9 vs. 8.8 months (HR, 0.57; p < 0.0001). The 24-month OS rates indicated sustained benefits in the experimental arm **(Table 2)**. With respect to PFS, improvements were observed in the overall population (6.3 vs. 5.8 months; HR, 0.65; p < 0.0001), the ESCC cohort (6.3 vs. 5.8 months; HR, 0.65; p < 0.0001) and the PD-L1 CPS ≥ 10 group (7.5 vs. 5.5 months; HR, 0.51; p < 0.0001). All subgroups benefited from the addition of pembrolizumab with respect to OS and PFS. Within the entire cohort, 45.0 % of pembrolizumab-treated patients vs. 29.3 % of those in the control arm responded (p < 0.0001). Median duration of response amounted to 8.3 vs. 6.0 months.

Comparable safety profiles were reported for the two treatment groups. Grade ≥ 3 TRAEs were seen in 71.9 % vs. 67.6 % and necessitated treatment discontinuation in 19.5 % vs. 11.6 %. Immune-mediated AEs and infusion reactions occurred in 25.7 % vs. 11.6 %, with most events graded as mild or moderate. The authors concluded that pembrolizumab plus chemotherapy should be a new first-line standard of care in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma.

Doubling of DFS with adjuvant nivolumab

In the setting of resectable locally advanced esophageal cancer and GEJ cancer, neoadjuvant chemoradiation therapy followed by surgery (i.e., trimodality therapy) is a widely used standard of care [18-20]. However, the risk of recurrence following trimodality therapy remains high, particularly in patients with residual pathologic disease, and established adjuvant treatment is lacking [18-21].

The adjuvant use of nivolumab was investigated in the CheckMate 577 trial, which is the first global, randomized, double-blind phase III study to evaluate a checkpoint inhibitor after trimodality therapy for esophageal/GEJ cancer [22]. At total of 794 patients with stage II/III disease and adenocarcinoma or squamous-cell histology were randomized to either nivolumab 240 mg Q2W for 16 weeks followed by 480 mg Q4W (n = 532) or placebo (n = 262). They had undergone neoadjuvant chemoradiotherapy and surgery within 4 to 16 weeks prior to randomization and had residual pathologic disease ≥ ypT1 or ≥ ypN1. The total treatment duration was up to 1 year.

Disease-free survival constituted the primary outcome. Adjuvant nivolumab conferred a significant benefit here, with a 31 % reduction in the risk of recurrence or death (22.4 vs. 11.0 months; HR, 0.69; p = 0.0003; **Figure 2**). Findings in all predefined subgroups favored the PD-1 inhibitor over placebo. Nivolumab was well tolerated and showed an acceptable safety profile. The majority of TRAEs were grade 1 or 2, and only 9 % prompted treatment discontinuation. Fatigue, diarrhea, pruritus and rash were reported as the most common TRAEs. Grade 3/4 select TRAEs occurred in < 1 % of patients in the nivolumab arm. Correspondingly, patient-reported outcome analyses revealed similar overall health status with

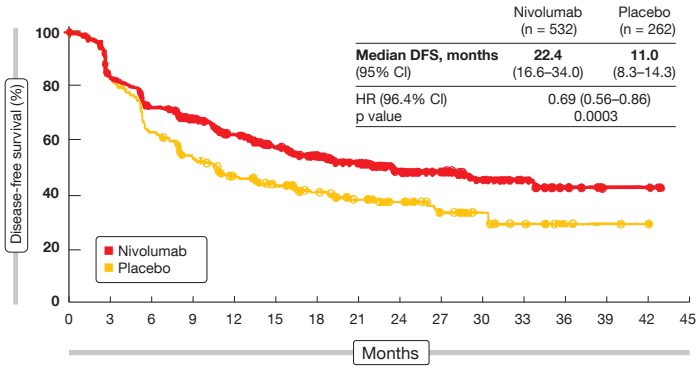

Figure 2: : Disease-free survival observed with adjuvant nivolumab in the CheckMate 577 trial

nivolumab and placebo according to the EQ-5D-3L instrument. As the authors noted, these results represent the first advance in years for patients with resected esophageal and GEJ cancer and potentially establish adjuvant nivolumab as a new standard of care.

Visually estimated CPS vs. conventional CPS

Although approved PD-1 inhibitors have shown encouraging improvements in survival in patients with gastroesophageal adenocarcinoma, many patients do not respond, which highlights the need of predictive biomarkers. PD-L1 expression can be assessed using the CPS and the Dako 22C3 assay, although utilization of this scoring method can be challenging in clinical practice. Therefore, a less time-consuming algorithm based on visual estimation of the PD-L1 expression on tumor and immune cells named visually estimated CPS (vCPS) has been developed for the VENTANA PD-L1 (SP263) assay. Chao et al. compared the clinical utilization of CPS (with Dako 22C3) and vCPS (with VENTANA PD-L1 SP263) based on post-hoc analyses of samples from the first-in-human BGB-A317-001 study that tested the PD-1 inhibitor tislelizumab in patients with gastroesophageal adenocarcinoma [23]. In this group of 81 individuals, PD-L1 expression was evaluable by CPS and vCPS in 49 and 74 patients with available formalin-fixed, paraffin-embedded tumors, respectively. Forty-five were evaluable using both assays.

The vCPS ≥ 5 % cutoff was determined as the optimal cutoff based on statistical analysis, prevalence, and pathological feasibility. This was further developed and analytically validated using the tumor samples. At the cutoffs assessed, both the VENTANA PD-L1 (SP263) assay with vCPS ≥ 5 % and the commercialized Dako 22C3 assay with CPS ≥1 aided in the identification of patients with high PD-L1 expression who were more likely to benefit from treatment than those with PD-L1–low tumors. The reproducibility of the VENTANA PD-L1 (SP263) assay with vCPS by different pathologists, materials, and laboratories indicated the highly trainable nature of the assay, as well as its consistency in gastric and GEJ adenocarcinoma.

Further clinical validation is underway for vCPS ≥ 5 % based on a phase III study designed to compare tislelizumab plus platinum/fluoropyrimidine versus placebo plus platinum/fluoropyrimidine as first-line therapy of gastric and GEJ cancer (RATIONALE 305; BGB-A317-305). ■

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INTERVIEW

Getting innovation from the laboratories into clinical practice

Which data presented at ESMO 2020 in the field of gastric cancer, gastroesophageal junction adenocarcinoma and esophageal cancer do you deem practice-changing?

The ESMO congress has provided amazing new data on gastroesophageal cancer, and great contributions by different authors all over the world have been presented. Patients with advanced gastric cancer used to have a median overall survival of less than 1 year when treated with conventional chemotherapy. For the first time, this was prolonged to more than 1 year due to the addition of checkpoint inhibition. Two randomized studies were reported at the Presidential Symposium III that showed outcome improvement for patients with gastric and gastroesophageal junction cancer when nivolumab was added to conventional chemotherapy [1, 2]. These are amazing findings, specifically for esophageal cancer that is also a very difficult disease and for which no new treatments have been developed over the last years. In patients with advanced or metastatic esophageal cancer, the addition of pembrolizumab, another checkpoint inhibitor, improved the response rate, progression-free survival and overall survival [3]. I also want to underline the findings obtained for nivolumab as postoperative treatment in patients with esophageal cancer who had received neoadjuvant chemoradiotherapy before surgery [4]. The preliminary data from this adjuvant study showed a significant prolongation of median disease-free survival of almost 1 year.

What has recently been achieved with regard to hepatocellular carcinoma?

The therapeutic landscape in hepatocellular carcinoma is evolving rapidly. At the ESMO Asia 2019, results for the combination of atezolizumab and bevacizumab, which is now the standard of care for first-line treatment of patients with advanced disease, was presented for the first time [5]. This year at ESMO, at the oral session of gastrointestinal non-colorectal cancers, an innovative approach assessed at the University of Guangzhou in South China was reported [6]. For patients with stage B hepatocellular carcinoma, the standard of care is transarterial chemoembolization, which was compared with hepatic intraarterial infusional chemotherapy with FOLFOX in more than 300 patients. The results of this randomized study showed that intraarterial chemotherapy is superior to transarterial chemoembolization, which means a new standard of care. I am sure that this approach will be incorporated into clinical practice.

Which emerging data with novel immunotherapeutic compounds are likely to impact future clinical research?

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I recommend watching the session on investigational immunotherapy at the ESMO 2020 as it provided a lot of information on new drugs and new ways of delivering immunotherapy. Most of these novel compounds are combined with checkpoint inhibitors. The new approaches include a fusion protein of interleukin-2 and interleukin-2 receptor alpha [7] as well as adoptive cell therapy with tumor-infiltrating lymphocytes in combination with checkpoint inhibitors in patients with various cancers [8]. Compounds have been developed with different mechanisms of action addressing new receptors such as TIM-3.

I really think that it is worthwhile to have a look at all these new possibilities that have been tested in phase I studies. In my opinion, they will be assessed in more advanced trials over the next few

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years. There is hope and many new data, and these data should be further developed to establish new approaches in the clinic. Getting innovation from the laboratories into clinical practice is the aim of our work.

What are your personal highlights from ESMO 2020?

For one, there are combinations of immunotherapy with targeted agents. An example of this is the study on the combined treatment with nivolumab and cabozantinib in patients with renal cell carcinoma that was presented at the Presidential Symposium I [9]. Compared to sunitinib, the combination demonstrated superior activity. Secondly, I would want to highlight the importance of early treatment in the setting of immunotherapy. These agents should not be used for refractory disease; they are gaining acceptance in first line and even in the adjuvant setting. The trial on adjuvant nivolumab in esophageal cancer is an example of this. Also, I want to point out new targeted agents such as the specific AKT inhibitor ipatasertib that has been shown to add to survival in patients with castration-resistant prostate cancer treated in a phase III trial [10]. ■

Ovarian cancer: taking PARP inhibition one step further

Individualized dosing of niraparib

Niraparib has been approved as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer (OC) based on the results of the NOVA trial [1]. The starting dose used in NOVA was 300 mg orally daily. A retrospective analysis indicated that individualized starting doses based on baseline body weight and platelet counts might improve the safety profile of niraparib without compromising efficacy [2]. This approach was tested by the NORA study conducted in Chinese patients with platinum-sensitive, recurrent OC that was of high-grade serous or high-grade predominantly serous histology or germline *BRCA*-mutated [3]. The women had received at least 2 lines of platinum-containing therapy and had experienced partial or complete responses to the last treatment. They were randomized to either niraparib (n = 177) or placebo (n = 88) until disease progression. Eleven patients who had a baseline body weight ≥ 77 kg and platelet counts ≥ 150,000/µl received an initial niraparib dose of 300 mg daily, while 155 with < 77 kg and platelet counts < 150,000/µl were treated with 200 mg daily. PFS determined by blinded independent central review constituted the primary outcome. NORA is the first fully powered phase III, randomized, controlled study to evaluate a PARP inhibitor in Chinese patients with OC.

The trial met its primary endpoint. PFS was markedly prolonged in the experimental arm of the ITT population, with a 68 % reduction in the risk of mortality and progression (18.3 vs. 5.4 months; HR, 0.32; p < 0.0001). Both patients with and without germline *BRCA* mutations derived significant PFS benefits (p < 0.0001 each; **Table 1**). Also, patients in the niraparib arm fared better with respect to the chemotherapy-free interval (18.5 vs. 9.7 months; HR, 0.34; p < 0.0001) and time to the first subsequent therapy (16.7 vs. 7.7 months; HR, 0.35; p < 0.0001). OS was immature at the time of the analysis.

The PFS benefits observed in NORA were consistent with those reported in the NOVA trial, while the safety profile was indeed improved **(Table 1)**. This particularly applied to hematological toxicities. Overall, the authors noted that niraparib at individualized starting doses is effective and safe and should be considered the standard clinical practice for maintenance therapy of patients with OC.

TABLE 1:
Indirect comparison of progression-free survival and select grade 3/4 adverse events across NORA and NOVA

	NORA		NOVA	
Outcome	**Niraparib**	**Placebo**	**Niraparib**	**Placebo**
Progression-free survival				
PFS in g*BRCA*-mutated patients (months)	Not reached	5,5	21.0	5.5
HR	0.22		0.27	
PFS in non-g*BRCA*-mutated patients (months)	11.1	3.9	9.3	3.9
HR	0.40		0.45	
Grade 3/4 adverse events (%)				
Anemia	14.7	2.3	25.3	0
Decreased platelet counts/thrombocytopenia	11.3	1.1	33.8	0.6
Decreased neutrophil counts/neutropenia	20.3	8.0	19.6	1.7
Hypertension	1.1	0	8.2	2.2

MEDIOLA: olaparib plus durvalumab ± bevacizumab

The combination of a VEGF inhibitor and olaparib has been shown to increase PFS compared with olaparib alone in patients with platinum-sensitive relapsed OC and compared with VEGF inhibition alone in the newly diagnosed maintenance setting [4, 5]. Initial results of the open-label, phase II basket trial MEDIOLA investigating olaparib plus durvalumab showed that the combination is well tolerated and active in patients with germline *BRCA*-mutant platinum-sensitive relapsed OC [6]. Two additional cohorts were sequen-

tially enrolled to test olaparib plus durvalumab (n=32) and olaparib plus durvalumab and bevacizumab (n=31) in patients with germline *BRCA*-wildtype, platinum-sensitive relapsed OC after a maximum of 2 chemotherapy lines. Disease control rate (DCR) at 24 weeks and safety/tolerability were defined as the primary endpoints. Drew et al. presented the findings at the ESMO Congress [7].

According to this analysis, the chemotherapy-free triplet combination of olaparib, durvalumab and bevacizumab showed promising efficacy. At 24 weeks, DCR was high at 77.4%, and median PFS amounted to 14.7 months. In the doublet combination cohort, 24-week DCR and PFS were 28.1% and 5.5%, respectively. Objective response rates were 87,1% and 34.4% for the triplet and doublet cohorts, respectively. An exploratory analysis suggested that the ORR achieved with the triplet regimen did not depend on the genomic instability status (GIS). GIS was positive by definition in patients with a loss of heterozygosity score ≥14, a somatic *BRCA* mutation or a mutation in one of 13 homologous recombination repair genes. The analysis showed consistently high response rates across the triplet cohort irrespective of GIS, indicating that the high ORR was not driven by differences in genomic instability status. Overall, the safety profiles of the doublet and triplet regimens matched the known safety profiles expected for the single agents. The combination of olaparib, durvalumab and bevacizumab is now being tested as part of a first-line maintenance regimen in the phase III DUO-O study.

TABLE 2:
Tumor responses to pamiparib in the platinum-sensitive (PSOC) and platinum-resistant (PROC) cohorts according to independent review committee

Outcome	PSOC (n = 82)	PROC (n= 19)
ORR, %	64.6	31.6
Best overall response, %		
Complete response	9.8	0.0
Partial response	54.9	31.6
Stable disease	30.5	63.2
Progressive disease	4.9	5.3
Not estimable	0.0	0.0
Disease control rate, %	95.1	94.7
Clinical benefit rate ≥24 weeks, %	74.4	52.6
Median time to response, months	1.7	1.4

Disease control rate: complete plus partial responses; clinical benefit rate: complete and partial responses plus stable disease ≥24 weeks

Pivotal phase II results for novel agent pamiparib

The investigational, potent, selective, oral PARP1/2 inhibitor pamiparib has demonstrated antitumor activity in patients with OC in the first-in-human BGB-290-AU-002 study that also established 60 mg orally twice daily as the recommended phase II dose (RP2D) [8]. BGB-290-102, an open-label, multicenter phase I/II study, is assessing the safety and antitumor activity of pamiparib in adult Chinese patients with advanced solid tumors whose disease has progressed despite standard therapy or for which no standard therapy is available. Wu et al. reported preliminary results of the RP2D-expansion of the trial for OC patients with *BRCA1/2*-mutation-positive, platinum-sensitive (PSOC; n=90) or platinum-resistant (PROC; n=23) disease [9]. ORR according to independent review committee was defined as the primary endpoint.

Pamiparib gave rise to clinically meaningful and durable responses. Most of the patients in the PSOC cohort responded (ORR, 64.6%), with 9.8% achieving complete remissions **(Table 2)**. Median duration of response was 14.5 months, and median PFS was 15.2 months. In the PROC group, ORR was 31.6%. Disease control was obtained by 95.1% and 94.7% of patients in the PSOC and PROC cohorts, respectively. In both groups, most patients experienced reductions in their target lesions from baseline. The CA-125 response rates were 79.7% and 38.1%, respectively.

Pamiparib 60 mg twice daily was generally well tolerated and showed an acceptable safety profile. Similar to other PARP inhibitors, hematologic toxicities were the most significant safety events observed, although they proved manageable. The management of these AEs was optimized using a proactive modification plan and close monitoring. No myelodysplastic syndrome was reported, and no significant complications potentially related to hematologic toxicity (e.g., grade ≥3 hemorrhage, fever, infection) occurred. The overall safety profile was generally consistent across the PSOC and PROC cohorts. ■

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Novel combination approaches in various solid tumors

Lenvatinib plus pembrolizumab

The anti-angiogenic multikinase inhibitor lenvatinib has been shown to exert immunomodulatory effects that enhance the anti-tumor activity of anti-PD-1 antibodies [1]. In the early-phase setting, lenvatinib plus pembrolizumab induced partial responses in patients with different tumor types [2]. The ongoing phase II LEAP-005 study is assessing lenvatinib 20 mg orally daily plus pembrolizumab 200 mg Q3W for up to 35 cycles in six types of pretreated, advanced solid tumors. These include triple-negative breast cancer (TNBC), ovarian cancer, gastric cancer, colorectal cancer (CRC), biliary tract cancer (BTC), and glioblastoma multiforme (GBM). ORR as well as safety and tolerability constitute the primary objectives of the study.

Lwin et al. at reported interim results for the first 187 patients enrolled in LEAP-005 at the ESMO 2020 Congress after a mean follow-up of 8.6 months [3]. For each of the tumor types assessed, 31 patients were included in the analysis with the exception of the CRC cohort that comprised 32 individuals. Notably, in this group, tumors belonged to the non-MSI-high/proficient mismatch repair category. Patients with TNBC were treated in the second or third line, those with ovarian cancer in the fourth line, those with gastric cancer and CRC in the third line and those with BTC and GBM in the second line.

Substantial disease control

The prespecified futility efficacy criteria for cohort expansion were met or even exceeded **(Figure)**. Regarding women's cancers, the ORRs were 29.0 % and 32.3 % in patients with TNBC and ovarian cancer, respectively. Disease control was achieved by 58.1 % and 74.2 %, respectively. With respect to gastrointestinal cancers, ORR was highest in the CRC group (21.9 %). Both patients with gastric cancer and BTC obtained ORRs of 9.7 %. DCRs were 46.9%, 48.4 % and 67.7 %, respectively. Patients with GBM responded in 16.1 % and achieved disease control in 58.1 %. Median duration of response was 5.3 and 3.2 months for the BTC and GBM cohorts and had not been reached yet for the other cohorts.

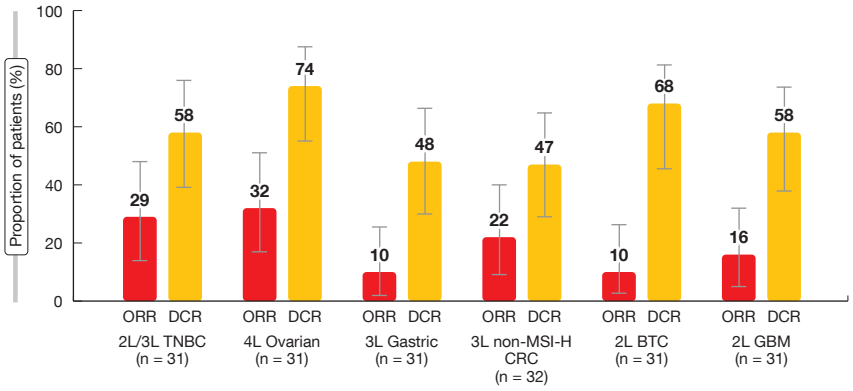

Figure: Objective response rates (ORR) and disease control rates (DCR) across the cohorts included in the LEAP-005 trial

Median PFS was longest in the BTC (median PFS, 6.1 months), ovarian cancer (4.4 months) and TNBC cohorts (4.2 months). For the other tumor types, PFS ranged between 2.3 and 2.8 months. The 6-month PFS rates in patients with TNBC and ovarian cancer were 48.9 % and 47.1 %, respectively. For gastric cancer, CRC and BTC, these were 22.2 %, 30.5 % and 56.5 %, respectively. In the GBM cohort, 11.5 % of patients were progression-free at 6 months.

Toxicity proved manageable in all cohorts. Grade 3 to 5 treatment-related AEs emerged in approximately half of patients in each cohort, although discontinuation rates due to grade 3 to 5 AEs were low at 6 % to 13 %. There was one fatal AE in each group except for the BTC cohort. Hypertension was generally the most common AE; also, fatigue, diarrhea, decreased appetite, hypothyroidism, and nausea were reported.

All-grade immune-mediated AEs occurred in 26 % to 48 %, with grade 3 to 5 events emerging in 3 % to 6 %. Infusion reactions were noted in one patient each in the TNBC, ovarian cancer and BTC cohorts. Overall, the safety profile was consistent with that previously seen with the combination of pembrolizumab and lenvatinib. 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.

PD-1/PD-L1 synergy: tislelizumab and BGB-A333

Simultaneous PD-1 and PD-L1 blockade has been hypothesized to provide synergistic anti-tumor effects [4]. An open-label, phase I/IIB clinical trial evaluated the combination of the PD-1 inhibitor tislelizumab, which is currently being tested in the phase III setting, with the investigational anti-PD-L1 antibody BGB-A333 [5]. During the dose-escalation part of the study that was conducted in 15 patients, the recommended phase II dose for BGB-A333 was established at 1.350 mg intravenously Q3W. This was followed by the dose expansion phase IIB part that involved 12 patients with locally advanced or metastatic urothelial carcinoma who had progressed after at least one platinum-containing regimen. They received tislelizumab 200 mg plus BGB-A333 1,350 mg Q3W. The results obtained for this combination were presented at ESMO 2020 after a median follow-up of 10 months. Six patients each fell into the PD-L1-high and PD-L1-low categories. Four had lymph-node-only disease.

Median duration of treatment was 6.2 months. Overall, 42 % of patients responded **(Table)**. ORR was higher in the group with PD-L1-high tumors (67 %) than in those with PD-L1-low tumors (17 %). However, given the small sample sizes, these differences should be interpreted with caution. Responses were durable and lasted for a median of 9.1 months. Median PFS amounted to 6.1

TABLE
Responses obtained with BGB-A333 plus tislelizumab in patients with urothelial carcinoma

Confirmed responses	PD-L1 high (n = 6)	PD-L1 low (n = 6)	Total (n = 12)
Complete response	2	1	3
Partial response	2	0	2
Stable disease	2	2	4
Progressive disease	0	2	2
Not evaluable	0	1	1
Objective response rate, % (95 % CI)	67 (22.3, 95.7)	17 (0.42, 64.1)	42 (15.2, 72.3)
Disease control rate, % (95 % CI)	100 (54.1, 100.0)	50 (11.8, 88.2)	75 (42.8, 94.5)

months in the total cohort; again, patients with PD-L1-high tumors fared better than those with PD-L1-low tumors (10.0 and 4.1 months, respectively).

Tislelizumab plus BGB-A333 was generally well tolerated, with most AEs showing mild or moderate severity. Fatigue constituted the most commonly reported treatment-related AE across the study. No fatal events occurred. Two patients in phase IIB experienced four immune-related AEs including grade 3 endocrine disorder, grade 3 hypophysitis, grade 2 musculoskeletal and connective tissue disorder, and grade 2 myositis. The authors noted in their conclusion that these data provide insights into combining tislelizumab with anti-PD-L1 antibody treatment.

Pamiparib plus temozolomide: biomarker analysis

Patients with various locally advanced or metastatic solid tumors are participating in the ongoing phase IB BGB-290-103 study that is evaluating the investigational PARP inhibitor pamiparib in combination with the alkylating agent temozolomide administered at low doses. A total of 114 patients were enrolled in the dose-escalation and dose-expansion phases. Most of them were heavily pretreated, with a median of 3 prior treatment lines. Pamiparib 60 mg on days 1 to 28 and temozolomide 60 mg on days 1 to 7 were identified as the recommended phase II doses.

At ESMO 2020, findings were presented from a retrospective biomarker analysis that was based on samples from patients included in both phases of the study [6]. Homologous recombination deficiency (HRD) testing was performed in archival tissue samples obtained at baseline and was expressed using the genomic instability score (GIS), which was determined based on large-scale transitions, telomeric allelic imbalance, and loss of heterozygosity. Samples with GIS ≥ 33 were defined as GIS-positive. Circulating tumor DNA next-generation sequencing was performed in blood samples obtained at baseline, with a focus on 16 core DNA damage response (DDR) genes including *ATM, BRCA1, BRCA2, CDK12, PALB2,* and *RAD51B*. A positive DDR mutational status was defined as ≥ 1 mutation in one of these 16 DDR genes. The investigators sought to establish correlations between the GIS/DDR status and overall response/disease control rates.

Robust results for GIS

Among 34 patients analyzed for *HRD*, 32 % were GIS-positive. These were shown to have higher ORR and DCR than GIS-negative individuals irrespective of the *BRCA1/2* mutation status. For the GIS-positive cohort, ORR and DCR were 81.8 % and 90.9 %, respectively, while they were 13.0 % and 56.5 % for the GIS-negative group. In the cohort of 86 patients evaluated for DDR status, 26 % proved DDR-positive. Here, positive patients also showed higher ORR than the negative cohort (27.3 % vs. 14.1 %), although responses occurred considerably less frequently compared to the GIS-positive cohort and depended on the *BRCA1/2* status. The majority of responding DDR-positive patients harbored *BRCA1/2* mutations rather than the *BRCA1/2* wildtype. DCRs were similar across DDR-positive and DDR-negative patients.

As the authors summarized, the GIS status, as a global measure of genomic instability, appears to be a robust biomarker for the prediction of response to pamiparib plus low-dose temozolomide. Also, this analysis confirms the observation that mutations in DDR genes other than *BRCA1/2* have limited utility in predicting responses to PARP inhibitors. Cohort 6 of the study is currently evaluating the anti-tumor activity of pamiparib plus low-dose temozolomide in patients with GIS-positive NSCLC, head and neck, esophageal, and soft tissue sarcoma tumors. ■

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