Review papers ESMO / EHA / ESTRO 2019, presented by the mentees of the Young Oncology Academy 2019

The Swiss Group for Clinical Cancer Research (SAKK) launched the Young Oncology Academy, a mentoring program for young oncologists, in 2016. The program is aimed at residents at the beginning of their medical career with a clear focus on cancer medicine, hematology or radio-oncology, who would like to actively contribute to clinical and translational research. In 2019, 6 mentees successfully concluded the program. As part of the program, the participants are to write a short review paper on the visited congress (EMO, EHA or ESTRO).

The call for application for the Young Oncology Academy 2020 is open. Please find further information on the SAKK website: sakk.ch/researchers/young-oncology-academy.

Highlights of 2019 EHA Congress - Chronic lymphocytic leukemia

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Introduction

Here, 3 personal highlights from the 2019 ICML congress in Lugano and the 2019 EHA congress in Amsterdam about chronic lymphocytic leukemia (CLL) are presented.

A new prognosticator for time to first treatment in patients with early stage CLL

Approximately 70% of patients with CLL present in an early phase of the disease. The probability of treatment need is hardly anticipated upfront and can only be defined after a period of observation. At the ICML meeting this year, Condoluci and colleagues presented the International Prognostic Score for patients with Early stage CLL (IPS-E) [1] developed with the aim of predicting the risk of intervention in patients with early stage disease. The primary endpoint of this retrospective study was time to first treatment (TTFT). A total of 4933 patient data were collected from clinical trial-, institutional-, and population based-series. By multivariate analysis, the covariates consistently associated with TTFT were unmutated IGHV genes, lymphocyte count and palpable nodes in the training and validation cohorts. IPS-E was the sum of the covariates, and significantly separated low-risk (score 0), intermediate-risk (score 1) and high-risk patients (score 2-3). By meta-analysis of the study cohorts, the TTFT discrimination ability of IPS-E was 0.7, and the risk of treatment was 2.0 events per 100 person-years, 6.1 events per 100 person-years, and 16.1 events per 100 person-years among low-risk, intermediate-risk and high-risk patients, respectively. IPS-E is a simple and robustly validated prognostic model that predicts the likelihood of need for therapy in patients with early stage CLL. IPS-E can support patients' counselling and clinical trials design, identifying the subgroup of patients who might have a potential benefit from an early intervention strategy.

Early stage setting – a potential new treatment strategy

In clinical practice, patients with early stage CLL should be monitored without therapy until disease progression or disease-related symptoms since no studies so far have shown any survival benefit with early treatment [2-5]. At the EHA congress 2019, Petra Langerbeins et al. reported the primary endpoint results of the phase 3 CLL12 trial from the German CLL study group, evaluating the benefit of ibrutinib treatment in patients with previously untreated, Binet stage A CLL [6]. Patients with intermediate, high, or very high risk of disease progression defined according to the GCLLSG score [7], were randomly assigned 1:1 to receive 420 mg/d of either ibrutinib (182 patients) or placebo (181 patients). The primary endpoint event free survival (EFS) was 47.8. months in the placebo cohort versus not reached in the ibrutinib cohort ($p<.0001$). Progression-free survival (PFS) was 14.8 months in the placebo cohort versus not reached in the ibrutinib cohort. Surprisingly, adverse events (AEs) of any grade occurred in 82.2% of patients in the ibrutinib group and 84.8% of the placebo group. However, atrial fibrillation, bleeding and hypertensive disorders occurred more frequently in the ibrutinib group and were the main reason for treatment discontinuation. This primary endpoint analysis shows that ibrutinib improves EFS in asymptomatic, early stage CLL patients at increased risk of progression but at a certain prize of more frequent treatment discontinuation. While waiting on survival analysis, observation is still recommended for this subgroup of patients.

First-line treatment – a valid option for unfit patients
Fixed-duration chemo-immunotherapy and continuous, indefinite targeted therapy with ibrutinib are used as first-line treatment for CLL. The phase 3 CLL14 trial, presented at the EHA congress 2019 and then published in the NEJM by Kirsten Fischer et al., evaluated the fixed-duration regimen with venetoclax plus obinutuzumab (GVe) in patients with comorbidities and treatment-naïve CLL [8]. The study enrolled 432 patients randomly assigned 1:1 to receive either GVe or chlorambucil plus obinutuzumab (GClb) for 12 cycles. The estimated 24-month PFS was 88.2% in the GVe group vs 64.1% in the GClb cohort (p<.0001). Importantly, the superiority of GVe was seen even in patients with poor prognostic risk factors, such as unmutated IGHV (59.8% of patients) and *TP53* disruption (13.8% of patients). The rates of MRD-negative complete responses were significantly higher in the GVe group. AEs that led to treatment discontinuation were reported in 16.0% (GVe) and 15.4% (GClb) of patients. No clinical tumor-lysis syndrome was reported in the experimental arm. In conclusion, fixed duration GVe can be safely administered to unfit patients with treatment-naïve CLL, providing a superior PFS with respect to GClb, and overcoming CLL unfavorable genetic features.

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Highlights of 2019 ESMO Congress – lung cancer and mesothelioma

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CheckMate-227 [1, 2]
The Phase III CheckMate-227 trial included patients with stage IV non-small cell lung cancer (NSCLC) who had received no prior treatment. Part 1 of the CheckMate-227 study consisted of 2 cohorts: patients with PD-L1 expression ≥1% (Part 1a) and <1% (Part 1b). In Part 1a, patients were randomized 1:1:1 to receive nivolumab plus low dose ipilimumab (1mg/kg q6w), standard dose nivolumab, or platinum-based chemotherapy. In Part 1b, patients were assigned 1:1:1 to nivolumab plus ipilimumab, chemotherapy, or nivolumab plus chemotherapy. The independent co-primary endpoints of the study compared nivolumab plus ipilimumab versus chemotherapy in terms of PFS in the high tumor mutational burden (TMB ≥10 mutations/Mb) population (results already published [3]) and OS in the PD-L1 ≥1% population. At the ESMO 2019 congress the latter co-primary endpoint was presented. Median OS with nivolumab and ipilimumab in the PD-L1 ≥1% population was superior to chemotherapy (17.1 vs. 14.9 months; HR 0.79; 95% CI, 0.65-0.96; p = 0.007). In an exploratory analysis of Part 1a, the median OS of single agent nivolumab was 15.7 months. In Part 1b (PD-L1 negative cohort), the combination of nivolumab and ipilimumab improved median OS from 12.2 months (chemotherapy) to 17.2 months. There were no new safety signals with the immunotherapy-combination; grade 3/4 treatment-related adverse events were reported in 33%, 19%, and 36% of patients in the nivolumab plus ipilimumab, nivolumab, and chemotherapy arm, respectively. Interestingly, exploratory subgroup analysis did not reveal a predictive role of TMB.

Conclusion: Nivolumab plus ipilimumab is a new first-line treatment option, although its role in the context of combined immuno-chemotherapy has to be defined.
FLAURA [4]

The phase III FLAURA trial included previously untreated patients with locally advanced or metastatic NSCLC harboring a sensitizing EGFR mutation. Patients were randomized 1:1 to receive osimertinib or standard-of-care (SoC) TKI (erlotinib or gefitinib). Patients with disease progression under standard TKI were allowed to cross-over to osimertinib. PFS as primary endpoint was significantly improved (median PFS 18.9 vs. 10.2 months) as previously published [5]. Both, objective response rate (ORR, 80% vs. 76%) and median duration of response (DoR, 17.2 vs. 8.5 months) were higher with osimertinib. At ESMO the final OS analysis was presented. Median OS was improved by 6.8 months with osimertinib. Median OS in the osimertinib arm was 38.6 months compared to 31.8 months in the SoC-arm (HR 0.799; 95% CI, 0.647-0.997; p = 0.0462). Patients remained longer on osimertinib-therapy (70% vs. 47% after 12 months) and time to first subsequent treatment was significantly prolonged with osimertinib (25.4 vs. 13.7 months). Cross-over to osimertinib occurred in 30% of patients. Importantly, 30% in both treatment arms received no subsequent anti-cancer therapy.
Conclusion: Osimertinib is the new SoC 1st-line treatment for patients with a sensitizing EGFR mutation.

PROMISE-meso [6]
In the phase III study PROMISE-meso, patients with relapsed malignant pleural mesothelioma after platinum-based chemotherapy were randomized 1:1 to receive pembrolizumab or institutional choice of chemotherapy (gemcitabine, vinorelbine). Cross-over was allowed. PFS assessed by blinded independent central review was the primary endpoint. The study missed the primary endpoint. Median PFS with pembrolizumab was 2.5 months compared to 3.4 months in the chemotherapy-arm. There was also no significant difference in OS (median OS 10.7 vs. 11.7 months). The substantially higher ORR with pembrolizumab (22% vs. 6%) did not translate into a longer DoR (4.6 months vs. 11.2 months).

Conclusion: Pembrolizumab monotherapy is not superior to standard chemotherapy in the 2nd-line setting. Further studies are investigating combination therapies and the use of checkpoint inhibitors in earlier settings.

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EHA 2019 Highlights – Multiple Myeloma

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The treatment of relapsed and refractory multiple myeloma is a challenge. The EHA congress 2019 provided several highlights on this topic.

COLUMBA trial: Intravenous versus subcutaneous administration of daratumumab
Daratumumab, a monoclonal antibody targeting CD38, has proven efficacy in multiple myeloma across all lines of therapy. Similar to the anti-CD20 antibody rituximab the intravenous administration lasts several hours; in particular, the first infusion takes an average of seven hours[1]. In contrast, a subcutaneous infusion will only take 3-5 minutes.
The Columba study presented by Maria Victoria Mateos, is a randomised phase III study, which compared the intravenous (IV) versus subcutaneous (SC) administration of daratumumab in patients with relapsed or refractory multiple myeloma (R/R MM) [2]. 522 patients with R/R MM and at least 3 prior lines of therapy were enrolled and randomised 1:1 to receive either daratumumab SC (1800mg) or daratumumab IV (16mg/kg). The overall response rate (ORR) and the maximum trough concentration, as the two primary end-points, were comparable between the subcutaneous and intravenous administration of daratumumab (41.1% vs 37.1% ORR and maximum trough concentration dara-SC/dara-IV: 107.93%).

In addition, the safety profile between two routes of administration was similar. Daratumumab SC was even associated with a significantly lower rate of infusion-related reactions (12.7 % for SC vs. 34.5% for IV; p < 0.0001).
In conclusion, the subcutaneous administration of daratumumab is both safe and effective and due to the shorter administration time convenient for patients and health care professionals.

The ICARIA-MM trial: Isatuximab plus pomalidomide and dexamethasone, a new therapy option in patients with R/R MM?
The ICARIA-MM trial presented by Paul Richardson from the Dana-Farber Cancer Institute focused on isatuximab, another anti-CD38 monoclonal antibody [3]. The function of isatuximab is in many ways similar to daratumumab. However, isatuximab has less complement-dependent cytotoxicity than daratumumab. Therefore, perhaps isatuximab leads to less infusion-related reactions and has a shorter infusion time than daratumumab.
In the ICARIA trial, an international phase III study, 307 patients with R/R MM and at least 2 prior lines of therapy were randomised 1:1 to receive either isatuximab together with pomalidomide and low dose dexamethasone (Isa-Pd) or pomalidomide and low dose dexamethasone alone (Pd) [4].
The median progression free survival was significantly higher in the patient cohort receiving Isa-Pd (11.53 months for the Isa-Pd arm vs. 6.47 for the Pd arm, (95% CI 0.44-0.81), P=0.001). In line with these findings, the overall response rate (ORR) was also significantly higher with 60.4% in the Isa-PD arm versus 35.3% in the Pd arm.
Overall, the safety profile was manageable, despite a higher rate of neutropenia and infections in the cohort with isatuximab.
In summary, isatuximab in combination with pomalidomide and dexamethasone is a new therapeutic option in R/R MM, but open questions remain: Is isatuximab still effective for myeloma patients who are refractory to daratumumab and/or elotuzumab? Can isatuximab be given after treatment with daratumumab?

AMG 420, an Anti-BCMA Bispecific T-Cell Engager (BITE®) Immunotherapy
B cell maturation antigen (BCMA) is a cell surface receptor, which belongs to the tumor necrosis factor receptor (TNFR) superfamily and is almost exclusively expressed on plasmacells and plasmablasts [5]. In the last few years multiple immunotherapies directed against BCMA haven been developed, such as BCMA CAR-T or BCMA-BiTE®. A BCMA-BiTE® links with CD3 on T-cells on one side and with BCMA on plasma cells on the other side.
At the EHA, Max Topp presented results of a first-in-human phase I dose escalation study with the anti-BCMA BiTE® AMG 420. Primary endpoints were dose limiting toxicity and maximum tolerated dose [6].
AMG 420 was given by continuous infusion in 6-week cycles for 5 cycles or until disease progression (PD) or toxicity. Dose limiting toxicity was reached in three of 42 patients and in two cases at a dose of 800ug/d. The maximum tolerated dose was thus 400ug/d.
Overall, 13 of 42 patients responded to the treatment with the highest response rate of 70% at a dose of 400ug/d (7 of 10 patients). Therefore, the recommended dose for further investigation is 400ug/d.

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ESMO Highlights 2019 Gastrointestinal malignancies

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This year's EMSO congress was again a firework of exciting new data. Importantly, a variety of interesting and long awaited data on gastrointestinal malignancies were presented. We will hereby present 3 highly relevant studies.

Hepatocellular Carcinoma – Checkmate 459
In advanced hepatocellular cancer first line treatment options consist in VEGF-directed tyrosine kinase inhibition (TKI) with sorafenib or lenvatinib [1]. Immune checkpoint blockade showed promising results in phase I/II trial [2].
However, immunotherapy and TKI therapy have never been compared in a phase III study, which was the aim of the CheckMate 459 study (#LBA38_PR). 743 patients with previously untreated advanced HCC were randomized to receive nivolumab or sorafenib. Disappointingly, the primary endpoint overall survival was not significantly different (16.4 vs 14.7; HR 0.85; p=0.0752). Nivolumab showed an objective response

rate (ORR) of 15 % vs. 7% with sorafenib. In patients with PD-L1 positive tumors (≥1%) ORR increased to 28% (20 patients) with nivolumab compared to 9% in the sorafenib group. Safety and quality of life analyses also favored the nivolumab group with the known low rate of grade 3/4 toxicity.
Even though overall survival was not superior over sorafenib, nivolumab showed clinically meaningful responses and long-term survival with a favorable safety profile. Due to the later separation of the survival curves, favoring nivolumab, final results of OS should be assessed after longer follow-up. Meanwhile, results of the IMbrave 150 trial (atezolizumab/bevacizumab vs sorafenib; phase III) were announced in a press release, indicating the IO arm to be superior for OS and PFS [3].

Locally advanced pancreatic cancer – NEOLAP trial
The majority of patients with newly diagnosed pancreatic ductal adenocarcinoma (PDAC) present in a locally-advanced or metastasized stage. The conversion of patients with unresectable, locally advanced PDAC using intensive induction therapy has shown to improve overall survival.
The German multicenter phase II NEOLAP trial (#671O) compared induction chemotherapy of gemcitabine/nab-paclitaxel (G/nP) with sequential therapy of G/nP and FOLFIRINOX.
168 patients with locally advanced PDAC were randomized to receive 4 cycles G/nP vs 2 cycles G/nP and 4 cycles FOLFIRINOX then both arms followed by surgery and another 3 cycles G/nP.
Due to the small sample size no significant difference was demonstrated neither in the resection rate (primary endpoint; 45.0 vs 30.6%; p=0.135) nor in OS and PFS (secondary endpoints). However, the 15% difference in resection rate suggests a clinically meaningful benefit of an intensive induction therapy with G/nP followed by FOLFIRINOX. Moreover, the study design of this small, randomized trial was suboptimal, a randomization of induction chemotherapy of FOLFIRINOX vs G/nP would have been more meaningful. Overall, FOLFIRINOX appears to be more active as induction chemotherapy for locally-advanced PDAC. Indeed, large cohort studies have shown resections rates of up to 60% [4] in this setting.

Metastatic colorectal cancer (mCRC) – BEACON trial
BRAF V600E mutated mCRC represents a very aggressive phenotype with bad prognosis in about 10% of mCRC patients [5]. Clearly there is a need for targeted therapy after failure of first line therapy. The BEACON trial (phase 3; #LBA32) compared two targeted therapy regimes consisting of encorafenib, binimetinib and cetuximab (triplet) or encorafenib and cetuximab (doublet) with standard chemotherapy plus cetuximab. 665 previously treated mCRC patients were included. Both targeted treatment arms showed significant improvements in ORR (primary endpoint; 35% (triplet) and 29% (doublet) vs 7%, p<0.0001) and overall survival (9.0 (triplet), 8.4 (doublet vs 5.4 months, HR 0.52, p<0.001). Comparison between the both TKI arms were not possible at this early interim analysis. All three arms proved to be safe with tolerable rates of grade 3 toxicity, however, being higher in the triplet compared to the doublet arm. Due to these positive results, targeted doublet or triplet therapy should be considered a new standard of care in this patient subset.

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ESTRO Highlights 2019: therapeutic implications

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European Society of Radiation Oncology (ESTRO) was founded in 1980. In 2019 the 38th edition came about in achieving the attendance of more than 6000 participants from 100 countries. I review three papers focussing on the effectiveness combining different drugs as targets or antibiotics with radiation and improving patient's quality of life shortening treatment time.

Hyprofractionated vs conventional radiotherapy for prostate cancer: 7 yr results from the HYPRO trial
Abstract OC-0272. L Incrocci [1].
The study is based on improving efficacy of treatment in prostate cancer using moderate HF. The use of a linear-quadratic model suggests that HF schema will produce less toxicity and will be more effective in prostate cancer. The HYPRO trial is a randomized phase III study investigating in 804 patients the superiority of hypofractionated (HF) vs conventionally fractionated (CF) radiotherapy for patients with intermediate- or high-risk, localized, prostate cancer, actualized at 7-years follow-up. Patients were randomized to HF (64.6Gy, in 19 fr) or CF (78Gy in 39 fr). The primary end-point was relapse-free survival (RFS) at 7 years. The results indicate that RFS was 71.7% (95% CI 66.4-76.4) for HF versus 67.6% (95% CI 62-72.5) for CF (p=0.52). Not statistical evidence of heterogeneity across subgroups was observed. Local RFS sub-analysis reflected a significant interaction between treatment arm and Gleason score ≥ 8. HF arm did not translate in superior tumor control. Under these results, HF cannot be implemented as new standard of care. In my view, after several randomized controlled trials (RCTs) it has been demonstrated that moderate HF confers similar prostate-cancer-control outcomes with similar rates of late toxicity. Considering the convenience of the patients and the cost of treatment, both options can be discussed with patients.

Stereotactic radiotherapy (SRT) for oligoprogressive NSCLC: clinical scenarios affecting survival
Abstract OC-0059. S Kroeze.
Outcome disease as well as toxicity is not well known in combination between SRT and target treatment. TOASTT trial is a DEGRO initiative muticentric registry. It evaluated in 108 patients SRT of 192 lesions undertaken in 16 clinics.OS, PFS, LC and time to systemic therapy-switch after SRT were analysed. Concurrent treatment was 60% ALK- or EGFR-TKI, 31% PD-L1/PD-1 inhibitors and 8% bevacizumab. Patients were divided in SRT of ≤5 metastases without additional disease, SRT of ≤5 progressive metastases with controlled disease of all other metastasis and SRT of ≤5 metastases with mixed response or uncontrolled disease. The results demonstrate that LC after SRT was excellent in all groups, with limited severe toxicity. Significant improve in OS for patients with limited progressive disease and PFS especially good in the fir st group was observed. A large number of patients could continue the same systemic treatment 1y after SRT (86%, 47% and 39%). The majority had oligometastatic recurrence treated most frequently with an ablative treatment. The abstract suggests that despite good results we need prospective trials. In my opinion, we must be careful to know the implication of radiation localisation and time between both.

Gut microbiota SCFAs (short chain fatty acids) modulate dendritic cell antigen presentation and impact in radiotherapy
Abstract SP-0331. A Facciabene.
The role of microbiota in immunomodulation can compromise the response to radiation treatment promoting specific T cell subset. Vancomycine was used here to evaluate this impact. They observed that vancomycine potentiates the RT-induced anti-tumor immune response and tumor growth inhibition in a melanoma and lung tumor model. The synergism between vancomycine-RT was dependent on TAA (tumor-associated antigens) cross presentation to cytolytic CD8+ T cells and on IFN-g. Vancomicine treatment increases overall and well-specific T cells infiltration in tumor and decreases the tumor draining lymph nodes. Supplementation of butyrate (SCFAsproduced by microbial fermentation) inhibited antigen presentation and prevent vancomycin-RT synergy.
In conclusion, depletion of vancomycine sensitive bacteria enhances the anti-tumor activity of RT, which has relevant clinical implications. To my mind, the implication from this work is that inhibitors of SCFA could potentially be delivered in combination with radiation to serve as radiosensitizers.

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ESMO Highlights 2019 Genitourinary tumors

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At this year's annual ESMO congress many interesting trial results have been presented in the field of genitourinary oncology. Here, we highlight four trials that are most important for daily practice.

In the RADICALS trial the effect of adjuvant radiotherapy vs early salvage radiotherapy after radical prostatectomy was investigated. The primary endpoint – freedom from distant metastases – has not been reached yet, but preliminary results regarding biochemical recurrence-free survival were currently presented. Patients after radical prostatectomy (with at least one of the following criteria: pT3/4, Gleason Score 7-10, preoperative PSA

≥10ng/ml or positive surgical margins) with a postoperative PSA ≤0.2ng/ml were randomized to adjuvant or early salvage radiotherapy (administered in case of consecutive rises and PSA >0.1mg/ml). Of 1'396 recruited patients the majority had locally advanced disease (pT3/4: 75%) and/or positive surgical margins (R1: 63%). After a median follow up of 5 years no benefit of adjuvant radiotherapy was found with regards to biochemical recurrence (hazard ratio [HR]: 1.1 [95%-CI: 0.81-1.49]; p=0.56). In the salvage arm 63% of patients did not require treatment. The preliminary results from the RADICALS trial therefore support the concept of early salvage radiotherapy by which >60% of patients can be spared from radiotherapy.

Ronald de Wit presented the results from the CARD trial, comparing Cabazitaxel to treatment with a new hormonal agent (NHA; Abiraterone or Enzalutamide) in the third line setting for metastatic castration-resistant prostate cancer (mCRPC) [1]. Patients with mCRPC having been treated with docetaxel and who progressed on NHA within 12 months were randomized to Cabazitaxel (n=129) or the NHA that had not been previously administered (n=126). In the Cabazitaxel and NHA-groups, median age was ≥75 years in 35% and 27%, and tumor progression was clinical in 67% and 71%, respectively. The primary endpoint of radiographic progression-free survival was much improved in the Cabazitaxel-group (8 months [95%-CI: 5.7-9.2]) compared to the NHA allocation (3.7 months [95%-CI: 2.8-5.1]) and statistically significant (HR: 0.54 [95%-CI: 0.40-0.73]; p<0.0001). Median overall survial (OS) was also significantly improved with 13.6 vs. 11.0 months (HR: 0.64 [95%-CI: 0.46-0.89]; p=0.0078). The CARD trial therefore marks a practice changing study making Cabazitaxel the new third line standard for mCRPC patients progressing after docetaxel and on a NHA within 12 months.

Treatment with a PARP-inhibitor in mCRPC patients with DNA repair gene alterations demonstrated interesting efficacy in a small Phase II study [2]. Based on these results, the PROFOUND trial evaluated the efficacy of the PARP-inhibitor Olaparib vs NHA in mCRPC patients with homologous recombination repair (HRR) alterations, who progressed after NHA-treatment. In total, 632 patients were recruited and allocated to Cohort A (BRCA1, BRCA2 and ATM alterations; n=245) and Cohort B (any other HRR gene alteration; n=142). Patients from both cohorts were randomized 2:1 to Olaparib or NHA (Abiraterone or Enzalutamide at the physician's choice). All patients were pretreated with a NHA, of which 19% had received both Abiraterone and Enzalutamide, and 65% had previously received Docetaxel, Cabazitaxel or both. In Cohort A the primary endpoint of radiographic progression free survival was more than doubled with Olaparib (HR: 0.34 [95%-CI: 0.25-0.47]; p<0.0001). The effect was most pronounced in patients with BRCA2-mutations whereas patients with other HRR alterations had less benefit. PROFOUND marks the first positive biomarker-selected phase III trial in mCRPC, supporting HRR testing in mCRPC-patients progressing after NHA to select for Olaparib-sensitivity.

The IMvigor130-trial randomized 1'213 platinum-eligible patients with untreated locally advanced or metastatic urothelial carcinoma to standard of care chemotherapy of platinum/gemcitabine, monotherapy with the anti-PD-L1 inhibitor atezolizumab or the combination of platinum/gemcitabine and atezolizuamb. Interestingly, a substantial number of patients received carboplatin instead of cisplatin based on the physician's choice despite fulfilling Galsky criteria for ciplatin-eligibility. It is unclear, what impact this has on the trial results. The primary endpoint of progression-free survival (PFS) for the combination-treatment vs platinum-based chemotherapy was reached and was positive (HR: 0.82 [95%-CI: 0.70-0.96]). The combination-treatment improved median PFS from 6.3 (6.2-7.0) months to 8.2 (6.5-8.3) months. In an interim analysis, OS was numerically improved for the combination of chemotherapy/atezolizumab (16.0 vs 13.4 months) but did not meet the prespecified statistical threshold. Longer follow-up will reveal if patients with metastatic urothelial carcinoma may have improved survival using the combination of chemotherapy and atezolizumab as first line treatment.

References

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