Springer Medizin

© Springer-Verlag 2020

www.memoinoncology.com

01/20

memo – inOncology SPECIAL ISSUE

Congress Report ESMO 2019

A GLOBAL DIGEST ON APPROACHES IN ADVANCED SOLID TUMORS

Report from the ESMO Congress,
27th September – 1st October 2019, Barcelona, Spain

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, AT, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43/(0)1/330 24 15-0, **Fax:** +43/(0)1/330 24 26, **Internet:** www.springer.at, www.SpringerMedizin.at. **Owner and Copyright:** © 2020 Springer-Verlag GmbH Austria, part of Springer Nature. **Managing Directors:** Joachim Krieger, Juliane Ritt, Dr. Alois Sillaber. **Medical Writer:** Dr. Judith Moser. **Corporate Publishing:** Elise Haidenthaller. **Editorial Support:** Stefanie Wurm, PhD. **Layout:** Katharina Bruckner. Published in Vienna. Produced in Kienberg. **Printer:** F&W Druck- und Mediencenter GmbH, Kienberg, Germany.
The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

The Publisher does not assume any legal liability or responsibility for the accuracy, completeness, or usefulness of the information supplied herein, nor for any opinion expressed. The Publisher, its agent, and employees will not be liable for any loss or damage arising directly or indirectly from possession, publication, use of, or reliance on information obtained from this report. It is provided in good faith without express of implied warranty.

Reference to any specific commercial product or service does not imply endorsement or recommendation by the Publisher. All articles are peer-reviewed and protected from any commercial influence.
This issue is intended only for healthcare professionals outside the US, the UK and Australia.

Table of Contents

© Alexey Trifonenko / stock.adobe.com

Editorial Board:

Hendrik-Tobias Arkenau, MD, PhD, FRCP, Sarah Cannon Research Institute, London, UK
Paolo G. Nuciforo, MD, PhD, Molecular Oncology Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain
Gert Schachtner, MD, Department of Urology, Medical University Innsbruck, Austria
Christian Schauer, MD, Department of Gynecology, Krankenhaus der Barmherzigen Brüder, Graz, Austria

Lecture Board for this issue:
Hendrik-Tobias Arkenau, MD, PhD; Nicoletta Colombo, MD; Pascal Hammel, MD; Maha Hussain, MD; Paolo Nuciforo, MD, PhD; Bertrand Routy, MD, PhD; Gert Schachtner, MD; Christian Schauer, MD; Agostina Stradella, MD.

Expert interviews at ESMO 2019

www.memo inoncology.com

Markus Moehler, MD, PhD, presents novel findings on anti-PD-1 therapies and explains differences regarding the outcome of anti-PD-1 therapies in Asian and Caucasian populations.

Florian Lordick, MD, PhD, on the use of anti-PD-1 and other emerging therapies in gastric and oesophageal cancers.

Simon Chowdhury, MA, MBBS, MRCP, PhD, talks about the use of PARP inhibitors in prostate cancer as well as the impact of pamiparib in patients with advanced solid tumors.

Hendrik-Tobias Arkenau, MD, PhD, FRCP, discusses combination studies of novel PARP inhibitors with other drugs.

BeiGene

Supported by BeiGene in the form of an unrestricted grant

Preface

Dear readers,

With "memo inOncology" Springer has created a medical education platform that is globally accessible and offers value to health care professionals in oncology (**www.memoinoncology.com**). Over the last four years, we have reported from major conferences such as ASCO, ESMO, WCLC, ELCC or ESMO Asia on recent highlights in the field of lung cancer. Our congress reports and translations thereof into Mandarin and Japanese have received great international interest. Hence, we have decided to expand on this success and create additional content on other solid tumors. This issue covers novel clinical research on anti-PD-1 treatment, a potential role of the microbiome in tumorigenesis as well as PARP inhibition in gynecological cancers and beyond. We hope that you will enjoy reading this report and find it useful.

Dr. Alois Sillaber
Managing Director
Springer-Verlag GmbH
Springer Nature

PD-1 inhibition in gastric and esophageal cancer, hepatocellular carcinoma, and urothelial carcinoma

Gastric and esophageal cancer

Adenocarcinoma of the stomach and gastroesophageal junction (GEJ) ranks fifth among the most common malignancies worldwide [1, 2] and is the third leading cause of cancer-related death in both sexes [3]. Most patients are diagnosed at an advanced stage due to the asymptomatic early feature of the disease. Despite a falling global incidence and significant progress in treatment, further efforts are necessary to improve prognosis [4].

Esophageal cancer is the seventh most common cancer worldwide [5]. In 2018, it ranked fifth in incidence and fourth in mortality of all cancer types in China [6]. The most common subtypes are squamous cell carcinoma (SCC) and adenocarcinoma (AC) [5, 7]. These entities show differences in etiology and prevalence across countries. Metastatic esophageal cancer has a poor prognosis, with a 5-year relative survival rate of ≤ 8 % [8, 9]. In both gastric/GEJ and esophageal cancer, systemic treatment in the advanced setting includes chemotherapy in the first- and second-line settings plus anti-HER2 tumors in first line, as well as the anti-VEGFR-antibody ramucirumab in second line. However, chemotherapy efficacy is limited, with substantial toxicity. The armamentarium is currently being expanded by PD-1 inhibitors, which are successfully tested in clinical trials.

Second-line nivolumab in esophageal SCC

The randomized, open-label, phase III ATTRACTION-3 study assessed nivolumab in patients with unresectable advanced or recurrent esophageal SCC who were refractory to or intolerant of one prior fluoropyrimidine/platinum-based chemotherapy. Patients in the experimental arm received nivolumab monotherapy (n = 210), while those in the control arm were treated with either docetaxel or paclitaxel (n = 209). Overall survival (OS) constituted the primary endpoint.

According to the final analysis reported at ESMO 2019, nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS compared to chemotherapy in pretreated advanced esophageal SCC, with a 23 % reduction in mortality risk (10.9 vs. 8.4 months; HR, 0.77; p = 0.019; **Figure 1**) [10]. Eighteen-month OS rates were 31 % vs. 21 % for the two arms. The subgroup analysis consistently favored nivolumab across various pre-specified subgroups, which also included PD-L1 expression. No meaningful difference between nivolumab and chemotherapy was achieved regarding progression-free survival (PFS; HR, 1.08). Also, the two treatment regimens gave rise to

 © Springer-Verlag

comparable objective response rates (ORRs; 19 % vs. 22 %), although, notably, responses proved more durable in the nivolumab arm (6.9 vs. 3.9 months).

Health-related quality of life (HRQol) was assessed using the EQ-5D-3L visual analog scale score. According to this exploratory analysis, the nivolumab-based treatment elicited significant overall improvement. This might also have been due to the lower rate of treatment-related adverse events (TRAEs) reported for nivolumab. Moreover, the PD-1 inhibitor gave rise to a greater percentage of low-grade AEs compared to high-grade AEs, whereas the opposite was the case for chemotherapy. The incidence of grade 3/4 AEs was more than 3 times higher in the control arm (18 % vs. 63 %). Grade 3/4 select TRAEs including endocrine, gastrointestinal, pulmonary and renal events occurred in ≤ 2 % of patients in both arms. In their conclusion, the authors stated that nivolumab represents a potential new standard second-line option for patients with advanced esophageal SCC.

Gastric cancer: real-world results with nivolumab

The benefit of nivolumab in pretreated patients with gastric or GEJ cancer has been established by the phase III ATTRACTION-2 study [11]. At ESMO 2019, Sunakawa et al. presented real-world data on the use of single-agent nivolumab in any line in 198 patients with advanced gastric or GEJ cancer [12]. In addition, the researchers investigated the association of outcomes with host-related factors. Ninety-two and 80 % of patients had already received taxanes and ramucirumab, respectively. Peritoneal metastases and ascites were present in approximately half of the cases.

Among 119 of patients with measurable lesions, 5.6 % responded to treatment, and disease control was achieved in 33.1 %. A subanalysis by patient background indicated that disease control rates (DCR) were 38 % for PS 0, 35 % for PS 1, and 22 % for PS 2. Also, the DCR was lower in those with peritoneal metastasis and ascites, as well as in patients with signet-ring cell histology compared to other histological subtypes. *HER2* mutation status and neutrophil-lymphocyte ratio, on the other hand, did not affect disease control.

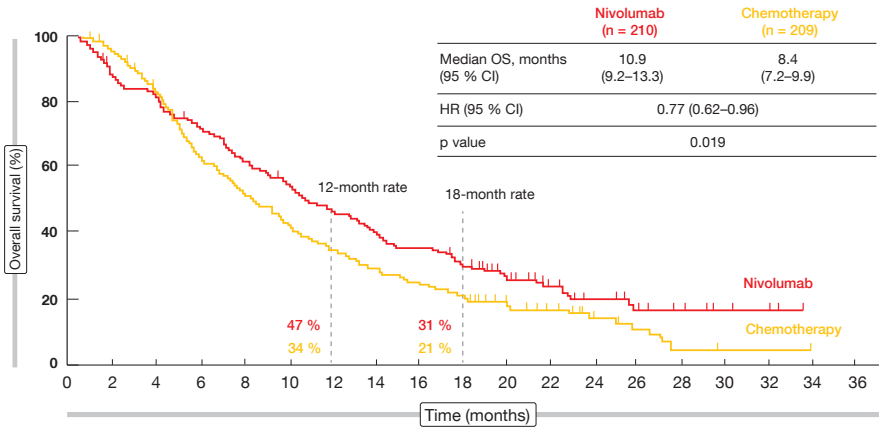

Figure 1: Superiority of nivolumab vs. chemotherapy regarding overall survival in esophageal squamous-cell carcinoma (ATTRACTION-3 study)

In 58.4 % of 105 evaluable patients, the tumor growth rate (i.e., the increase in tumor volume during 1 month) decreased after the introduction of nivolumab. Twenty-six (24.8 %) were identified as patients with hyper-progressive disease (HPD), i.e. those with a ≥ 2-fold increase of the tumor growth rate during nivolumab as compared to before nivolumab. According to a subanalysis, HPD occurred more commonly in patients with body mass index ≥ 25 (40.0 % vs. 24.0 % in those with BMI < 25) and peritoneal metastases (33.3 % vs. 20.8 % in those without). Moreover, compared to patients who had not received the respective agents, HPD showed higher incidence after previous use of taxanes (25.5 % vs. 14.3 %) and irinotecan (40.0 % vs. 21.1 %). Age, PS, *HER2* status and history of use of antibiotics did not correlate with the HPD rate. None of the patients with signet-ring cell histology experienced HPD.

KEYNOTE-181: pembrolizumab vs. chemotherapy in Chinese patients

Single-agent pembrolizumab was assessed in the global, randomized, phase III KEYNOTE-181 trial that included patients with advanced AC or SCC of the esophagus or Siewert type 1 AC of the GEJ, who had progressed during or after first-line therapy. The control arm received chemotherapy including paclitaxel, docetaxel, or irinotecan according to investigator's choice. In each arm, 314 patients were treated. The final analysis of the trial reported by Kojima et al. showed that pembrolizumab substantially improved OS over chemotherapy in patients with PD-L1 combined positive score (CPS) ≥ 10 [13].

Given the differences in disease etiology between SCC and AC and the overwhelming prevalence of SCC in Chinese patients, Chen et al. focused on the results obtained in the Chinese subgroup of KEYNOTE-181 (n = 123) [14]. Sixty-two and 61 of these patients received pembrolizumab and chemotherapy, respectively. Almost the entire cohort had SCC histology (97 % in each treatment arm). PD-L1 CPS ≥ 10 was present in 40.3 % and 47.5 % in the pembrolizumab and chemotherapy arms, respectively.

Meaningful OS activity irrespective of PD-L1 status

The primary end point was OS in patients with PD-L1 CPS ≥ 10 (n = 54), those with SCC histology (n = 119), and the total population (ITT; n = 123). Indeed, pembrolizumab resulted in survival improvement compared to chemotherapy for all of these cohorts, with HRs amounting to 0.34, 0.55, and 0.55. Twelve-month OS rates for pembrolizumab *versus* chemotherapy in the three groups were 53.1 % vs. 16.1 %, 35.7 % vs. 15.3 %, and 36.3 % vs. 16.7 %. For PFS, which was defined as a secondary endpoint, pembrolizumab showed no superiority, with similar 6-month rates in the two treatment arms. Objective response rates in the experimental arm substantially exceeded those observed in the control arm in all three groups. Overall, median duration of response had not been reached yet for pembrolizumab and was 3.2 months for chemotherapy.

© Springer-Verlag

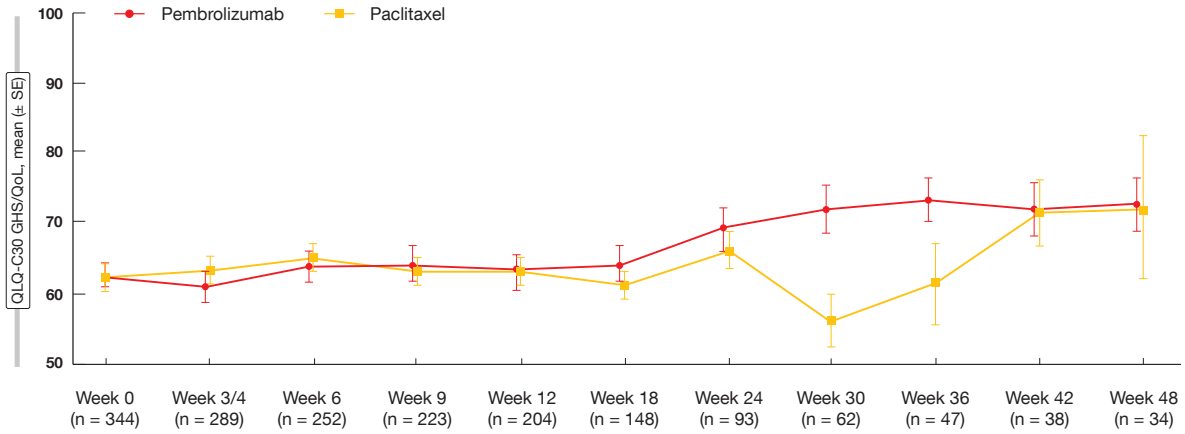

Figure 2: KEYNOTE-061: global health status/quality of life scores over time with pembrolizumab and paclitaxel

At the same time, the PD-1 inhibitor demonstrated improved tolerability, with fewer patients experiencing any-grade, grade 3-5 TRAEs or TRAEs that resulted in discontinuation. Hypothyroidism, ALT increases and asthenia ranged among the most common AEs.

In their conclusions, the authors noted that although most patients in the Chinese cohort had SCC histology, pembrolizumab showed clinically meaningful OS improvement regardless of PD-L1 status. This was consistent with the OS prolongation noted in the Asian subgroup of the full global cohort. Overall, these results suggested that pembrolizumab could be a novel standard-of-care agent in the second-line treatment of Chinese patients with advanced esophageal cancer.

HRQoL in KEYNOTE-061

Patients with advanced adenocarcinoma of the stomach or GEJ and PD-L1 CPS ≥ 1 received second-line treatment with either pembrolizumab or paclitaxel in the randomized, multicenter, open-label, phase III KEYNOTE-061 trial. Here, the primary analysis had not yielded any significant differences in terms of OS or PFS [15]. However, pembrolizumab therapy induced more durable responses and a better safety profile than paclitaxel. Van Cutsem et al. reported results of pre-specified exploratory HRQoL analyses conducted in the primary analysis population from KEYNOTE-061 [16]. Changes from baseline HRQoL were assessed using the EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires. For the characterization of health status, EuroQol EQ-5D-3L was used. The HRQoL population included 371 patients.

Global health status/QoL scores worsened over the first 12 weeks in both treatment groups but improved in the experimental arm compared to the control arm from week 18 **(Figure 2)**. Median time to deterioration in QLQ-C30 and QLQ-STO22 scores was similar for pembrolizumab and paclitaxel, which also applied to the pre-specified nausea/vomiting and appetite loss subscales in QLQ-C30 and the pain subscale in QLQ-STO22. The authors noted that together with previously presented efficacy and safety data, these findings from the KEYNOTE-061 study underscore the need for further research to identify patients likely to benefit from single-agent pembrolizumab.

KEYNOTE-062: first-line pembrolizumab monotherapy

Two different first-line pembrolizumab regimens were assessed by the global, randomized, placebo-controlled three-arm KEYNOTE-062 study that enrolled patients with advanced, PD-L1–positive (CPS ≥ 1) gastric or GEJ adenocarcinoma [17]. Pembrolizumab was administered either as monotherapy for up to 35 cycles (n = 256) or together with chemotherapy (n = 257). Patients in the control arm (n = 250) received placebo plus chemotherapy. CPS scores ≥ 10 prevailed in 79 %, 65 %, and 53 %, respectively. Microsatellite instability-high (MSI-H) status was found in 5 %, 7 %, and 8 %, respectively. More than two thirds of patients had been diagnosed with gastric cancer. OS and PFS were defined as coprimary endpoints.

Pembrolizumab monotherapy did not increase median OS compared to chemotherapy in the overall population (HR, 0.91), but reduced the mortality risk by 31 % in patients who had CPS ≥ 10 (17.4 vs. 10.8 months; HR, 0.69), although this was only an exploratory analysis. MSI-H expression enhanced OS benefits both in the total group (not reached vs. 8.5 months) and the CPS ≥ 10 cohort (not reached vs. 13.6 months). No PFS benefit was observed irrespective of PD-L1 expression. However, the pembrolizumab-treated patients in the MSI-H group did derive PFS improvement (11.2 vs. 6.6 months; HR, 0.72) as well as improved ORR (57.1 % vs. 36.8 %) and longer duration of response (21.2 vs. 7.0 months). In the overall population, response rates with pembrolizumab were relatively lower than in the control arm (CPS ≥ 1: 14.8 % vs. 37.2 %; CPS ≥ 10: 25.0 % vs. 37.8 %), although responses proved considerably more durable. Fewer patients in the pembrolizumab arm than in the chemotherapy arm experienced any-grade AEs.

Findings with pembrolizumab plus chemotherapy

With respect to the comparison between the pembrolizumab/chemotherapy arm and the chemotherapy-only arm, the additional benefit of the combination was generally modest. Pembrolizumab plus chemotherapy did not convey any OS improvement regardless of CPS scores. For PFS, only the results obtained for the CPS ≥ 10 cohort suggested some improvement (HR, 0.73). ORRs were relatively higher with the combination than with chemotherapy

© Springer-Verlag

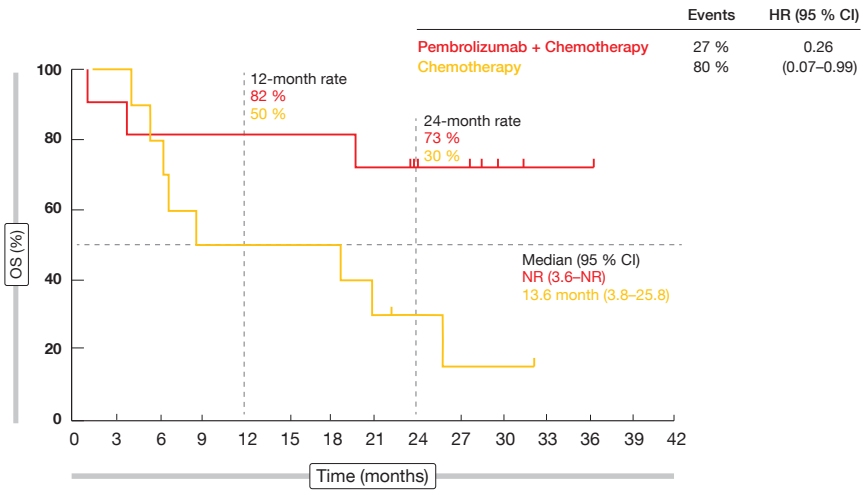

Figure 3: MSI-H cohort in the KEYNOTE-062 study: pembrolizumab plus chemotherapy vs. chemotherapy in patients with gastric or gastroesophageal carcinoma

(CPS ≥ 1: 48.6 % vs. 37.2 %; CPS ≥ 10: 52.5 % vs. 37.8 %), with responses lasting longer in the CPS ≥ 10 population (8.3 vs. 6.8 months).

Efficacy outcomes were enhanced in the presence of MSI-H regardless of CPS status. MSI-H patients, when treated with both pembrolizumab and chemotherapy, derived substantial reductions in mortality risk compared to those receiving chemotherapy only (median OS in CPS ≥ 1: not reached vs. 8.5 months; HR, 0.37; CPS ≥ 10: not reached vs. 13.6 months; HR, 0.26; **Figure 3**). Also, substantial benefits resulted in the MSI-H population with regard to PFS (not reached vs. 6.6 months; HR, 0.45) and ORR (64.7 % vs. 36.8 %; duration of response, not reached vs. 7.0 months). Grade 3 to 5 AEs rates were similar across the two arms (73 % vs 69 %). Immune-related events occurred more often in the experimental arm but were mostly grade 1 or 2.

Hepatocellular carcinoma

Liver cancer is the sixth most commonly diagnosed type of cancer worldwide, with hepatocellular carcinoma (HCC) representing 75 % to 85 % of cases [5]. Current systemic treatment options in the advanced stage include the tyrosine kinase inhibitors sorafenib and lenvatinib in the first line and regorafenib and cabozantinib in the second line, as well as the monoclonal antibody ramucirumab for patients with high serum alpha-fetoproteine levels. However, there is still an unmet need to prolong survival and improve tolerability. Research is focusing on the first- and second-line use of the PD-1 inhibitors pembrolizumab and nivolumab, as well as other aspects such as patient selection and quality of life.

CheckMate 459: nivolumab vs. sorafenib

The single-arm, phase I/II CheckMate 040 trial has yielded durable objective responses and promising long-term survival with nivolumab in advanced HCC with or without chronic viral hepatitis [18]. Based on these insights, nivolumab was approved by the FDA for the treatment of HCC in patients who have previously received sorafenib. The randomized CheckMate 459 study was designed to compare nivolumab with sorafenib in previously untreated patients with advanced HCC. Overall, 743 patients participated who had advanced HCC not amenable to surgical resection and/or loco-regional therapy (LRT) or had progressed after surgery and/or LRT. Positive PD-L1 tumor staining (> 1 %) was found in only approximately 20 %.

With respect to the primary outcome of OS, Checkmate 459 did not meet the predefined threshold of statistical significance, although OS improvement in the nivolumab arm was deemed clinically meaningful (16.4 vs. 14.7 months; HR, 0.85; p = 0.0752) [19]. Likewise, median PFS did not differ across arms (3.7 vs. 3.8 months; HR, 0.93), although at 24 months, a greater proportion of nivolumab-treated patients remained progression-free (14 % vs. 6 %). Objective responses occurred in 15 % versus

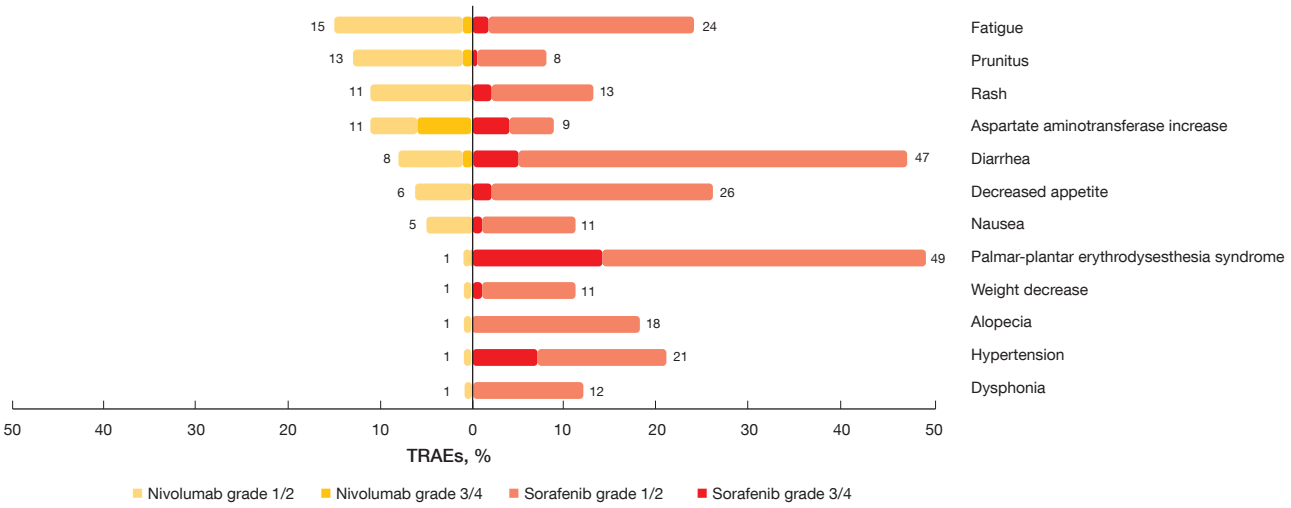

Figure 4: Treatment-related adverse events observed in the CheckMate 459 study on first-line nivolumab vs. sorafenib in hepatocellular carcinoma

© Springer-Verlag

7 % (OR, 2.41), including a higher rate of complete remissions (4 % vs. 1 %).

Overall survival results did not depend on PD-L1 baseline expression status, with a trend towards better OS in those with PD-L1 ≥ 1 % (HR, 0.80). Nivolumab demonstrated a favorable and manageable safety profile consistent with previous reports. Compared with sorafenib, fewer grade 3/4 TRAEs occurred (22 % vs. 49 %; **Figure 4**), which also applied to TRAEs leading to discontinuation. Also, the analysis demonstrated improved HRQoL according to the FACT-Hep questionnaire, with clinically meaningful differences in favor of nivolumab through week 113. Treatment burden was reduced in the experimental arm; through week 89, fewer patients who received nivolumab experienced worsening of side effects compared with sorafenib. Although CheckMate 459 did not meet its primary endpoint, the authors summarized that the study confirms the findings observed with second-line nivolumab in CheckMate 040.

Real-world experience with nivolumab

In similar vein, real-world data collected with nivolumab at the Mount Sinai Hospital in New York resembled those obtained in the CheckMate 040 study [20]. One hundred and four patients with HCC received nivolumab, with 67 and 37 being treated in the first and subsequent lines, respectively. Among the later-line patients, 27 had progressed on sorafenib. In 31 %, LRT was performed concurrently. The median duration on treatment was 26 weeks, and median follow-up was 17 months.

Median OS was 23 and 12 months for patients treated in the first and subsequent lines, respectively. This difference did not reach statistical difference (p = 0.1013). Median PFS was estimated at 16 and 6 months, respectively. Ten percent of patients achieved complete remissions; all of these received LRT before or during the application of nivolumab. Partial responses and stable diseases were observed in 11 % and 38 %, respectively. In complete and partial responders, median OS had not been reached yet at the time of the analysis, while it was 23 months in patients who obtained disease stabilization.

TABLE 1
REFLECT trial: lenvatinib plus pembrolizumab in unresectable hepatocellular carcinoma according to modified RECIST by independent imaging review

Parameter	n = 67
Best objective response, n (%)	
Complete response	5 (7.5)
Partial response	26 (38.8)
Disease stabilization	26 (38.8)
Disease progression	5 (7.5)
Objective response rate, n (%)	31 (46.3)
Median duration of response (responders), months	9.0
Median time to response (responders), months	2.4
Disease control rate, n (%)	57 (85.1)
Median progression-free survival, months	9.7
Median time to progression, months	11.8
Median overall survival, months	20.4

HRQoL in the KEYNOTE-240 trial

Like nivolumab, pembrolizumab has received accelerated FDA approval for the treatment of sorafenib-pretreated patients with HCC; this was based on the results of the open-label phase II KEYNOTE-224 study [21]. In the phase III setting, the double-blind, randomized, placebo-controlled KEYNOTE-240 trial tested best supportive care plus either pembrolizumab or placebo in 413 patients with advanced HCC who showed progression on or intolerance to sorafenib. OS and PFS indeed favored pembrolizumab here, although the results did not meet significance according to the pre-specified statistical plan [22].

At ESMO 2019, Merle et al. reported the pre-specified exploratory HRQoL analyses that were conducted in KEYNOTE-240 using the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires [23]. In light of the poor patient prognosis, the impact of treatment on quality of life is an important consideration in HCC. The HRQoL population included 398 patients, with 271 and 127 randomly assigned to pembrolizumab and placebo, respectively.

The EORTC QLQ-C30 global health status/quality of life scores remained stable in both treatment groups. At 12 weeks, EORTC QLC-C30 and EORTC QLQ-HCC18 scores as well as all functional and symptoms domain scores were similar between pembrolizumab and placebo. Time to deterioration did not differ for the pre-specified symptoms of abdominal swelling, fatigue, and pain according to EORTC QLQ-HCC18. The authors concluded that these data, together with the efficacy and safety results from KEYNOTE-240, indicate a favorable risk-benefit balance for pembrolizumab in the second-line setting.

Lenvatinib plus pembrolizumab

The anti-angiogenic multikinase inhibitor lenvatinib has been approved for the first-line treatment of unresectable HCC in many countries worldwide based on the findings obtained in the phase III REFLECT study [24]. Given potential synergistic effects between lenvatinib and pembrolizumab, an open-label, phase Ib study assessed lenvatinib 12 or 8 mg/d (depending on body weight) plus pembrolizumab in patients with unresectable HCC. After part 1 (n = 6) had revealed no dose-limiting toxicities, the protocol was amended to enroll approximately 94 patients to the part 2 expansion cohort. Sixty-seven patients were included in the follow-up analysis presented at ESMO 2019, with almost half of them still undergoing study treatment at the time of data cutoff [25].

Indeed, the results demonstrated strong anti-tumor activity of lenvatinib plus pembrolizumab, with a 46.3 % confirmed ORR by modified RECIST and independent imaging review **(Table 1)** and median PFS of 9.7 months. Disease control occurred in 85.1 %. Most patients experienced reductions

© Springer-Verlag

in tumor size that appeared to be durable. Median OS amounted to 20.4 months. No unexpected safety signals were observed, and toxicities were manageable with dose modifications and interruptions. The combination of lenvatinib and pembrolizumab has been granted a Breakthrough Therapy designation for patients with advanced unresectable HCC who are not amenable to locoregional treatment.

Novel PD-1 inhibition: tislelizumab

The investigational humanized IgG4 monoclonal antibody tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Tislelizumab shows higher affinity for PD-1 than pembrolizumab and nivolumab, with an approximately 100- and 50-fold slower off-rate, respectively [26]. The novel PD-1 inhibitor is currently being tested in clinical studies at a dose of 200 mg every 3 weeks. Analyses presented at ESMO 2019 aimed to determine the feasibility of extended dosing schedules and to develop a population pharmacokinetic (PK) model for tislelizumab.

Data supporting the 6-week regimen

Extended dosing schedules have already proven feasible in other PD-1 inhibitors such as nivolumab and pembrolizumab, which can be administered every 4 or 6 weeks, respectively. Wu et al. conducted an exposure-response analysis for tislelizumab in subjects with advanced tumors to inform the benefit-risk assessment and to explore the feasibility of alternative schedules [27]. The relationships between tislelizumab exposure and both efficacy and safety endpoints were tested using data collected from the three clinical BGB-A317-001, BGB-A317-102, and BGB-A317-203 studies. These trials included a total of 745 patients with solid tumors (e.g., gastric/esophageal cancer, HCC, ovarian cancer, non-small-cell lung cancer, urothelial carcinoma) and 70 patients with classical Hodgkin's lymphoma. The individual model-predicted PK parameters used as the exposure measures comprised steady-state trough and peak concentrations, as well as time-averaged concentrations over the first 42 days and at steady-state. For response measures, ORR was defined as the efficacy endpoint. Safety endpoints included immune-related AEs, infusion-related AEs, grade > 3 AEs, AEs leading to dose modification, and those leading to drug discontinuation.

This analysis showed a lack of clinically significant exposure-response relationships for ORR and safety endpoints across the range of tested solid tumors and Hodgkin lymphoma, which supports the evaluation of the 6-weekly 400 mg regimen in future clinical trials. This regimen is not expected to be clinically different from the 3-weekly 200 mg schedule in terms of safety and efficacy outcomes.

Linear pharmacokinetics

Another analysis based on the BGB-A317-001, BGB-A317-102, and BGB-A317-203 studies was conducted to develop a population PK model for tislelizumab and to quantify the impact of demographic and disease characteristics on tislelizumab pharmacokinetics [28]. Typical values and interpatient variability of PK parameters in cancer patients were estimated, and the effects of demographic, pathophysiologic, and disease-related covariates on the PK of tislelizumab were determined to better understand clinical factors that might affect exposure in individual patients. The final population PK model was developed from a dataset of 798 subjects.

Tislelizumab PK was confirmed to be linear in the dose range tested. The authors noted that it can be adequately described by a three-compartment disposition model with linear clearance. No time-varying clearance was observed in this analysis. The covariates tested did not have a clinically meaningful impact on tislelizumab exposure.

Sensitivity analysis results support the use of the current clinical dose of 200 mg every 3 weeks. No dose adjustment appeared necessary based on patient age, body weight, race, sex, tumor type, and tumor size.

Urothelial carcinoma

Urothelial carcinoma is the most common type of bladder cancer. Until recently, initial treatment options for patients with metastatic urothelial carcinoma were limited to platinum-based chemotherapy regimens. However, a considerable proportion of patients with advanced disease cannot receive standard chemotherapy because of renal dysfunction, poor performance status, or other comorbidities. Therefore, the availability of additional options is a highly unmet medical need.

PD-1 inhibitors offer new possibilities here. Pembrolizumab has shown activity in both advanced urothelial carcinoma and non–muscle-invasive bladder cancer unresponsive to Bacillus Calmette-Guérin. Phase II data generated for the novel agent tislelizumab in a Chinese population denote it as a promising agent in urothelial carcinoma.

KEYNOTE-045: later-line pembrolizumab

Pembrolizumab has received approval for the second-line treatment of locally advanced or metastatic platinum-refractory urothelial carcinoma based on the phase III KEYNOTE-045 study. In this trial, pembrolizumab gave rise to survival prolongation and improved tolerability compared with paclitaxel, docetaxel, or vinflunine as per investigator's choice (10.3 vs. 7.4 months) [29]. Patients with urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra who had disease progression after one or two lines of platinum-based chemotherapy or recurrence within 12 months after perioperative platinum-based therapy were randomized to either pembrolizumab (n = 270) or chemotherapy (n = 272). Even after more than 2 years, the PD-1 inhibitor showed durable clinical benefit.

At ESMO 2019, Necchi et al. presented the 3-year follow-up from the KEYNOTE-045 study [30]. According to this analysis, pembrolizumab continued to show substantial improvement compared with chemotherapy. Median OS was 10.1 vs. 7.2 months (p = 0.00030). At 36 months, 20.7 % vs. 11.0 % of patients were alive. OS benefits with pembrolizumab were observed across subgroups.

Although median PFS was not improved in the experimental arm (HR, 0.96), the 36-month PFS rate favored pembrolizumab (9.8 % vs. 2.0 %), suggesting a long-term PFS benefit for

© Springer-Verlag

some patients. At 36 months, 22 patients (10 %) in the pembrolizumab arm remained progression-free; in this group, complete and partial remissions occurred in 68.2 % and 27.3 %, respectively. In the overall cohort, ORRs were 21.1 % vs. 11.0 %, with complete responses observed in 9.6 % vs. 2.9 %. Among patients who achieved complete or partial remissions, duration of response was 29.7 vs. 4.4 months, and responses that lasted for ≥ 36 months were found in 44.0 % vs. 28.3 % **(Figure 5)**. The safety profile of pembrolizumab was better than that of chemotherapy, with lower rates of TRAEs (62.0 % vs. 90.6 %) and grade 3 to 5 TRAEs (16.9 % vs. 50.2 %).

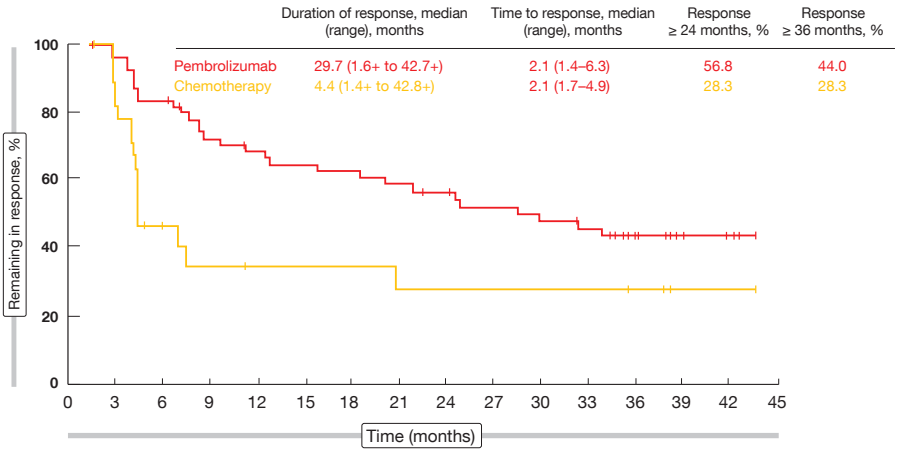

Figure 5: Duration of response and time to response in patients with complete or partial remissions on second-line pembrolizumab vs. chemotherapy in urothelial carcinoma

Non–muscle-invasive tumors: KEYNOTE-057

Approximately 75 % of patients with urothelial carcinoma of the bladder present with tumors confined to the mucosa and submucosa. In patients with high-risk non–muscle-invasive bladder cancer (HR NMIBC), standard-of-care therapy is transurethral resection and intravesical Bacillus Calmette-Guérin (BCG) [31], although responses are often not durable. Due to the high risk of disease progression, radical cystectomy is a recommended standard option for patients with BCG-unresponsive NMIBC. However, surgery results in significant morbidity and mortality and has a negative impact on quality of life. There is an unmet need for novel therapies to reduce the risk of recurrence and raise bladder preservation rates.

A rationale for the use of anti-PD-1 therapies exists here as the PD-1 pathway has been implicated in BCG resistance [32]. De Wit et al. hypothesized that the use of pembrolizumab will result in clinically meaningful and durable complete response rates in HR NMIBC that is unresponsive to BCG therapy. Therefore, the open-label, single-arm, multicenter, phase II KEYNOTE-057 study tested pembrolizumab in patients with HR NMIBC with carcinoma in situ with or without papillary tumors (cohort A) or patients who had HR NMIBC without carcinoma in situ (cohort B). At ESMO 2019, the updated results from cohort A including HRQoL findings were reported [33].

Striking complete response rates

Patients enrolled in this cohort (n = 102) had histologically confirmed carcinoma in situ with or without papillary disease of predominantly transitional cell histology, BCG-unresponsive disease despite adequate BCG therapy, and were ineligible for or refused to undergo radical cystectomy. Pembrolizumab continued to show encouraging anti-tumor activity with a compelling complete response rate of 41.2 %. Forty-five percent of the 42 complete responders had ongoing responses at the time of data cutoff, while 47.6 % experienced recurrent NMIBC after complete remission. No patient developed muscle-invasive or metastatic disease while on study therapy. Median duration of CR was 16.2 months, and 41.3 % of patients responded for at least 18 months. Median OS had not been reached yet, which also applied to median PFS to worsening of grade/stage or death and PFS to muscle-invasive or metastatic disease or death. For the two PFS endpoints, 12-month rates were 83.4 % and 96.9 %, respectively. Ninety-eight percent of patients were alive at 12 months. Among patients who never achieved complete remission (n = 60), 46.7 % underwent cystectomy after a median time of 2.6 months from the last pembrolizumab dose. In the group of initial complete responders whose disease recurred (n = 23), 43.5 % had cystectomy after discontinuation; here, the median time from the last pembrolizumab dose to surgery was 4.2 months.

Pembrolizumab showed an AE profile consistent with observations from previous studies. HRQoL was measured by the Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-BI) and Core Lower Urinary Tract Symptom Score (CLSS). Both patient-reported outcome instruments showed that HRQoL was maintained among pembrolizumab-treated patients. HRQoL and symptom scores were stable from baseline to week 51. According to a prespecified analysis conducted in week 39, cancer-specific subscales and physical well-being scores from baseline were improved or stable in more than 70 % of patients. The phase III KEYNOTE-676 study is currently evaluating pembrolizumab plus BCG in patients with HR NMIBC that persists or has recurred after BCG induction.

Phase II data demonstrate activity of tislelizumab

Urothelial carcinoma is one of the most common urological malignancies in China. According to cancer statistics for China, bladder cancer accounted for approximately 80,500 new cancer cases and 32,900 deaths in 2015 [34]. The novel PD-1 inhibitor tislelizumab might contribute to expanding the immunotherapeutic armamentarium in this patient group. Recent data from two phase I studies (NCT02407990; CTR20160872) conducted in patients with urothelial carcinoma suggested that single-agent tislelizumab was generally well tolerated and demonstrated antitumor activity (data on file). Clinical responses were observed for both PD-L1–positive and PD-L1–negative/unknown tumors, with ORRs amounting to 24 % and 21 %, respectively.

© Springer-Verlag

The single-arm, multicenter, phase II CTR20170071 study was conducted in China and other Asian countries to evaluate tislelizumab at the recommended phase II dose of 200 mg every 3 weeks in patients with locally advanced or metastatic PD-L1–positive urothelial carcinoma previously treated with ≥ 1 platinum-containing therapy [35]. PD-L1 positivity was present if ≥ 25 % of tumor cells or immune cells had PD-L1 expression. ORR was defined as the primary endpoint. A total of 113 patients received treatment. Overall, 104 patients were evaluable for tumor response.

TABLE 2
Response to tislelizumab in patients with PD-L1–positive urothelial carcinoma after at least one previous treatment line

Disease response	n = 104
Best overall response, n (%)	
Complete response	8 (7.7)
Partial response	16 (15.4)
Stable disease	14 (13.5)
Progressive disease	49 (47.1)
Not evaluable for response	17 (16.3)
Objective response rate, % (95 % CI)	23.1 (15.4, 32.4)
Disease control rate, % (95 % CI)	36.5 (27.3, 46.6)
Clinical benefit rate, % (95 % CI)	27.9 (19.5, 37.5)

Disease control in a third of patients

At cutoff, median study follow-up was 7.6 months, and 30 patients remained on treatment. The median duration of treatment was 15.3 weeks. Confirmed objective responses occurred in 24 patients (23.1 %), including 8 complete and 16 partial responses according to independent review committee assessment **(Table 2)**. Disease control and clinical benefit rates amounted to 36.5 % and 27.9 %, respectively. The subgroup analyses indicated that response rates were not considerably influenced by baseline factors. As the authors noted, the response rates reported here were similar to pooled data from the two phase I studies mentioned above that investigated tislelizumab in PD-L1–positive and PD-L1–negative/unknown tumors.

REFERENCES

1 World Cancer Research Fund. http://www.wcrf.org/int/cancer-facts-figures/worldwide-data (accessed August 2018)
2 Torre LA et al., Global cancer statistics, 2012. CA Cancer J Clin 2015; 65(2): 87-108
3 GLOBOCAN Stomach Cancer Fact Sheet. http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp (accessed August 2018)
4 Pasechnikov V et al., Gastric cancer: prevention, screening and early diagnosis. World J Gastroenterol 2014; 20(38): 13842-13862
5 Bray F et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 2018; 68(6): 394-424
6 International Agency for Research on Cancer. Cancer Today 2018. https://gco.iarc.fr/today (accessed September 12, 2019)
7 Lin Y et al., Epidemiology of esophageal cancer in Japan and China. J Epidemiol 2013; 23(4): 233-242
8 https://cancerstatisticscenter.cancer.org/#!/ (accessed September 9, 2019)
9 https://ganjoho.jp/en/profressional/statistics/table_download.html (accessed September 9, 2019)
10 Cho BC et al., Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma: the ATTRACTION-3 study. ESMO 2019, abstract LBA11
11 Kang YK et al., Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 201; 390(10111): 2461-2471
12 Sunakawa Y et al., Interim analysis of an observational/translational study for nivolumab treatment in advanced gastric cancer: JACCRO GC-08 (DELIVER trial). ESMO 2019, abstract 820P
13 Kojima T et al., Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. J Clin Oncol 37, 2019 (suppl 4; abstr 2)
14 Chen J et al., Pembrolizumab versus chemotherapy in patients with advanced/metastatic adenocarcinoma of squamous cell carcinoma of the esophagus as second-line therapy, analysis of the Chinese subgroup in KEYNOTE-181. ESMO 2019, abstract 760P
15 Wainberg Z et al., KEYNOTE-059 update: efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal (G/GEJ) cancer. ESMO 2017, abstract LBA28_PR
16 Van Cutsem E et al., Impact of pembrolizumab versus paclitaxel on HRQoL in patients with advanced gastric or gastroesophageal junction cancer that has progressed after first-line chemotherapy (KEYNOTE-061). ESMO 2019, abstract 791P
17 Shitara K et al., Pembrolizumab with or without chemotherapy vs chemotherapy in patients with advanced G/GEJ cancer including outcomes according to microsatellite instability-high status in KEYNOTE-062. ESMO 2019, abstract LBA44
18 El-Khoueiry AB et al., Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017; 389(10088): 2492-2502
19 Yau T et al., CheckMate 459: a randomized, multi-center phase 3 study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. ESMO 2019, LBA38
20 Dharmapuri S et al., Outcomes of hepatocellulcar carcinoma patients treated with nivolumab: the Mount Sinai Hospital (New York) experience. ESMO 2019, abstract 759P
21 Zhu AX et al., Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018; 19(7): 940-952
22 Finn RS et al., Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J Clin Oncol 37, 2019 (suppl; abstr 4004)
23 Merle P et al., Health-related quality-of-life impact of pembrolizumab versus best supportive care in previously systemically treated patients with advanced hepatocellular carcinoma: KEYNOTE-240. ESMO 2019, abstract 676PD
24 Kudo M et al., Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391(10126): 1163-1173
25 LLovet JM et al., A phase Ib trial of lenvatinib plus pembrolizumab in unresectable hepatocellular carcinoma: updated results. ESMO 2019, abstract 747P
26 Feng Y et al., The molecular binding mechanism of tislelizumab, an investigational anti-PD-1 antibody, is differentiated from pembrolizumab and nivolumab. 110th Annual Meeting of the American Association for Cancer Research, abstract 2382
27 Wu CY et al., Tislelizumab exposure-response analyses of efficacy and safety in patients with advanced tumors. ESMO 2019, abstract 482P
28 Wu CY et al., Population pharmacokinetics of tislelizumab in patients with advanced tumors. ESMO 2019, abstract 483P
29 Fradet Y et al., Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol 2019; May 3. pii: mdz127. doi: 10.1093/annonc/mdz127. [Epub ahead of print]
30 Necchi A et al., Three-year follow-up from the phase 3 KEYNOTE-045 trial: pembrolizumab versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer. ESMO 2019, abstract 919P
31 NCCN Clinical Practice Guidelines (NCCN guidelines): bladder cancer (Version 4.2019)
32 Fukumoto K et al., Clinical role of programmed cell death-1 expression in patients with non-muscle-invasive bladder cancer recurring after initial Bacillus Calmette-Guérin therapy. Ann Surg Oncol 2018; 25(8): 2484-2491
33 De Wit R et al., Health-related quality of life and updated follow-up from KEYNOTE-057: phase 2 study of pembrolizumab for patients with high-risk non–muscle-invasive bladder cancer unresponsive to Bacillus Calmette-Guérin. ESMO 2019, abstract 916P
34 Chen W et al., Cancer statistics in china, 2015. CA Cancer J Clin 2016; 66(2): 115-132
35 Dingwei Y et al., First report of efficacy and safety from a phase 2 trial of tislelizumab, an anti-PD-1 antibody, for the treatment of PD-L1+ locally advanced or metastatic urothelial carcinoma in Asian patients. ESMO 2019, abstract 920P

 © Springer-Verlag

Thirty-four patients (33%) had reductions of ≥ 30 % in the sum of target lesion diameter from baseline. At the data cut-off date, the median duration of response had not been reached yet, with 79 % of responders showing ongoing responses. Median PFS and OS were 2.1 and 9.8 months, respectively. At 12 months, 46.5 % and 16.8 % of patients were alive and progression-free, respectively. Tislelizumab was generally well tolerated. The only treatment-emergent AEs occurring in > 15 % of patients included anemia (27 %), decreased appetite (19 %), and pyrexia (17 %). Anemia (7 %) was the only grade 3-4 treatment-emergent AE reported in ≥ 5 % patients. A total of 64 % of patients experienced immune-related treatment-emergent AEs, although no grade ≥ 3 immune-related events occurred in > 5 % of patients. Based on preliminary results from this trial, tislelizumab has received a priority review by China's National Medical Product Administration. ■

Potential role of the microbiome in carcinogenesis and response to checkpoint inhibition

Bacteria are of eminent importance for health and the functioning of the human body that contains more bacterial than human cells, at a ratio of 1.3 to 1 [1, 2]. More than 10,000 different microbe species have been identified in the body. Ten to 100 trillion symbiotic microbial cells are harbored by each individual, primarily in the gut. Their genes outnumber the genes in the human genome by approximately 100 to 1. The intestinal microbiome fulfills a number of important tasks relating to metabolism and modulation of the immune system **(Table)** [3].

TABLE
Tasks of the human intestinal microbiome

Digestion of complex carbohydrates (extraction of energy from food)
Modulation of the immune system
Vitamin synthesis
Lipid metabolism
Control of blood glucose levels
Brain-gut axis mediation

Here, the concept of dysbiosis comes into play, i. e. the persistent departure of the host symbiotic microbial ecosystem from the health-associated, homeostatic state towards a cancer-promoting and/or -sustaining phenotype [4, 5]. Nevertheless, dysbiosis appears to be specific to the individual, the disease, and the niches. A similar "core microbiome" was found at the phylum level (*Bacteroidetes* and *Firmicutes*), although at lower taxonomic levels, differences prevailed in apparently healthy individuals.

Microbes and cancer

Microbes can be both commensals and pathogens, with a potential role in the etiopathogenesis of cancer. Many of the most common cancers are at least partly attributable to infection. Estimates range from 20 % in lymphomas and leukemias to almost 100 % in cervical cancer [6]. Other types of cancer that are less obviously related to infections might also be triggered or promoted by dysfunctional bacterial growth. The first report suggesting the importance of microbiota in bowel carcinoma was published in 1969 [7]. Meanwhile, various studies have established a relationship between *Fusobacterium nucleatum* and colorectal cancer. This pathogen was shown to be enriched in colorectal cancer as compared to normal tissues [8, 9]. Distinct gut microbiome patterns correlate with consensus molecular subtypes [10], and an association was found with specific anatomic location, stage, and molecular features [11, 12]. Most recently, *Fusobacterium* was also detected in colorectal liver metastases by metagenomic sequencing, visualized by *in situ* hybridization and isolated by culture, suggesting that colorectal tumor cells provide a specific niche for this microbe [13]. These data have led to investigation of a causative role for *Fusobacterium* and the gut microbiome in general in CRC development and progression.

Models of underlying mechanisms

Specific microbes have been shown to modulate numerous hallmarks of cancer through diverse mechanisms [14]. All of these result in prolonged host cell survival, enhanced replicative capacity, and dedifferentiation. Two conceptual frameworks have been suggested that best describe the promotion of carcinogenesis by the human microbiome. The alpha-bug hypothesis states that certain microbiome members possessing unique virulence traits are directly pro-oncogenic and, in addition, capable of remodeling the colonic bacterial community, eventually inducing colon cancer [15]. On the other hand, according to the driver-passenger hypothesis, driver bacteria are outcompeted by passenger bacteria as mutations accumulate and adenoma turns into carcinoma [16].

© Springer-Verlag

In 2019, the International Cancer Microbiome Consortium published a consensus statement on the role of the human microbiome in carcinogenesis [17]. The panel concluded that, despite mechanistic and supporting evidence from animal and human studies, there is currently no direct evidence that the human commensal microbiome is a key determinant in the etiopathogenesis of cancer. A principal deciding factor in this was the lack of large longitudinal cohort studies. However, at the same time, expert opinion was that the microbiome, alongside environmental factors and an epigenetically/genetically vulnerable host, represents one apex of a tripartite, multidirectional interactome that drives carcinogenesis.

Data from large, international, longitudinal cohort studies should therefore be a future research priority to confirm the role of the human microbiome in the etiopathogenesis of cancer. There is also a need to put an increased focus on interventional studies, integration of data with other oncology research, and standardization as well as transparency in reporting microbiome research.

Antibiotics and response to immunotherapy

From the therapeutic point of view, the microbiome has emerged as a biomarker of response to immune checkpoint inhibition (ICI). As the mouse model suggests, the absence of an intact gut microbiome negatively affects the efficacy of immunotherapy [18, 19]. This implies that the use of antibiotics plays an important role here. Indeed, a recently published paper by Elkrief et al. summarized multiple clinical studies including more than 1,800 patients that demonstrated the negative predictive impact of broad-spectrum antibiotics in ICI-treated patients [20]. The data indicated that the deleterious effect is particularly pronounced if antibiotics are prescribed preceding (rather than during) immunotherapy. Thus, pre-ICI antibiotic treatment represents one risk factor of resistance through altering the diversity and composition of the intestinal microbiota. Microbiome profiling revealed that higher diversity and certain immunogenic bacteria such as *Akkermansia*, *Firmicutes* and *Bifidobacterium* were overrepresented in NSCLC and melanoma patients who responded to immunotherapy [18, 21, 22]. The current mechanism linking these immunogenic bacteria to $CD4^+$ and $CD8^+$ T cell priming appears to be involved in the reduction of ICI activity.

Survival outcomes can change considerably as a function of anti-microbial pretreatment. Derosa et al. showed that in patients with renal cell carcinoma, use of antibiotics compared with no use was associated with an increased risk of primary progressive disease (75 % vs. 22 %; $p < 0.01$), shorter PFS (1.9 vs. 7.4 months; $p < 0.01$], and shorter OS (17.3 vs. 30.6 months; $p = 0.03$) [23]. In patients with lung cancer, PFS was decreased (1.9 vs. 3.8 months; $p = 0.03$), as well as OS (7.9 vs. 24.6 months; $p < 0.01$; **Figure**). Controversy remains, however, as antibiotic treatment might simply constitute a surrogate marker of unfit or immunodeficient patients.

How to restore microbiome health?

Nevertheless, modification of the gut microbiome is already being evaluated as an innovative therapeutic opportunity in immuno-oncology. Multiple clinical trials are ongoing that attempt to favorably shift the microbiome composition. The methods assessed here include fecal microbiota transplantation (FMT) from ICI responders or healthy donors, bacterial consortia/mixtures, high fiber/whole food dietary intervention, and co-administration of charcoal-based capsules with antibiotics. Patients with a range of tumor types including melanoma, gastric cancer and lung cancer have been enrolled. A phase I trial that assessed FMT and re-induction of anti-PD-1 therapy in patients with refractory metastatic melanoma found that FMT was safe [24]. According to the conclusion of the authors, this treatment may alter recipient gut microbiota to resemble that of a responder donor, with resulting intra-tumoral T-cell activity which translated to a clinical and radiological benefit.

Also, there may be an association between the gut microbiome and immune-mediated colitis. Wang et al. reported the first case series of ICI-associated colitis successfully treated with FMT [25]. The researchers observed reconstitution of the gut microbiome and a relative increase in the proportion of regulatory T cells within the colonic mucosa. These preliminary data provide evidence that modulation of the gut microbiome may abrogate ICI-associated colitis.

General recommendations

Elkrief et al. recommended various steps promoting the judicious use of antibiotics in ICI-treated patients [20]. If there is high suspicion of a bacterial infection in a given patient, the diagnosis should be confirmed with appropriate testing (e. g., blood cultures, imaging) before the prescription of an antibiotic. Narrow-spectrum agents should be pre-

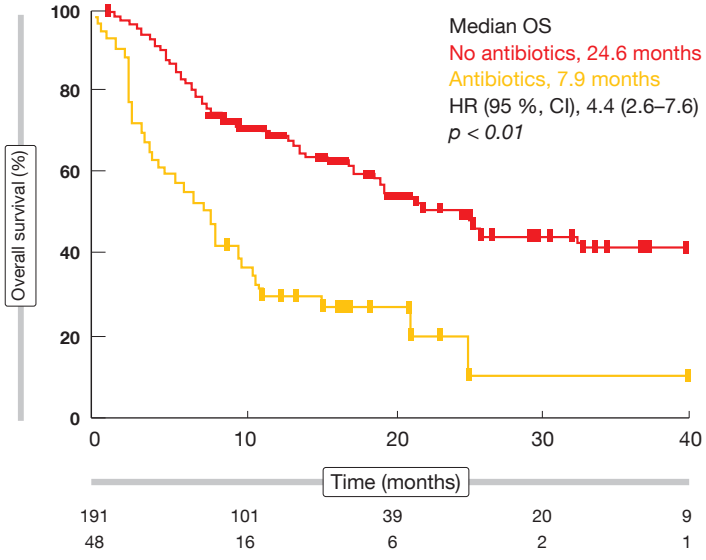

Figure: Impact of use of antibiotics on overall survival results in patients with lung cancer

© Springer-Verlag

ferred, and a shorter course should be followed if possible. Infectious disease consultations can be considered for antibiotic stewardship. The use of antibiotics should be avoided for one month preceding immunotherapy.

Overall, although the clinical significance of the gut microbiome still requires further elucidation, it constitutes a potential biomarker that needs to be included in personalized immuno-oncology trials. ■

Source:

Lecture "The importance of the microbiome in cancer", Paolo Nuciforo, MD, PhD, Vall d'Hebron Institute of Oncology, Barcelona, Spain; ESMO Congress 2019, 29th September

Lecture "Working on the microbiome", Bertrand Routy, MD, PhD, University of Montreal Medical Center, Canada; ESMO Congress 2019, 28th September

REFERENCES

1 Sender R et al., Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 2016; 164(3): 337-340
2 Turnbaugh PJ et al., The human microbiome project: exploring the microbial part of ourselves in a changing world. Nature 2007; 449(7164): 804-810
3 Kinross JM et al., Gut microbiome-host interactions in health and disease. Genome Med 2011; 3(3): 14
4 Hall AB et al., Human genetic variation and the gut microbiome in disease. Nature Rev 2017; 18(11): 690-699
5 Gilbert JA et al., Current understanding of the human microbiome. Nature Med 2018; 24(4):392-400
6 www.cancer.org/canceratlas
7 Aries V et al., Bacteria and the aetiology of cancer of the large bowel. Gut 1969; 10(5): 334-335
8 Kostic AD et al., Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 2012; 22(2): 292-298
9 Castellarin M et al., Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res 2012; 22(2): 299-306
10 Purcell RV et al., Distinct gut microbiome patterns associate with consensus molecular subtypes of colorectal cancer. Scientific Reports 2017; 7(1): 11590
11 Mima K et al., Fusobacterium nucleatum in colorectal carcinoma tissue according to tumor location. Clin Transl Gastroenterol 2016; 7(11): e200
12 Mima et al., Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. Gut 2016; 65(12):1973-1980
13 Bullman S et al., Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. Science 2017; 358(6369): 1443-1448
14 Fulbright L et al., The microbiome and the hallmarks of cancer. PLoS Pathog 2017; 13(9): e1006480.
15 Sears CL & Pardoll DM, Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. J Infect Dis 2011; 203(3): 306-311
16 Tjalsma H et al., A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. Nat Rev Microbiol 2012; 10(8): 575-582
17 Scott AJ et al., International Cancer Microbiome Consortium consensus statement on the role of the human microbiome in carcinogenesis. Gut 2019; 68: 1624-1632
18 Routy B et al., Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018; 359(6371): 91-97
19 Vétizou M et al., Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015; 350(6264): 1079-84
20 Elkrief A et al., The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: a new independent prognostic factor? Ann Oncol 2019 Jul 3. pii: mdz206. doi: 10.1093/annonc/mdz206. [Epub ahead of print]
21 Matson V et al., The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 2018; 359(6371): 104-108
22 Gopalakrishnan V et al., Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018; 359(6371): 97-103
23 Derosa L et al., Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol 2018; 29(6): 1437-1444
24 Baruch EN et al. Fecal microbiota transplantation (FMT) and re-induction of anti-PD-1 therapy in refractory metastatic melanoma patients – preliminary results from a phase I clinical trial (NCT03353402). AACR Annual Meeting 2019, abstract CT042
25 Wang Y et al., Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat Med 2019; 25(1): 188

PARP inhibition in gynecological cancers: recent insights

Poly(ADP-ribose) polymerase (PARP) inhibitors have been established as an important drug class for the treatment of advanced ovarian cancer (OC), which is a leading cause of cancer deaths in women. Olaparib and niraparib have been widely approved for maintenance treatment of OC patients who responded to platinum-based chemotherapy. Data presented at ESMO 2019 provide information on the use of PARP inhibition in earlier lines as well as in combination with other drug classes. Moreover, studies conducted with veliparib indicate combinability of this PARP inhibitor with chemotherapy in both ovarian and breast cancer.

BAROCCO: olaparib plus cediranib

Novel strategies are called for in the treatment of platinum-resistant OC, which represents a high unmet medical need. Weekly paclitaxel is regarded as the most effective chemotherapy regimen, although it has limited clinical activity. A new potential approach is the combined administration of the PARP inhibitor olaparib and the VEGFR tyrosine kinase inhibitor cediranib, which may have a synergistic effect. This combination was investigated by the randomized, three-arm BAROCCO trial that included patients with platinum-resistant OC who had any germline *BRCA* mutation status [1]. Another objective of BAROCCO was the question of whether an intermittent schedule of this combination would improve the gastrointestinal tolerability in terms of diarrhea severity. The experimental group consisted of two arms that either received the continuous schedule (cediranib 20 mg/day 7 days/week plus olaparib 300 mg twice daily 7 days/week) or the intermittent schedule (cediranib 20 mg/day 5 days/week plus olaparib 300 mg twice daily 7 days/week) in any line of treatment and any last line. Patients in the control arm were treated with paclitaxel 80 mg/m^2

© Springer-Verlag

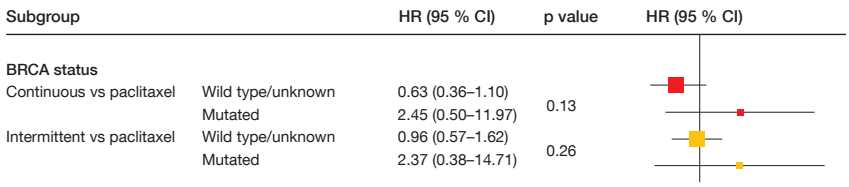

Figure 1: BAROCCO: greatest reduction in the risk of progression or death with continuous cediranib plus olaparib vs. weekly paclitaxel in patients with *BRCA* wildtype or unknown status

weekly. Each of the three arms included 41 women. Two independent primary comparisons were conducted in terms of PFS, which was defined as the primary endpoint, between each of the schedules and the comparator regimen. Overall, this was a difficult-to-treat population 59 % of whom had already received ≥ 3 treatment lines, with a median platinum-free interval of < 3 months in all arms. The majority (89 %) had *BRCA* wildtype or unknown *BRCA* status. BAROCCO was the first trial to evaluate olaparib plus cediranib in platinum-resistant OC that contained a control arm.

No beneficial effect of intermittent administration

Only the continuous combination schedule was shown to be superior to chemotherapy, although not significantly so (median PFS, 5.7 vs. 3.1 months; HR, 0.76). For the intermittent schedule, PFS was 3.8 months (HR for the comparison with chemotherapy, 1.08). According to the subgroup analysis, the PFS benefit achieved with the continued administration was greatest in patients with *BRCA* wildtype or unknown *BRCA* status (5.8 vs. 2.1 months; HR, 0.63; **Figure 1**). With respect to response outcomes, clinical benefit was obtained with continuous treatment in 84.6 %, while this was 62.8 % and 54.1 % for the intermittent and chemotherapy groups, respectively. Correspondingly, duration of response was longest in the continuously treated arm (6.2 months compared to 2.7 and 4.4 months).

At the same time, the continuous regimen was well tolerated, with few severe side effects. Grade ≥ 3 diarrhea occurred only in 5 % of patients (intermittent schedule, 3 %). Moreover, the rates for any-grade and severe adverse events (AEs) in terms of anemia, fatigue and hypertension did not differ across the two schedules. The authors concluded that the continuous schedule showed a promising trend for improved PFS, particularly in patients with germline *BRCA* wildtype. While the interruption of cediranib administration for two days might have a detrimental effect on PFS with no toxicity benefit, the regimen of cediranib 20 mg daily and olaparib 300 mg twice daily represents an active, feasible, oral regimen that deserves further investigation. These results support ongoing trials investigating the same combination in the setting of platinum-resistant OC.

Addition of olaparib to bevacizumab maintenance: PAOLA-1/ENGOT-ov25

PAOLA-1/ENGOT-ov25 is the first phase III study to evaluate maintenance therapy with a PARP inhibitor in patients with advanced OC regardless of *BRCA* mutation status who receive first-line standard-of-care treatment including the anti-VEGF antibody bevacizumab [2]. Newly diagnosed patients who had obtained complete response (CR), partial response (PR) or no evidence of disease with debulking or non-debulking, upfront or interval surgery and platinum-based chemotherapy plus at least 3 cycles of bevacizumab were randomized to maintenance treatment with either olaparib plus bevacizumab (n = 537) or placebo plus bevacizumab (n = 269) for 2 years. Tumor *BRCA* mutations were present in 30 % in each arm.

The trial met its primary objective, demonstrating a statistically significant PFS improvement with olaparib plus first-line standard-of-care bevacizumab maintenance therapy (22.1 vs. 16.6 months; HR, 0.59; p < 0.0001). Furthermore, the combination conferred a significant advantage regarding time to first subsequent treatment (24.8 vs. 18.5 months; HR, 0.59; p < 0.0001). For OS, the data were still immature.

The safety profile of the combination was generally consistent with previous trials of each drug. Dose interruptions due to AEs became necessary in 54 % and 24 %, respectively, and treatment was discontinued due to AEs in 20 % vs. 6 %. The tolerability of bevacizumab was not reduced by the addition of olaparib. Among AEs of special interest for olaparib, the rate of new primary malignancies was shown to be comparable for the two arms (1.3 % and 1.1 %, respectively). Pneumonitis occurred in 1.1 % and 0 %, respectively. Health-related quality of life (HRQoL) was not reduced by the addition of olaparib.

Findings according to *BRCA* and HRD status

Prespecified subgroup analyses showed that patients with tumor *BRCA* mutations and those with a positive homologous recombination deficiency (HRD) status derived the greatest PFS benefits **(Table)**. In the *BRCA*-positive group, PFS was 37.2 vs. 21.7 with olaparib plus bevacizumab compared to bevacizumab only (HR, 0.31), whereas the non-*BRCA*-mutant population benefited to a markedly lesser extent from

TABLE
Biomarker subgroup analyses conducted in PAOLA-1/ENGOT-ov25

	Olaparib + bevacizumab (n = 157)	Placebo + bevacizumab (n = 80)	Hazard ratio
PFS according to tumor *BRCA* mutation status			
Mutated	37.2	21.7	0.31
Non-mutated	18.9	16.0	0.71
PFS according to HRD status			
HRD-positive, including tumor *BRCA*-mutated	37.2	17.7	0.33
HRD-positive, excluding tumor *BRCA*-mutated	28.1	16.6	0.43
HRD-negative/unknown	16.9	16.0	0.92

© Springer-Verlag

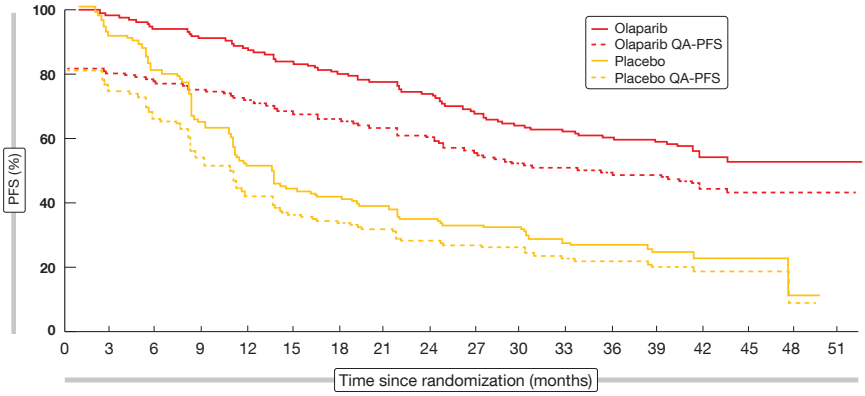

Figure 2: Significant improvement of mean quality-adjusted progression-free survival (QA-PFS) with olaparib maintenance vs. placebo

the addition of olaparib (18.9 vs. 16.0 months; HR, 0.71). With respect to HRD status, several populations were assessed. Those with HRD positivity including tumor *BRCA* mutations demonstrated a 67 % risk reduction (median PFS, 37.2 vs. 17.7 months; HR, 0.33). For the HRD-positive population excluding tumor *BRCA* mutations, this was 57 % (28.1 vs. 16.6 months; HR, 0.43). The combined analysis of patients with HRD negativity and those with unknown HRD status showed no difference with regard to PFS (16.9 vs. 16.0 months; HR, 0.92), although when viewed separately, the HRD-unknown subgroup derived PFS benefit (HR, 0.71), whereas HRD-negative patients did not (HR, 1.00).

The authors pointed out that these results reveal a patient population beyond tumor *BRCA*-mutant patients who are HRD-positive and experience substantial benefit from maintenance treatment with olaparib and bevacizumab. The activity of the combination was apparent in a broad front-line population not restricted by surgical outcome or *BRCA* mutation status.

MEDIOLA: olaparib plus durvalumab

The rationale for combining PARP-targeted agents with immune checkpoint inhibitors is based on the observation that PARP inhibition may upregulate PD-L1 expression [3]. Therefore, the phase I/II, open-label, multicenter MEDIOLA trial assessed olaparib in combination with the PD-L1 inhibitor durvalumab in patients with advanced solid tumors including germline *BRCA*-mutant, platinum-sensitive relapsed OC after ≥ 1 platinum-based chemotherapy. Following an initial 4-week treatment phase with olaparib monotherapy, patients received olaparib plus durvalumab until disease progression. Preliminary data from this study demonstrated an objective response rate (ORR) of 72 % [4]. At ESMO 2019, Drew et al. presented updated findings from the germline *BRCA*-mutant, platinum-sensitive relapsed OC cohort of MEDIOLA after an additional follow-up of one year (n = 34) [5].

Disease control rate at 12 weeks, which constituted the primary endpoint, was 81.3 %. At 28 weeks, this still amounted to 65.6 %. Median PFS was 11.1 months, while median OS had not been reached yet. At the time of data cutoff, the ORR was 71.9 (n = 23), with CRs observed in 25.0 % (n = 8). While ORR was consistent with the previous report, CR had increased with longer follow-up. Median duration of response was 10.2 months. Patients after only one or two lines of previous therapy fared better than those who had received at least 3 lines. The less pretreated group showed longer PFS (15.4 and 12.0 months after 1 and 2 lines of treatment, respectively, vs. 8.3 months after ≥ 3 lines) and contained seven of eight complete responders.

PD-L1 expression on tumor cells was analyzed in 31 patients. This showed that positive (≥ 1 %) baseline PD-L1 expression correlated with longer PFS (13.6 vs. 10.3 months for PD-L1–negative patients). The combination continued to be well tolerated. Ever since the latest analysis one year previously, only one patient had discontinued treatment due to an AE. In all, the findings indicated that the combination of olaparib and durvalumab is most effective in early-line patients; over time, the addition of durvalumab might drive deeper responses. Further analysis in a larger patient population is warranted to assess the role of PD-L1 expression as a predictor for treatment benefit. According to the authors, it remains to be determined whether this regimen has the potential to replace chemotherapy in patients with germline *BRCA*-mutant, platinum-sensitive relapsed OC. An expansion cohort in the early-line setting is underway.

Secondary analyses of the SOLO1 trial

The randomized, double-blind, international phase III SOLO1 trial evaluated maintenance therapy with olaparib (n = 260) *versus* placebo (n = 131) after first-line chemotherapy in patients with newly diagnosed, advanced OC who had germline or somatic *BRCA1* or *BRCA2* mutations. Olaparib treatment led to a substantial PFS benefit compared to placebo (HR, 0.30; p < 0.001) [6] and thus was widely approved for the maintenance treatment of patients with *BRCA*-mutated advanced OC who achieved CR or PR to first-line platinum-based chemotherapy.

At ESMO 2019, Oaknin et al. reported time from randomization to second disease progression or death (PFS2) and time from randomization to second subsequent therapy from the SOLO1 trial [7]. According to this analysis, maintenance olaparib provided benefit beyond first progression, increasing both PFS2 (not reached vs. 41.9 months; HR, 0.50; p = 0.0002) and time to second subsequent therapy (not reached yet vs. 40.7 months; HR, 0.45) compared to placebo. These benefits were clinically meaningful and suggested that olaparib does not diminish the patient ability to receive subsequent therapy and respond to it.

Considering the importance of high tolerability of maintenance therapy in a setting where most patients do not usually have OC-related symptoms, Friedlander et al. evaluated the patient-centered outcomes of quality-adjusted PFS and time without symptoms of disease or toxicity [8]. For both outcomes, olaparib maintenance, as compared to placebo, showed patient-centered benefits. Mean quality-adjusted PFS improved to a clinically meaningful extent,

© Springer-Verlag

with a highly significant difference of 12.17 months between groups **(Figure 2)**. Likewise, time without symptoms of disease or toxicity increased in a clinically meaningful manner with olaparib *versus* placebo; here, the between-group difference was 12.92 months and highly significant. These results provided further support indicating that prolongation of PFS did not take place at the expense of reduced HRQoL due to toxicity.

Using tumor samples from 341 patients included in the SOLO1 trial, Gourley et al. found that *BRCA*-gene–specific loss of heterozygosity (LOH) and genome-wide LOH scores are no feasible biomarkers in newly diagnosed, *BRCA*-mutated, advanced OC as they do not discriminate the extent of olaparib benefit [9]. Significant benefit was observed with olaparib in patients with both high and low genome-wide LOH scores. The utility of this marker in *BRCA* wildtype patients who receive first-line treatment for OC requires further investigation.

Niraparib in newly diagnosed OC

Niraparib was the first oral PARP inhibitor to be approved as maintenance therapy for all patients with recurrent OC that is both *BRCA*-mutant and *BRCA*-wildtype. Considering the high unmet need for many patients with newly diagnosed advanced OC after platinum-based chemotherapy, the PRIMA/ENGOT-OV26/GOG-3012 trial assessed niraparib in this setting [10]. Overall, 733 patients were randomized in a 2:1 fashion to either niraparib or placebo after response to first-line platinum-based chemotherapy. The population included patients at high risk of relapse. Stage IV disease was present in 35 % of cases, and almost 100 % of those with stage III OC had residual disease after primary debulking surgery. In 67 %, neoadjuvant chemotherapy had been administered. First-line chemotherapy had given rise to CR and PR in 69 % and 31 %, respectively. In 30 %, *BRCA* mutations were identified. Fifty-one and 34 % of patients had homologous recombination (HR)-deficient and HR-proficient tumors, respectively. PFS was defined as the primary endpoint.

Niraparib provided a clinically significant PFS improvement after first-line chemotherapy in all patients. In the overall population, PFS was 13.8 vs. 8.2 months (HR, 0.62; p < 0.001). Patients with HR-deficient tumors benefited to an even greater extent from treatment, deriving a 57 % reduction in the risk of relapse or death (21.9 vs. 10.4 months; HR, 0.43; p < 0.001; **Figure 3**). Subgroup analyses according to *BRCA* mutation status showed that within the HR-deficient population, the PFS benefit obtained with niraparib was similar for both *BRCA*-mutant and -wildtype patients (HRs, 0.40 and 0.50, respectively). The HR-proficient subgroup experienced a 32 % risk reduction (HR, 0.68).

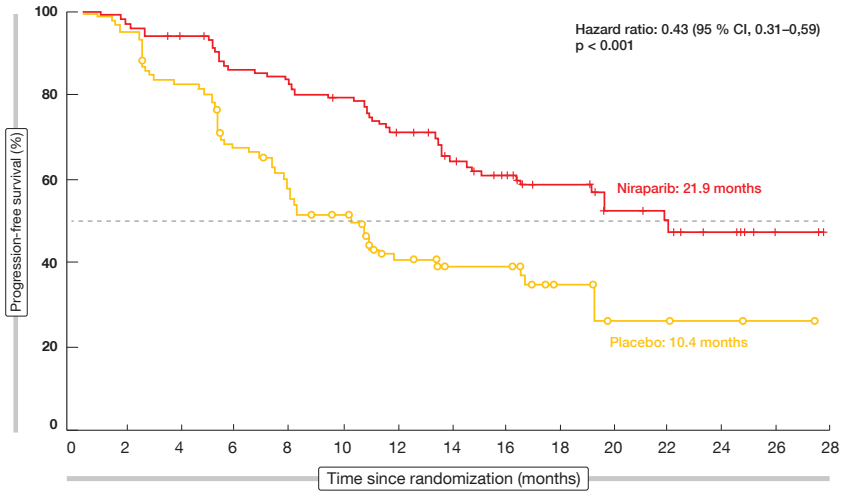

Figure 3: Niraparib vs. placebo: progression-free survival in the HR-deficient population

A pre-planned interim analysis of OS, which represented a key secondary endpoint, numerically favored niraparib over placebo. At 2 years, 91 % vs. 85 % of patients with HR-deficient tumors were alive; in the HR-proficient group, this was 81 % vs. 59 %. No new safety signals were observed, with reversible myelosuppression being the most common treatment-emergent AE. Evaluation of the FACT Ovarian Symptom Index Adjusted Health Utility Index Score showed that quality of life was maintained on both niraparib and placebo throughout the trial.

Based on these findings, the authors noted that niraparib is the first PARP inhibitor to demonstrate benefit in patients across biomarker subgroups after platinum-based chemotherapy in frontline. Significant activity was observed in patients at the highest risk of early disease progression.

Integration of veliparib in frontline and maintenance

Combinations of PARP inhibitors with chemotherapy have been historically challenging due to hematologic toxicity. However, the specific binding characteristics of veliparib, primarily increased PARylation and decreased PARP trapping, were assumed to allow for use together with chemotherapy [11, 12]. The

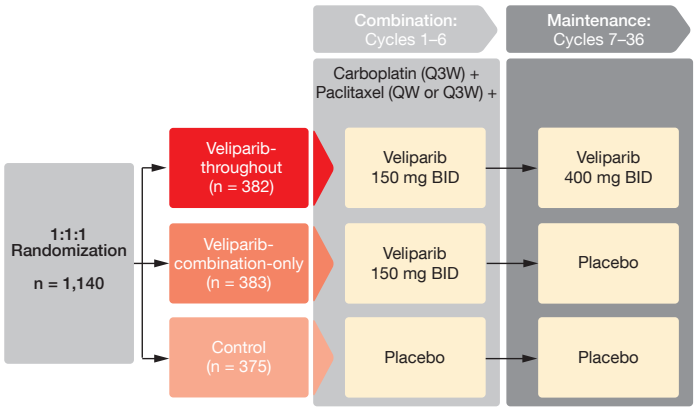

Figure 4: Design of the VELIA/GOG-3005 trial

© Springer-Verlag

placebo-controlled, phase III VELIA/GOG-3005 trial assessed the integration of veliparib with front-line chemotherapy and maintenance in women with high-grade serous epithelial OC. This is the first randomized study designed to enroll all previously untreated patients with advanced-stage high-grade serous cancer regardless of *BRCA* status, surgical management, or response to treatment. Overall, 1,140 patients were randomized to one of three arms **(Figure 4)**. In the veliparib throughout arm, veliparib 150 mg twice daily was added to carboplatin and paclitaxel for six cycles and followed by veliparib 400 mg twice daily as maintenance during cycles 7 to 36 (n = 382). The veliparib-combination-only arm received veliparib 150 mg twice daily plus chemotherapy, while placebo was administered during maintenance (n = 383). Patients in the control arm were treated with chemotherapy plus placebo followed by placebo (n = 375).

PFS for the veliparib-throughout regimen compared to controls was defined as the primary endpoint, with PFS including both the combination and maintenance phases. At ESMO 2019, Coleman et al. reported the results for this outcome [13]. *BRCA* mutations were present in the two arms in approximately 30 %, and HRD positivity was observed in 63 % each.

Benefits regardless of biomarker status

The analysis showed that the addition of veliparib to chemotherapy and continuation as maintenance significantly extended PFS in all patient cohorts regardless of biomarker, choice of surgery, or paclitaxel regimen. Median PFS in the ITT population was 23.5 vs. 17.3 months for veliparib throughout vs. controls (HR, 0.68; $p < 0.001$). The *BRCA*-mutant population derived a 56 % risk reduction for disease progression and death (34.7 vs. 22.0 months; HR, 0.44; $p < 0.001$). In the HRD population, this was 43 % (31.9 vs. 20.5 months; HR, 0.57; $p < 0.001$). Smaller PFS benefits were observed for the non-HRD population (HR, 0.81), the *BRCA* wildtype/HRD group (HR, 0.74), and the *BRCA* wildtype patients (HR, 0.80). Moreover, the choice of surgery (primary vs. interval surgery) did not affect outcomes, which also applied to the paclitaxel regimen (weekly vs. every 3 weeks).

The importance of maintenance treatment is demonstrated by an analysis comparing the veliparib-combination-only arm with the control arm; here, no PFS benefit was gained (HR, 1.07). This finding was similar across the *BRCA*-mutant, HRD, and ITT populations. However, at the end of the combination phase, both veliparib-containing arms showed numerically higher ORRs than the control arm (84 % and 79 % vs. 74 %).

Veliparib could be safely administered together with carboplatin and paclitaxel. AEs observed with veliparib were consistent with chemotherapy during the combination phase, with cytopenia constituting the majority of grade 3 or 4 AEs. During maintenance phase, the AEs were in keeping with the known safety profile. HRQoL was assessed using the disease-related symptom – physical score category of the NCCN-FACT ovarian symptom index-18. Here, differences in mean change from baseline between arms and within all subgroups were small and not considered clinically significant. In their conclusion, the authors noted that veliparib plus chemotherapy should be considered a new treatment option for women with newly diagnosed, advanced-stage serous OC.

Veliparib plus chemotherapy in breast cancer: BROCADE3

The use of veliparib plus chemotherapy in patients with advanced *HER2*-negative breast cancer and germline *BRCA1* or *2* mutation after ≤ 2 prior lines of cytotoxic therapy for metastatic disease was tested in the randomized, placebo-controlled phase III BROCADE3 study [14]. Veliparib plus carboplatin/paclitaxel (n = 337) was compared to placebo plus carboplatin/paclitaxel (n = 172). A maximum of 1 prior line of platinum was permitted; also, progression must have occurred at least 12 months after completion of chemotherapy. Most of the patients (81 % in each arm) had had no prior chemotherapy for metastatic disease. Prior (neo-)adjuvant chemotherapy had been administered in approximately 70 % in each arm. Investigator-assessed PFS constituted the primary endpoint.

Patients treated with veliparib plus chemotherapy experienced a statistically significant and clinically meaning-

REFERENCES

1 Colombo N et al., Italian multicenter randomized phase II study of weekly paclitaxel vs. cediranib-olaparib with continuous schedule vs. cediranib-olaparib with intermittent schedule in patients with platinum resistant high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. ESMO 2019, abstract LBA58
2 Ray-Coquard I et al., Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced OC treated with platinum-based chemotherapy and bevacizumab as standard of care. ESMO 2019, abstract LBA2_PR
3 Jiao S et al., PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017; 23(14): 3711-3720
4 Drew Y et al., 2018. Available at: https://www.sgo.org/wpcontent/uploads/2018/03/Late-Breaking-Abstracts-2018-SGOAnnual-Meeting-on-Womens-Cancer.pdf. Last accessed 2 August 2019
5 Drew Y et al., Phase II study of olaparib + durvalumab (MEDIOLA): updated results in the germline BRCA-mutated (BRCAm) platinum-sensitive relapsed (PSR) ovarian cancer (OC) cohort. ESMO 2019, abstract 1190PD
6 Moore K et al., Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018; 379(26): 2495-2505
7 Oaknin A et al., Time to second progression and second subsequent therapy for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation treated with maintenance olaparib – phase III SOLO1 trial. ESMO 2019, abstract 998PD
8 Friedlander M et al., Patient-centred outcomes with maintenance olaparib in newly diagnosed patients with advanced OC and *BRCA* mutations in the phase III SOLO1 trial to support the clinical benefit of prolongation of progression-free survival. ESMO 2019, abstract 996PD
9 Gourley C et al., Analysis of tumour samples from SOLO1: frequency of BRCA-specific loss of heterozygosity (LOH) and progression-free survival (PFS) according to homologous recombination repair (HRR) deficiency LOH score. ESMO 2019, abstract 998PD
10 González-Martin A et al., Niraparib therapy in patients with newly diagnosed advanced ovarian cancer (PRIMA/ENGOT-OV26/GOG-3012). ESMO 2019, abstract LBA1
11 Donawho CK et al., ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res 2007; 13(9): 2728-2737
12 Gray HJ et al., Phase I combination study of the PARP inhibitor veliparib plus carboplatin and gemcitabine in patients with advanced ovarian cancer and other solid malignancies. Gynecol Oncol 2018; 148(3): 507-514
13 Coleman RL et al., VELIA/GOG-3005: Integration of veliparib with front-line chemotherapy and maintenance in women with high-grade serous carcinoma of ovarian, fallopian tube, or primary peritoneal origin. ESMO 2019, abstract LBA3
14 Diéras V et al., Phase 3 study of veliparib with carboplatin and paclitaxel in HER2-negative advanced/metastatic g*BRCA*-associated breast cancer: BROCADE3. ESMO 2019, abstract LBA9

© Springer-Verlag

ful PFS benefit (14.5 vs. 12.6 months; HR, 0.705; p = 0.002). At 24 and 36 months, 34 % and 26 %, respectively, were alive and progression-free. These results were confirmed by independent central review, with median PFS of 19.3 vs. 13.5 months (HR, 0.695; p = 0.005) as well as 24- and 36-month rates of 44 % and 37 %. The durable benefit of the combination was also demonstrated by the longer duration of response (14.7 vs. 11.0 months), although ORRs were similar across treatment arms (75.8 % vs. 74.1 %), as were clinical benefit rates at 24 weeks (90.7 % vs. 93.2 %). Moreover, patients treated in the experimental arm experienced a significant benefit with respect to PFS2, i.e. the time from randomization until disease progression on subsequent therapy or death (21.3 vs. 17.4 months; HR, 0.760; p = 0.020). An interim OS analysis revealed non-significant superiority of the veliparib treatment (median, 33.5 vs. 28.2 months; HR, 0.945) after a substantial crossover. Among patients treated with chemotherapy only, 44 % elected to receive open-label veliparib as their first subsequent treatment.

Veliparib plus chemotherapy was well tolerated, with less than 10 % of patients discontinuing treatment due to AEs. The addition of veliparib did not substantially alter the toxicity profile of carboplatin/paclitaxel. For select AEs of special interest, it was shown that the rates of infections within 14 days of neutropenia did not differ across treatment arms; this was also true for hemorrhages within 14 days of thrombocytopenia, and myelodysplastic syndromes. In their conclusion, the authors noted that BROCADE3 is the first phase III trial to evaluate a PARP inhibitor with highly active platinum chemotherapy in patients with advanced breast cancer and a germline *BRCA* mutation. ■

New applications of PARP inhibitors

Metastatic castration-resistant prostate cancer

Metastatic castration-resistant prostate cancer (mCRPC) that progresses after androgen-receptor(AR)–targeted therapy (i.e., enzalutamide or abiraterone) and taxane-based chemotherapy is associated with a poor prognosis [1]. Only few treatment options are available for these patients. Up to 25 % of men with mCRPC harbor deleterious germline and/or somatic alterations in *BRCA1*, *BRCA2, ATM* or other DNA damage repair (DDR) genes, including those with direct or indirect roles in homologous recombination repair (HRR) [2-4]. These alterations are associated with sensitivity to PARP inhibition [5]. Emerging data suggest clinical activity of PARP inhibitors in patients with mCRPC and DDR gene anomalies [6-8]. The PROfound, GALAHAD and TRITON2 studies investigated the clinical benefit of PARP inhibition with olaparib, niraparib and rucaparib, respectively, in advanced mCRPC.

Olaparib: primary analysis of PROfound

Patients whose disease had progressed on enzalutamide or abiraterone and who had alterations in any of 15 predefined genes that play a direct or indirect role in HRR were enrolled into randomized, open-label, phase III PROfound trial that evaluated olaparib compared to AR-targeted therapy. Cohort A included 245 patients with alterations in *BRCA1*, *BRCA2* or *ATM*, while Cohort B included 142 patients with one of 12 other HRR alterations ranging from *BRIP1* to *RAD54L*. Both cohorts were randomized in a 2:1 ratio to either olaparib or AR-targeted therapy according to physician's choice. Patients progressing on physician's choice treatment were allowed to cross over to olaparib. The primary endpoint was radiographic progression-free survival (rPFS) in Cohort A as assessed by blinded independent central review.

Hussain et al. reported that in Cohort A, olaparib indeed provided a statistically significant rPFS improvement compared to enzalutamide or abiraterone (7.39 vs. 3.55 months; HR, 0.34; p < 0.0001; **Figure 1**) [9]. This was also observed in the overall population including both cohorts with alterations in any qualifying gene (5.82 vs. 3.52 months; HR, 0.49; p < 0.0001). In cohort A, the objective response rate (ORR) in patients who had measurable disease was 33.3 % with olaparib compared to 2.3 % with enzalutamide or abiraterone (odds ratio, 20.86; p < 0.0001). Median time to pain progression had not been reached with olaparib *versus* 9.92 months for the hormonal agents, representing a 56 % reduction (HR, 0.44; p = 0.0192). Olaparib showed a favorable trend with respect to overall survival (OS) for patients with alterations in *BRCA1*, *BRCA2* or *ATM* (18.5 vs. 15.11 months; HR, 0.64; p = 0.0173) and in the overall population (17.51 vs. 14.26 months; HR, 0.67; p = 0.0063). This was achieved despite a cross-over of more than 80 %. However, OS data are still immature.

Olaparib was well tolerated. The most common adverse events (AEs) included anemia (46.1 % vs. 15.4 %), nausea (41.4 % vs. 19.2 %), fatigue (41.0 % vs. 32.3 %), and decreased appetite (30.1 % vs. 17.7 %). The authors concluded that PROfound is the first positive biomarker-selected phase III study evaluating a molecularly targeted therapy in men with mCRPC. Also, these findings highlight the importance of genomic testing in this population.

GALAHAD: interim data on niraparib

The ongoing, open-label, single-arm, phase II GALAHAD study is assessing the safety and efficacy of niraparib in patients with mCRPC and DNA repair defects (DRD) who have progressed on

© Springer-Verlag

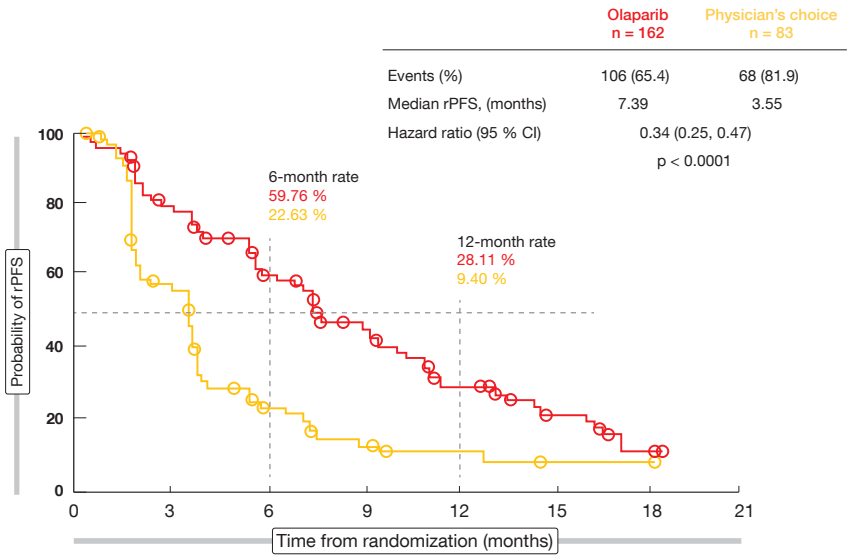

Figure 1: Radiographic progression-free survival with olaparib vs. enzalutamide or abiraterone in mCRPC patients with *BRCA1*, *BRCA2*, or *ATM* alterations

≥ 1 line of AR-targeted therapy and ≥ 1 line of taxane-based chemotherapy. At ESMO 2019, Smith et al. presented results from a pre-specified interim analysis [10]. Overall, 223 patients were screened for eligibility, and 165 patients with DRD (defined as pathogenic mutation in *BRCA1/2 [BRCA], ATM, FANCA, PALB2, CHEK2, BRIP1* or *HDAC2 [non-BRCA];* monoallelic or biallelic) were enrolled.

The findings indicate that niraparib has high clinical activity in patients with mCRPC, particularly in those with biallelic *BRCA* DRD (n = 46). This group showed an ORR of 41 %, and objective responses lasted for 5.6 months. The composite response rate, which was defined as ORR by RECIST 1.1, or conversion of circulating tumor cells from ≥ 5/7.5 mL to < 5/7.5 mL of blood, or ≥ 50 % decline in PSA, amounted to 63 %. Patients with measurable disease showed a composite response rate of 66 %; for those with non-measurable disease, this was 59 %. Median rPFS and OS were 8.2 and 12.6 months, respectively. On the other hand, patients with non-*BRCA* biallelic DRD (n = 35) responded only in 9 %, and the composite response rate was 17 %. Median rPFS and OS for this group were 5.3 and 14.0 months, respectively. Declines in PSA levels of ≥ 50 % occurred in 50 % and 3 % of patients with *BRCA* and non-*BRCA* biallelic DRD, respectively.

Overall, niraparib treatment has shown a manageable safety profile with no new safety signals identified. The most common grade 3/4 AEs comprised anemia (29 %), thrombocytopenia (15 %), and neutropenia (7 %). Niraparib in patients with mCRPC and DRD will continue to be evaluated in ongoing trials including GALAHAD, MAGNITUDE and QUEST.

Promising activity of rucaparib in TRITON2

Another ongoing phase II trial testing a PARP inhibitor in the mCRPC setting is TRITON2. Here, patients with mCRPC and DDR alterations including *BRCA1/2, ATM, CDK12* and *CHEK2*, who have progressed on AR-targeted therapy and chemotherapy, are being treated with rucaparib. According to the analysis presented at ESMO 2018, patients with deleterious *BRCA1/2* alterations showed confirmed ORR and PSA responses in 44.0 % and 51.1 %, respectively [11]. At ESMO 2019, Abida et al. presented an update from TRITON2 after a median follow-up of 13.1 months for a total of 190 patients [12].

In keeping with prior reports, rucaparib demonstrated promising efficacy. Among evaluable patients with *BRCA1/2* alterations, 43.9 % experienced confirmed investigator-assessed radiographic responses. Fifty-two percent of all men with *BRCA1/2* mutations had confirmed PSA responses (i. e., ≥ 50 % decreases). Patients with germline and somatic *BRCA1/2* alterations responded to a similar extent. Also, confirmed radiographic and PSA responses occurred in the group with alterations in other DDR genes, including *ATM, CDK12,* and *CHEK2* **(Table 1)**. Among patients with *BRCA1/2* alterations who demonstrated confirmed radiographic responses, the majority (60.0 %) responded for more than 24 weeks.

The safety profile of rucaparib was consistent with prior reports from TRITON2 and the experience obtained in patients with ovarian cancer and other solid tumors [7, 13-15]. At 17.9 %, the most

TABLE 1
Confirmed investigator-assessed overall and PSA response rates in rucaparib-treated patients

Response	DNA damage repair gene				
	BRCA1/2	*ATM*	*CDK12*	*CHEK2*	Other
Objective response rate, %	43.9	9.5	0	0	38.5
Complete response, %	5.3	0	0	0	7.7
Partial response, %	38.6	9.5	0	0	30.8
Stable disease, %	45.6	47.6	55.6	60.0	46.2
Progressive disease, %	8.8	38.1	33.3	40.0	7.7
Not evaluable, %	1.8	4.8	11.1	0	7.7
PSA response rate, %					
All evaluable patients	52.0	3.5	7.1	14.3	35.7
With measurable disease	59.6	9.5	11.1	20.0	38.5
With no measurable disease	41.5	0	0	0	0
Median time to PSA progression, months	6.5	3.1	3.5	5.6	5.8

© Springer-Verlag

common grade ≥ 3 treatment-emergent AE was anemia. In addition to ongoing enrolment into TRITON2, the randomized, phase III TRITON3 study is evaluating rucaparib *versus* second-line AR-directed therapy or docetaxel in chemotherapy-naïve mCRPC patients with deleterious alterations in *BRCA1, BRCA2*, or *ATM*, who progressed on one prior AR-targeted therapy. Here, rPFS has been defined as the primary objective.

Pancreatic cancer: analyses of the POLO trial

POLO is the first phase III trial to evaluate maintenance therapy with a PARP inhibitor in metastatic pancreatic cancer. In this randomized, international study, pancreatic cancer patients with germline *BRCA1* and/or *BRCA2* mutations whose disease had not progressed during ≥ 16 weeks of first-line platinum-based chemotherapy received either olaparib or placebo. Indeed, olaparib treatment resulted in a statistically significant and clinically meaningful PFS benefit compared with placebo (7.4 vs. 3.8 months; HR, 0.53; p = 0.004) [16]. At ESMO 2019, results for prespecified secondary efficacy analyses of the study and data on health-related quality of life were presented.

Time to treatment discontinuation and subsequent therapy

Secondary endpoints of the POLO trial included time to treatment discontinuation as well as time to first and second subsequent therapies. Since maintenance treatment with olaparib provided a PFS benefit, patients in the experimental arm were less likely to require a subsequent therapy than those in the placebo arm. Van Cutsem et al. demonstrated that olaparib maintenance led to a meaningful prolongation of time to treatment discontinuation compared to placebo, translating to a 55 % risk reduction (7.2 vs. 3.8 months; HR, 0.45; p = 0.0001) **(Figure 2)** [17]. Furthermore, there were meaningful increases in time to initiation of both first (8.6 vs. 5.7 months; HR, 0.50; p = 0.0013) and second subsequent treatments (13.2 vs. 9.2 months; HR, 0.68; p = 0.083).

Among the patients who did receive subsequent treatment, the majority in both arms were treated with cytotoxic chemotherapy. Hence, maintenance olaparib can meaningfully delay the need of second-line treatments for metastatic pancreatic cancer, and data suggest that this effect may be maintained up to the third line. The authors concluded that maintenance olaparib following first-line platinum-based treatment may provide the opportunity to delay the subsequent use of standard cytotoxic chemotherapies with their associated toxicities.

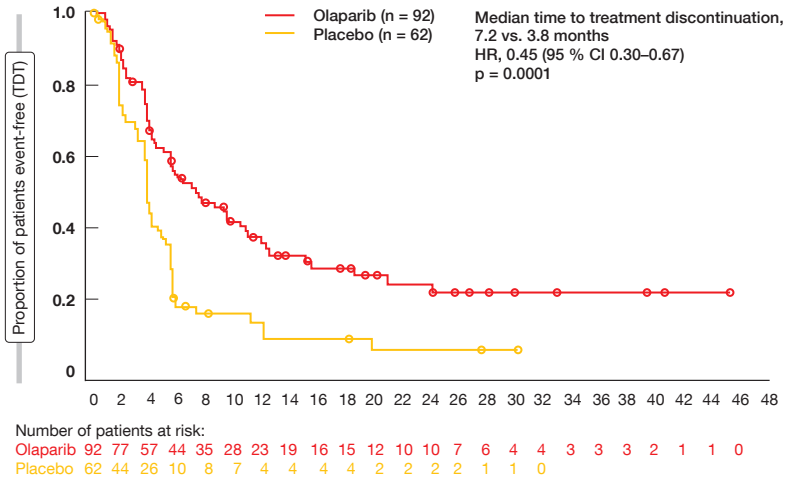

Figure 2: Superior time to treatment discontinuation with olaparib maintenance compared to placebo

Health-related quality of life

In addition to efficacy benefits, preservation of patient health-related quality of life (HRQoL) is a major therapeutic goal in the maintenance setting. A prespecified secondary objective of the POLO study was the effect of maintenance olaparib on HRQoL, specifically evaluating the adjusted mean change from baseline in global health status using the EORTC QLQ-C30 questionnaire [18]. Analyses were conducted in 89 of 92 patients in the olaparib arm and 58 of 62 patients in the placebo arm with evaluable baseline forms (overall compliance was 96.6 % and 94.8 %, respectively).

Patients treated in both arms of the POLO study had high baseline global health status scores (70.4 vs. 74.3) and physical functioning scores (83.3 vs. 84.9) following successful first-line chemotherapy. Global health status remained relatively stable over time for both treatment arms without a statistically significant or clinically meaningful difference in the overall between-group adjusted mean change from baseline. For physical functioning, the scores improved over time in both arms **(Figure 3)**, although the adjusted mean change from baseline between groups did not reach the threshold considered

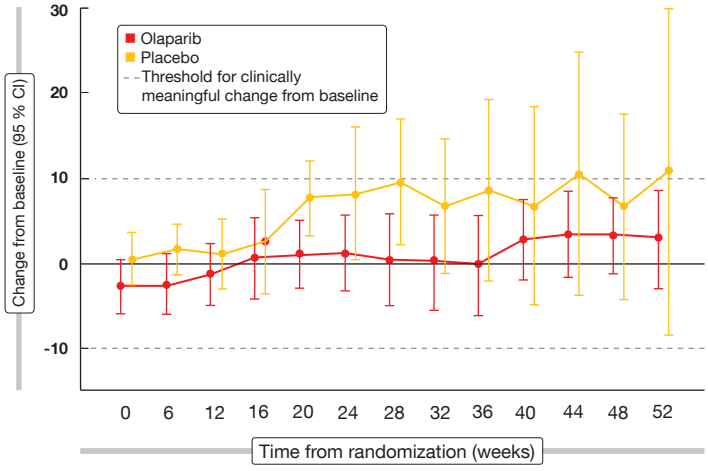

Figure 3: Improvement of physical functioning over time in both arms of the POLO trial

© Springer-Verlag

to be clinically meaningful. There was no difference in time to sustained clinically meaningful deterioration for olaparib *versus* placebo for global HRQoL (21.2 vs. 6.0 months; HR, 0.72; p = 0.25). Overall, olaparib maintenance treatment was shown to preserve the HRQoL benefits achieved with first-line chemotherapy.

Novel PARP inhibition

Pamiparib monotherapy in advanced solid tumors

Pamiparib is a potent and selective oral PARP1/2 inhibitor that has demonstrated promising antitumor activity in ovarian cancer in a phase Ia study [19]. Single-agent recommended phase II dose was defined as 60 mg twice daily in the dose-escalation part. The dose-expansion component of the study was conducted in patients with ovarian, breast, prostate, gastric, and small-cell lung cancer. Voskoboynik et al. reported updated safety data from the study and updated efficacy data from the cohorts with ovarian cancer and associated tumors [20].

As of June 2019, 101 patients were enrolled in the dose-escalation (n = 64) and dose-expansion (n = 37) cohorts. Out of these, 63 patients had ovarian, fallopian, or peritoneal cancer, and 28 received pamiparib at the recommended phase II dose. Confirmed complete or partial responses were observed in 23 of 58 evaluable ovarian and associated cancer patients (39.7 %). The median duration of response was 14.9 months. Among the 58 evaluable patients, 31 had germline or somatic *BRCA* mutations, while 27 had either germline or somatic *BRCA* wildtype or unknown *BRCA* status. Pamiparib treatment elicited higher ORR in the mutated group compared to the other cohorts (61.3 % vs. 14.8 %). ORRs by platinum-sensitivity status were 77.3 %, 17.4 % and 8.3 % for the platinum-sensitive, platinum-resistant and platinum-refractory populations, respectively. In the platinum-sensitive group, higher ORR was achieved in *BRCA*-mutant patients than in the groups with *BRCA* wildtype or unknown status (83.3 % vs. 50.0 %; **Table 2**).

In the safety population (n = 101), treatment-emergent AEs observed in 10 % or more of patients included nausea, fatigue, anemia, diarrhea, vomiting, and decreased appetite. The most common treatment-emergent ≥ grade 3 AE was anemia. Pamiparib plasma exposure increased linearly with increasing dose, with a median terminal half-life of approximately 13 hours. Hence, pamiparib can be administered independent of food intake. The authors concluded that pamiparib continued to be generally well-tolerated and demonstrated promising antitumor activity in patients with ovarian and associated cancer.

TABLE 2
Objective response rates for patients with ovarian cancer and associated tumors according to *BRCA*/homologous repair deficiency status vs. platinum sensitivity status

	Platinum-sensitive	Platinum-resistant	Platinum-refractory	Total
***BRCA* status (%)**				
Mutant	83.3	20.0	50.0	61.3
Wildtype	50.0	25.0	0.0	15.4
Unknown	50.0	11.1	0.0	14.3
HRD status (%)				
Positive	83.3	15.4	50.0	55.9
Negative	0.0	100.0	0.0	11.1
Unknown	66.7	11.1	0.0	20.0
Total	77.3	17.4	8.3	

Combination with temozolomide

A dose-escalation/expansion study is evaluating pamiparib together with oral low-dose temozolomide in patients with locally advanced and metastatic tumors. The rationale for this combination is based on the hypothesis that DNA damage caused by low-dose temozolomide synergizes with PARP inhibition. This synergy might lead to increased antitumor activity via enhanced PARP-dependent tumor cell killing. PARP inhibition results in the accumulation of highly cytotoxic adducts, leading to cell death.

During dose escalation, patients received pamiparib 60 mg twice daily plus escalating doses of temozolomide daily on days 1-7 (Arm A; pulsed) or continuously (Arm B; continuous flat) for each 28-day cycle. According to a preliminary analysis, pamiparib 60 mg twice daily combined with pulsed or continuous-flat–dosed temozolomide showed antitumor activity and was generally well tolerated, with the expected toxicity of bone marrow suppression [21].

Stradella et al. presented updated results of this phase Ib study including data on the recommended phase II dose and schedule of the combination, which was determined to be pamiparib 60 mg twice daily on days 1-28 and pulsed temozolomide 60 mg daily on days 1-7 [22]. A total of 113 patients with solid tumors had been enrolled, with 66 and 47 patients included in the dose-escalation and dose-expansion cohorts, respectively.

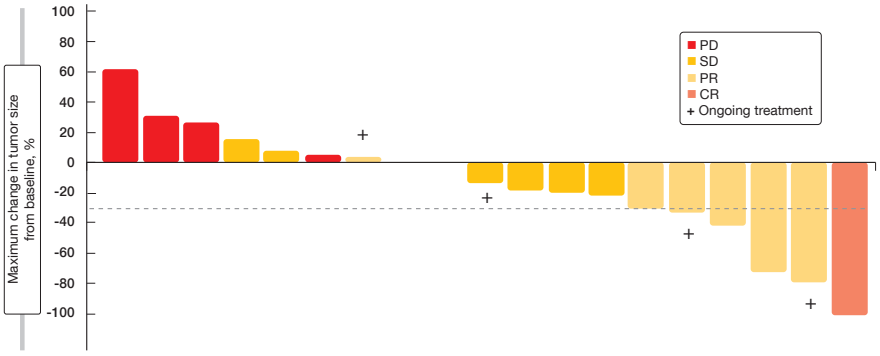

Figure 4: Maximum tumor reduction obtained with pamiparib plus temozolomide in evaluable patients with extensive-stage small-cell lung cancer

© Springer-Verlag

Disease control in up to 80 % of SCLC patients

Promising preliminary efficacy was found in patients with extensive-stage small-cell lung cancer enrolled in the expansion phase (n = 22). In this group, out of 19 patients evaluable for response, 31.6 % showed responses to treatment, and the disease control rate was 78.9 % (**Figure 4**). Twenty patients with gastric/gastroesophageal junction cancer were also enrolled in the expansion phase, with 15 being evaluable for response. Disease control was achieved in 33.3 % of patients in this cohort.

The dose-escalation phase enrolled all comers, with 57 of 66 patients being evaluable for response (52 with measurable disease). For this group, ORR and disease control rate were 19.3 % and 64.9 %, respectively. Responses lasted for a median of 6.4 months.

Eight patients with homologous recombination deficient (HRD) tumors were included in the dose-escalation phase. Irrespective of *BRCA* mutational status, these showed a response rate of 62.5 %. According to the conclusion of the authors, HRD status may be a promising biomarker for sensitivity to treatment with pamiparib plus low-dose temozolomide, regardless of tumor type. The combination showed a manageable safety profile, with cytopenias representing the most frequent grade ≥ 3 events.

Fluzoparib in patients with advanced solid tumors

Fluzoparib (SHR3162) is a selective oral PARP1 inhibitor that has shown anti-tumor activity in both cell lines and xenograft models [23]. Li et al. presented results from the first-in-human, phase I trial investigating fluzoparib in patients with advanced solid tumors [24]. At five centers in China, 48 and 31 patients were enrolled into the dose-escalation and dose-expansion arms, respectively. Ovarian cancer represented the largest proportion of tumor types (59.5 %), followed by breast (20.3 %), colorectal (10.1 %), and other types of cancer (10.1 %). In the dose-escalation phase, fluzoparib was administered once or twice daily at 11 dose levels from 10 mg/day to 400 mg/day. The dose-expansion phase evaluated fluzoparib at 80 mg, 100 mg or 150 mg twice daily in patients with ovarian cancer. Dose-limiting toxicity was reported in two patients who received 400 mg/day. The maximum tolerated dose was 150 mg twice daily, which was determined to be the recommended phase II dose.

All patients experienced AEs during this study. Hematologic AEs of all grades included anemia (53.2 %), thrombocytopenia (17.7 %) and decreased neutrophil counts (24.1 %). The main non-hematologic AEs comprised fatigue (48.1 %), vomiting (17.7 %), nausea (34.2 %), and decreased appetite (29.1 %). Approximately 42 % of patients experienced grade 3/4 AEs, with the most common being anemia (8.9 %) and decreased neutrophil counts (5.1 %). The treatment was discontinued in three patients due to AEs. No treatment-related deaths occurred.

The ORR observed with fluzoparib was 8.1 % for ovarian cancer and 7.7 % for breast cancer. No responses occurred in colorectal and gastric cancer or other tumor types. For the 11 ovarian cancer patients with *BRCA*-mutation, median PFS was 8.5 months. Among patients treated with fluzoparib ≥ 120 mg/day, median PFS was 10.2 months in the platinum-sensitive cohort. In their conclusion, the authors noted that fluzoparib was well tolerated at a dose of 150 mg twice daily in advanced solid malignancies. This selective PARP1 inhibitor demonstrated single-agent antitumor activity in breast and ovarian cancer, particularly in *BRCA*-mutated and platinum-sensitive ovarian cancer. ■

REFERENCES

1 Rathkopf DE et al., Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. Clin Cancer Res 2017; 23(14): 3544-3551

2 Robinson D et al., Integrative clinical genomics of advanced prostate cancer. Cell 2015; 161(5): 1215-1228

3 Pritchard CC et al., Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016; 375: 443-453

4 Abida W et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017. doi: 10.1200/PO.17.00029

5 Mateo J et al., DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015; 373(18): 1697-1708

6 Smith MR et al., Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): Preliminary results of GALAHAD. J Clin Oncol 37, 2019 (suppl 7S; abstr 202)

7 Abida W et al., Preliminary results from TRITON2: a phase 2 study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. ESMO 2018, abstract 793PD

8 Mateo J et al., TOPARP-B: A phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations. J Clin Oncol 37, 2019 (suppl; abstr 5005)

9 Hussain M et al., PROfound: Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations. ESMO 2019, abstract LBA12_PR

10 Smith MR et al., Pre-specified interim analysis of GALAHAD: A phase 2 study of niraparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD). ESMO 2019, abstract LBA50

11 Abida et al., Preliminary results from TRITON2: a phase 2 study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. ESMO 2018, abstract 793PD

12 Abida W et al., Preliminary results of the TRITON2 study of rucaparib in patients with DNA damage repair (DDR)-deficient metastatic castration resistant prostate cancer (mCRPC): updates analyses. ESMO 2019, abstract 846PD

13 Kristeleit R et al., A Phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. Clin Cancer Res 2017; 23(15): 4095-4106

14 Swisher EM et al., Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017; 18(1): 75-87

15 Coleman RL et al., Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390(10106): 1949-1961

16 Golan T et al., Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 2019; 381: 317-327

17 Van Cutsem et al., POLO: Time to treatment discontinuation and subsequent therapies following maintenance olaparib for patients with a germline BRCA mutation and metastatic pancreatic cancer. ESMO 2019, abstract 693P

18 Hammel P et al., Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib. Ann Oncol 2019 Sep 28. pii: mdz406. doi: 10.1093/annonc/mdz406. [Epub ahead of print]

19 Lickliter J et al., Dose escalation/expansion study to investigate the safety, pharmacokinetics, food effect, and antitumor activity of BGB-290 in patients with advanced solid tumors. ESMO 2017, abstract 368PD

20 Voskoboynik M et al., Safety, antitumor activity, and pharmacokinetics of pamiparib (BGB-290), a PARP1/2 inhibitor, in patients with advanced solid tumors: Updated phase 1 dose-escalation/expansion results. ESMO 2019, abstract 452PD

21 Johnson M et al., Preliminary results of pamiparib (BGB-290), a PARP1/2 inhibitor, in combination with temozolomide in patients with locally advanced or metastatic solid tumors. ESMO 2018, abstract 421P

22 Stradella A et al., Updated results of the PARP1/2 inhibitor pamiparib in combination with low-dose temozolomide in patients with locally advanced or metastatic solid tumors. ESMO 2019, abstract 451PD

23 Wang L et al., Pharmacologic characterization of fluzoparib, a novel poly(ADP-ribose) polymerase inhibitor undergoing clinical trials. Cancer Sci 2019; 110(3): 1064-1075

24 Li H et al., Phase I dose-escalation and expansion study of the PARP inhibitor, fluzoparib (SHR3162), in patients with advanced solid tumors. ESMO 2019, abstract 345P

 © Springer-Verlag

Interview: Hendrik-Tobias Arkenau, MD, PhD, FRCP, Sarah Cannon Research Institute, London, UK

Increasing PARP inhibitor activity via several mechanisms of action

What is your take-home message from ESMO 2019 in relation to the use of PARP inhibitors in solid tumors?
Several studies showing favorable results with PARP inhibitors have been reported at this year's ESMO Congress. In particular, the results of the PAOLA study can be considered a major breakthrough [1]. The addition of olaparib to bevacizumab maintenance therapy in patients with ovarian cancer after first-line chemotherapy resulted in improved progression-free survival, not only in patients whose tumors were *BRCA*-mutant, but also in those with *BRCA* wildtype. In the overall population, PFS was increased by 6 months. For patients with *BRCA* mutations, PFS was 37.2 vs. 21.7 months with olaparib plus bevacizumab and bevacizumab, respectively. Also, new PARP inhibitors were discussed in the drug development therapeutic sessions, for example pamiparib that showed interesting results in small-cell lung cancer (SCLC) but also in pancreatic cancer and others.

What are the most important outcomes from the trial investigating pamiparib in combination with low-dose temozolomide in locally advanced or metastatic tumors [2]?
We know that PARP inhibitors alone have been very successful in patients with *BRCA* mutations, significantly improving survival. They have been widely approved for the treatment of ovarian and breast cancer and most recently in *BRCA*-mutant pancreatic and prostate cancer. I think that the field is moving forward with respect to how PARP inhibition can be extended beyond the *BRCA* mutational status, and in this context the study presented at ESMO is very interesting. In theory, low-dose temozolomide is a strong DNA-damaging agent and the PARP inhibitor pamiparib enhances this effect by inducing cell apoptosis. The combination has been proven to be safe. However, tumors for which we usually do not use PARP inhibitors, especially SCLC, have also been responsive. Patients with extended-stage SCLC showed response rates of > 30 % and an overall disease control rate of more than 70 %.

© author's own

Hendrik-Tobias Arkenau, MD, PhD, FRCP, Sarah Cannon Research Institute, London, UK

Will biomarkers help to inform patient selection?
Preclinical work and a biomarker study of this study showed that homologous repair deficiency (HRD) effectively predicted response in patients who had a high HRD score; therefore, this may be a useful biomarker and needs to be validated in future larger studies. Importantly, the treatment even worked beyond *BRCA* mutations. Other gene alterations in *ATR*, *PALB-2*, *P53*, *RAD-1*, among others, have to be considered in the treatment selection for those patients with such mutations.

In addition, by combining PARP inhibitors with other drugs, for example anti-angiogenic compounds like bevacizumab, we can achieve something called 'chemical BRCAness', which means that in patients who do not have a *BRCA* mutation, it is possible to effectively mimic a phenotype of BRCAness through a hypoxia-induced process. This strategy was elegantly demonstrated in the PAOLA study. I think that this is where the future of combination therapies lies.

However, there were other interesting combinations presented at ESMO and other meetings, for example PARP inhibitors plus other DNA damage repair pathway drugs such as ATR and CHCK 1 or 2 inhibitors. The translational work conducted in those studies indicated increased responses in the presence of pathway alterations including aberrations of *ATR*, *CHCK 1/2* and others, thus supporting pamiparib plus temozolomide here. Interestingly, the risk of secondary resistance after single-agent use of PARP inhibitors is often driven by *ATR* aberrations, which means that combining PARP inhibitors with ATR inhibitors is a potential strategy to overcome resistance.

What challenges might arise in the context of combining PARP inhibitors with other drugs?
The combination of PARP inhibition with classical chemotherapies confers a risk of potential overlapping toxicities, particularly of the bone marrow. Low hemoglobin, neutropenia and thrombocytopenia often occur. In the study presented at ESMO, these adverse events proved manageable. Of course, a big question is how to combine PARP inhibition with immunotherapy. We know that immune checkpoint inhibitors generally elicit higher responses in tumors that express PD-L1, and there is very good preclinical evidence indicating that PARP inhibition can actually increase PD-L1 expression [3]. Potential combinations of PARP inhibitors with DNA damage repair-directed therapies, cytotoxic drugs, anti-angiogenic agents and immunotherapy represent an exciting field of research. Combinations and sequencing of these drugs in an ideal manner will have to be investigated. ■

REFERENCES

1 Ray-Coquard I et al., Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced OC treated with platinum-based chemotherapy and bevacizumab as standard of care. ESMO 2019, abstract LBA2_PR
2 Stradella A et al., Updated results of the PARP1/2 inhibitor pamiparib in combination with low-dose temozolomide in patients with locally advanced or metastatic solid tumors. ESMO 2019, abstract 451PD
3 Jiao S et al., PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017; 23(14): 3711-3720

 © Springer-Verlag