Review papers
Young Oncology Academy 2020

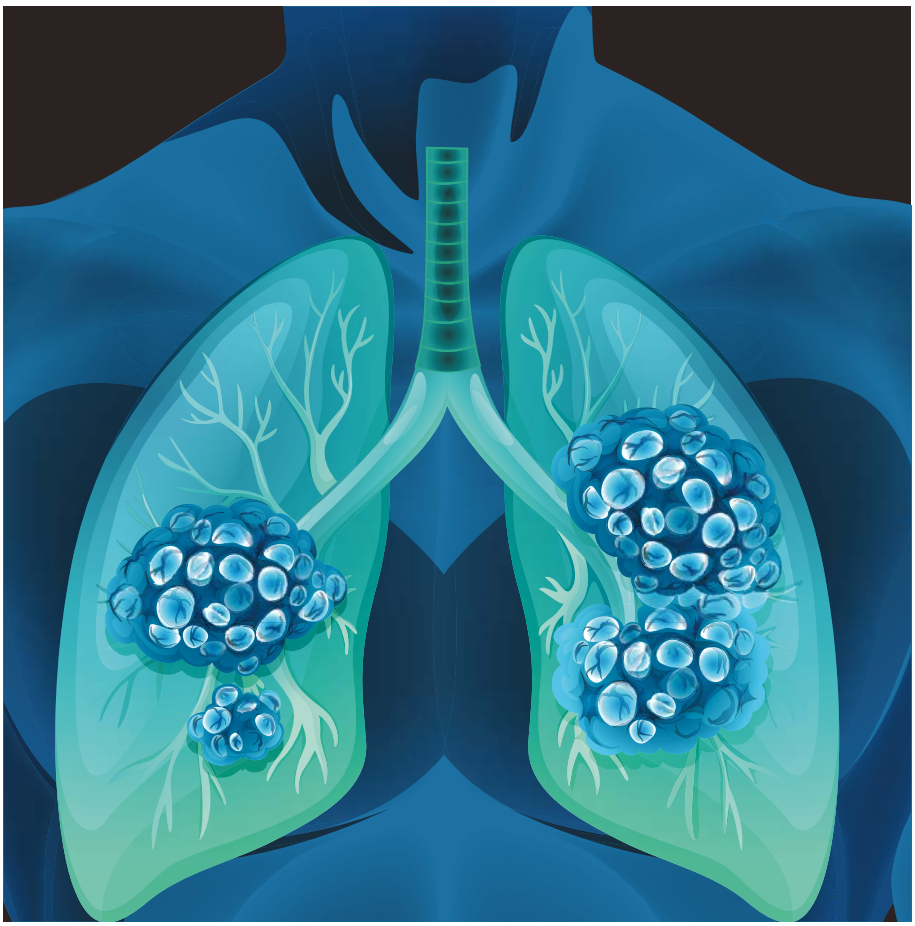
The Swiss Group for Clinical Cancer Research (SAKK) launched the Young Oncology Academy, a mentoring program for young oncologists, since 2016. The program is aimed for residents at the beginning of their medical career with a clear focus on cancer medicine, hematology or radio-oncology, who would like to actively contribute to clinical and translational research. In 2020, 9 mentees successfully concluded the program. As part of the program, the participants write a short review paper about abstracts in 2020. The call for application for the Young Oncology Academy 2021 is open. Please find further information on the SAKK website: sakk.ch/researchers/young-oncology-academy.

Lung Cancer Highlights of 2020 ESMO Congress

At this year's annual ESMO congress many interesting trial results have been presented in the field of lang cancer. This is a summary of three important trials.

CROWN Trial

The phase III CROWN trial investigated Lorlatinib, a potent 3rd-generation ALK (anaplastic lymphoma kinase) inhibitor vs Crizotinib in untreated patients with advanced ALK-mutated, non-small cell lung cancer (NSCLC).[1] This trial randomized 296 patients 1:1 to receive either Lorlatinib (100 mg daily) or Crizotinib (250 mg twice daily). The primary end point was progression-free survival (PFS) by BICR (blinded independent central review) while secondary endpoints included ORR (overall response rate), IC (intracranial) responses, overall survival (OS), safety and others. At the data cut-off on March 20th, 2020 the reported median follow-up for PFS by BICR was 18.3 months (95 % CI: 16.4–20.1) in the Lorlatinib arm and 14.8 months (95% CI: 12.8–18.4) for Crizotinib. The PFS by BICR was significantly longer in patients who received Lorlatinib compared to Crizotinib (not estimable vs 9.3 months; HR: 0.28; 95 % CI: 0.19–0.41; $p < 0.001$) resulting in a 72 % reduction in the risk of disease progression or death. The achieved ORR (by BICR) was higher with Lorlatinib vs Crizotinib (76 % vs.



58 %; odds ratio [OR]: 2.25; 95 % CI: 1.35–3.89). Moreover, patients with brain metastases at baseline demonstrated a higher IC-OR (via BICR), if treated with Lorlatinib (66 % vs 20 %; OR: 8.41; 95% CI: 2.59–27.23). The safety profile for both ALK-TKIs (tyrosin kinase inhibitors) was consistent with what has been previously seen in clinical trials with a higher rate of grade 3/4 adverse events leading to treatment discontinuation in the Lorlatinib arm (73% vs. 56 %).

Conclusion

Lorlatinib is clearly more active than Crizotinib in the the 1st-line setting for advanced ALK-positive, non-small cell lung cancer patients. As the current 1st-line standard is Alectinib, it remains to be shown whether Lorlatinib will be best used in 1st line or 2nd line after Alectinib.

LungART Trial

The long-awaited phase III LungART Trial investigated the role of post-operative radiotherapy (PORT) in patients with completely resected NSCLC with N2-nodal involvement.[2] In this large European study, 501 patients with R0-resected NSCLC and a histologically proven mediastinal nodal involvement (pN2) were randomized 1:1 to receive adjuvant Radiotherapy (54 Gy in 27–30 fractions) or no radiotherapy in the control group. The primary endpoint was the disease-free survival (DFS) and secondary endpoints included OS, safety, local failure and others. The study reported a median follow-up of 4.8 years. Most of the patients received (neo-)adjuvant Chemotherapy (96 %), PORT was performed as 3D-conformal radiotherapy in most of the cases (89 %), while only 11 % of the patients received IMRT (intensity modulated radiotherapy). The study did not reach its primary endpoint as PORT did not significantly prolong the median DFS reported as 30,5 months in the PORT arm vs 22.8 months in the control arm (HR: 0,85, 95 % CI: 0,67–1,07; p=0,16). The trial demonstrated remarkably high 3-year OS-rates in both groups (66.5 % with PORT vs. 68.5 % with no PORT). The adjuvant radiotherapy reduced the mediastinal relapse rate (25 % vs. 46,1 % in the control arm), while death as the first DFS-event was more frequent in patients who received PORT (14,6 % vs 5,3 %). Furthermore, the rate of grade 3/4 late cardio-pulmonary toxicities was twice as high as with PORT compared to the control group (10,8 % vs. 4,9 %).

Conclusion

PORT cannot be recommended as standard of care for completely resected pN2-NSCLCfpatients.

ADAURA Trial: central nervous system (CNS) disease recurrence

Osimertinib, a 3rd-generation EGFR (epidermal growth factor receptor) TKI with high CNS-activity, demonstrated a significant clinical benefit in the adjuvant setting for patients with stage IB, II or IIIA *EGFR*-mutated NSCLC in the phase III ADAURA trial, initially presented at the ASCO 2020 meeting.[3,4] Osimertinib lead to a 79 % risk reduction for disease recurrence or death compared to the placebo. Exploratory data of the ADAURA Trial, including an update on CNS efficacy, was presented at the ESMO Virtual Congress 2020 at a median follow-up of 22 months. The reported CNS recurrence rate for patients on adjuvant treatment with Osimertinib was 1 % compared to 10 % among patients in the placebo arm, resulting in a remarkable 82 % reduction in risk for CNS disease recurrence (based on a CNS-DFS HR of 0.18; 95 % CI: 0.10–0.33; p<0.0001). The conditional probability of CNS-disease recurrence at 12 months was less than 1 % in patients with Osimertinib vs. 7 % in the placebo arm.

Conclusion

Adjuvant Osimertinib leads to a clinically and statistically significant improvement in DFS and CNS-DFS in patients with completely resected EGFR+ NSCLC.

Author:
Dr. med. **Nino Fejzibegovic**
Onkozentrum, Hirslanden Zürich

Mentor:
Prof. Dr. med. **Miklos Pless**
Medizinische Onkologie
Kantonsspital Winterthur

Literature:

1 Solomon B et al.: Lorlatinib vs crizotinib in the first-line treatment of patients with advanced ALK-positive non–small cell lung cancer: results of the phase 3 CROWN study. ESMO Virtual Congress 2020; Abstract LBA2 **2** Le Pechoux C et al.: An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-0503, UK NCRI, SAKK). ESMO Virtual Congress 2020, Abstr. LBA3_PR **3** Herbst RS et al.: ASCO Virtual Meeting 2020, Abstract LBA5 **4** Yi-Long Wu et al.: Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer, N Engl J Med 2020; 383:1711-1723 **5** Masahiro Tsuboi et al., ESMO Virtual Congress 2020, LBA1 - Osimertinib adjuvant therapy in patients (pts) with resected EGFR mutated (EGFRm) NSCLC (ADAURA): Central nervous system (CNS) disease recurrence

Acknowledgment

I would like to thank SAKK for the opportunity to participate in the Young Oncology Academy 2020, as well as my mentor, Prof. M. Pless, for the valuable support throughout the entire program.

Highlights of the virtual ESMO Congress 2020 – SARS-CoV-2 and cancer

The COVID-19 pandemic has drastically impacted healthcare systems around the globe and thus also resources for the care of cancer patients. Early studies conducted with small numbers of patients, predominately coming from China, showed that cancer patients are at an increased risk of being infected with SARS-CoV-2, suffering severe complications and mortality.[1,2] Therefore, e. g. in Switzerland, cancer patients undergoing active treatment were considered a population at risk. This review summarizes an update on the most important findings concerning SARS-CoV-2 and cancer, presented at the ESMO conference in 09/2020.

Outcome

In Europe's largest prospective study, Palmieri et al. (Abstract 1670O) have shown that patients with cancer and COVID-19 have a significantly higher mortality rate compared to patients without cancer, with a hazard ratio of 1.62 (95 % CI: 1.56–1.68; $p<0.001$).[3] Similarly, the SAKK 80/20 study (Abstract LBA80) by Joerger et al. corroborates a higher mortality rate in infected Swiss cancer patients (17.8 %).[4]

Factors impacting the outcome

The studies presented at ESMO 2020 shed light on various factors which influence the outcome. Grivas et al. (Abstract LBA72) have identified patient-related factors, laboratory diagnostics and cancer-related factors that are associated with an increased 30-day mortality in cancer patients. Patient-related factors include older age, male sex, black race, smoking, ≥3 actively treated comorbidities and an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 points. Laboratory findings include low lymphocyte count, high/low neutrophil count, low platelets, and abnormal levels of creatinine, D-dimers, high-sensitivity troponin or C-reactive protein. Cancer-related factors include progressive cancer, recent therapy within 3 months, haematological cancer and multiple malignancies.[5]

Analysing the effects of therapies in depth, Wise-Draper et al. (Abstract LBA71) have shown in a large retrospective study that applied therapies prior to the occurrence of the COVID-19 infection have an impact on the outcome in cancer patients. Chemo-/immunotherapy, administered within 2 weeks prior to a COVID-19 infection, and a targeted therapy which include anti-CD-20 antibody treatment, given within 1–3 months of the infection, are associated with an increased 30-day mortality.[6]

The pandemic even affects therapy strategies in cancer patients *without* a proven COVID-19 infection. Van Mol et al. (Abstract LBA78) have found a treatment delay of more than seven days in 13.4 % of patients. Additionally, 27 % of lockdown patients received some form of a modified therapy. According to the simulation model, 2 % of patients will suffer a major change in prognosis.[7]

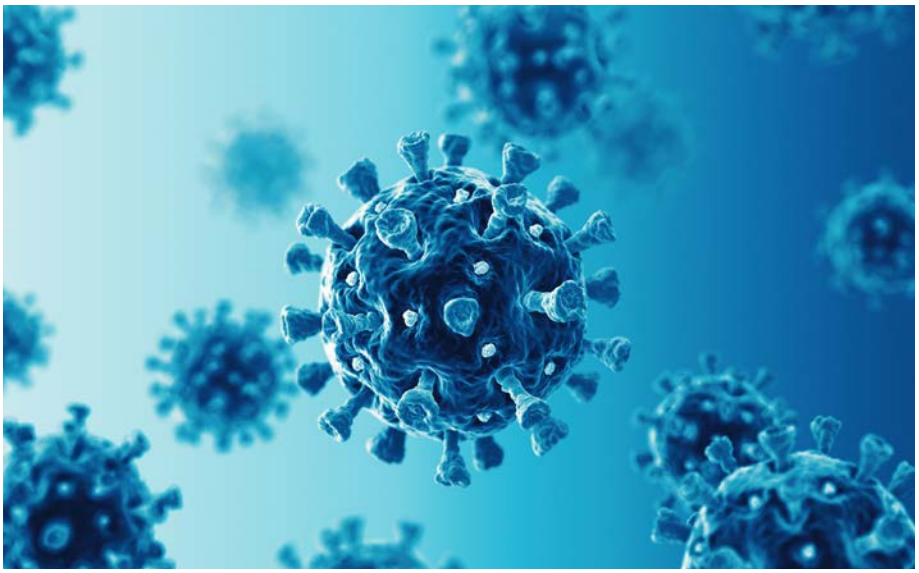
Finally, Palmieri et al. have pointed out that patients with a history of cancer or ongoing cancer treatment are less likely to be admitted to a critical care unit and mechanically ventilated than patients without cancer in times of limited resources.[3]

Guidelines

Due to the increased risk for cancer patients, the ESMO guidelines provide a priority list with regard to the urgency of any oncological intervention, based on expert advice and recommendations.[8] However, these guidelines have not been based on in-depth clinical trials.

Conclusion

As a result of both indirect and direct consequences, cancer patients have a poorer outcome and a higher mortality rate than patients without cancer during the pandemic. This was also confirmed by more recent studies.[9,10] Great threats to the patients are – beside the COVID-19 infection itself – treatment delays and dosage reductions, unjustified by solid data.[7] In contrast to the situation in spring 2020, there are currently sufficient resources



available in most parts of Switzerland to provide the established treatment strategies to our patients. However, cancer care prioritization and treatment have to be constantly adapted, especially as the pandemic situation is worsening again and changing rapidly.

Nevertheless, there are still many open questions emphasising the need for further studies, e. g. on better defined and homogenous populations, regarding cancer types or treatment strategies, and certainly studies with a longer follow-up. The quality of studies on COVID-19 has to be critically evaluated as e. g. many publications have been retracted shortly after publication. Without doubt, the pandemic has led to various difficulties and suboptimal situations when sharing information globally and publishing trustworthy data quickly to adapt to this new healthcare challenge.[11]

Authors:
Eveline Daetwyler, MD
Kantonsspital Aarau/Tucare Bülach
PD Dr. med. **Urban Novak**
Inselspital Bern

Literature:

1 Liang W et al.: Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21(3): 335-7 **2** Zhang L et al.: Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020; 31(7): 894-901 **3** Palmieri C et al.: 1670O Prospective data of first 1,797 hospitalised patients with cancer and COVID-19 derived from the COVID-19 Clinical Information Network and international Severe Acute Respiratory and emerging Infections Consortium, WHO Coronavirus Clinical Characterisation Consortium. Ann Oncol 2020; 31: S992-S **4** Joerger M.: Therapieergebnis und Prognose von Krebspatienten mit Coronavirus-Infektion SAKK 80/20 CaSA; available from: https://www.sakk.ch/de/studie/therapieergebnis-und-prognose-von-krebspatienten-mit-coronavirus-infektion (accessed: 31.10.2020) **5** Grivas P et al.: LBA72 Assessment of clinical and laboratory prognostic factors in patients with cancer and SARS-CoV-2 infection: The COVID-19 and Cancer Consortium (CCC19). Ann Oncol 2020; 31: S1202-S3 **6** Wise-Draper TM et al.: LBA71 Systemic cancer treatment-related outcomes in patients with SARS-CoV-2 infection: A CCC19 registry analysis. Ann Oncol 2020; 31: S1201-S2 **7** Van Mol P et al.: LBA78 A microsimulation model to assess the impact of SARS-CoV-2 on cancer outcomes, healthcare organization and economic burden. Ann Oncol 2020; 31: S1207-S **8** Cancer Patient Prioritisation; available from: https://www.esmo.org/guidelines/covid-19-adapted-recommendations-slide-sets (accessed: 31.10.2020) **9** Rösch R et al.: Characteristics and clinical course of SARS-CoV-2 infection in tumor patients in Germany: Results of the ADHOK Coronavirus Cancer Registry (CoRe) 2020 **10** Rüthrich MM: COVID-19 bei Krebspatienten: Klinische Charakteristika und Outcome – Eine erste Analyse der Daten aus dem LEOSS Register. 2020 **11** Curioni A: Dozens of COVID19-Related Articles Retracted: How to Assess the Quality of Research in the COVID-19 Era; available from: https://www.esmo.org/meetings/past-meetings/esmo-virtual-congress-2020/daily-reporter/daily-reporter-news/dozens-of-covid19-related-articles-retracted-how-to-assess-the-quality-of-research-in-the-covid-19-era (accessed: 31.10.2020)

Acknowledgments:

ED would like to thank SAKK and their sponsors for the opportunity to participate in the Young Oncology Academy (YOA). Many thanks go to PD Dr. U. Novak for his support and feedback during the whole program.

Highlights of ESMO 2020 World Congress – Gastrointestinal Cancer

We summarize three studies presented at this years ESMO Congress focussing on gastrointestinal cancer.

CheckMate-649

Results of the CheckMate-649 Study were presented: Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC).[1] This randomized, open-label, phase III trial included patients with previously untreated, unresectable locally advanced or metastatic GC (approx. 70 % of the population), GEJC or EAC. The patients were randomized 1:1:1 to receive nivo + ipilimumab, nivo + chemo (XELOX or FOLFOX), or chemo alone. Results were reported for the arms nivo + chemo (n = 789) vs chemo alone (n = 792). The dual primary endpoints were overall survival (OS) and progression-free survival (PFS) for patients with a PD-L1 combined positive score (CPS) ≥ 5. The median OS was significantly higher for the nivo + chemo arm compared to the standard arm (14.4 versus 11.1 months; P < 0.0001; HR: 0.71). Also, PFS was significantly increased in the nivo + chemo arm compared to the chemo alone arm (7.7 versus 6.0 months; P < 0.0001; HR: 0.68). Treatment related adverse events leading to discontinuation were observed in 36 % of the nivo + chemo treated population and in 24 % of the chemo alone treated population.

In conclusion, the combination of nivo + chemo is associated with significantly improved OS and PFS and represents a new potential standard 1L treatment for patients with advanced GC/GEJC/EAC and CPS ≥ 5.

KEYNOTE-590

Results from the KEYNOTE-590 trial were presented: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer.[2] This study is a randomized phase III double-blinded, placebo-controlled trial enrolling treatment-naïve patients with unresectable locally advanced or metastatic esophageal or GEJ cancer. Of all patients, 26.5 % had an adenocarcinoma, 73.5 % a squamous cell carcinoma. Patients were 1:1 randomized to receive pembrolizumab (200 mg Q3W for ≤ 35 cycles) + chemotherapy (Cisplatinum/5-Fu Q3W for ≤ 6 cycles) (n = 373) or placebo + chemotherapy (n = 376). Dual-primary endpoints of the study were OS and PFS. The median OS for pembrolizumab + chemotherapy was 12.4 months compared to 9.8 months in the placebo + chemotherapy arm (P < 0.0001; HR 0.73). In patients with CPS ≥ 10, the OS benefit was even more relevant (13.5 months versus 9.4 months, P < 0.0001, HR: 0.62). The

median PFS was also significantly longer for the pembrolizumab + chemotherapy treatment (6.3 months versus 5.8 months; P<0.0001; HR: 0.65). Treatment related adverse events led to discontinuation in 19% of the pembrolizumab + chemotherapy treated population and in 11% in the standard arm.

In conclusion, the combination of pembrolizumab + chemotherapy is associated with significantly improved OS as well as PFS and should be considered a potential new standard-of-care 1L therapy for patients with unresectable locally advanced or metastatic esophageal/GEJ cancer.

Checkmate 577

Kelly RJ et al. presented first results of the Checkmate 577 study: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT).[3] This double-blinded, placebo-controlled trial enrolled patients with stage II/III EC and GEJC (both adeno- and squamous cell carcinoma). After neoadjuvant CRT and R0 resection, patients who did not achieve a compete pathologic remission were 2:1 randomized to receive nivolumab (240 mg Q2W for 16 weeks, then 480 mg Q4W, up to 1 year; n=532) or placebo (n=262). In an interim analysis, the primary endpoint DFS was met with a median of 22.4 months for patients receiving nivolumab compared to 11.0 months in the standard arm (P=0.0003; HR: 0.69). Treatment related adverse events led to discontinuation in 9% of the nivolumab treated population and in 3% of patients in the standard arm.

In conclusion, nivolumab significantly prolongs disease-free survival compared to placebo in esophageal/GEJ cancer patients without complete pathologic remission after tri-modality treatment. Longer follow-up data as well as information on OS will be needed to decide whether adjuvant nivolumab should become a new standard of care.

Authors:
Dr. med. Dr. sc. nat. **Ferdinando Cerciello**
Department of Medical Oncology, Inselspital Bern
University Hospital, University of Bern
Prof. Dr.med. **Ulrich Güller**
Chief
Center for Hematology and Oncology
Spital STS AG, Thun

Literature:

1 Moehler M et al.: Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. Ann Oncol 2020; 31 (suppl_4): S1142-S1215 2 Kato K et al.: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study. Ann Oncol 2020; 31 (suppl_4): S1142-S1215 3 Kelly RJ et al.: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study. Ann Oncol 2020; 31 (suppl_4): S1142-S1215

Highlights of 2020 EHA Congress – Multiple Myeloma

We are presenting three personal highlights regarding the treatment of relapsed or refractory Multiple Myeloma (RRMM) from the 2020 European Haematology Association (EHA) annual congress.

Isatuximab plus Carfilzomib and Dexamethasone

Isatuximab (Isa) is an intravenous IgG1 monoclonal antibody targeting a specific epitope of CD38 with direct apoptotic effect, less infusion-related reactions and shorter infusion time than intravenous daratumumab.

IKEMA is an ongoing, phase III, randomized, open-label study evaluating the effect of adding Isa to carfilzomib and dexamethasone (Kd) in patients with RRMM compared with Kd alone, with an allocation ratio 3:2, until disease progression or intolerable adverse events.[1] Its primary end point is progression-free survival (PFS). The study has enrolled 302 patients with a median age of 64 years (3–90) and 24% of patients had high-risk cytogenetics. Eligibility criteria included having undergone 1 to 3 prior lines of treatment. Patients could not have previous exposure to carfilzomib and could not be refractory to anti-CD38 monoclonal antibody treatment.

With a median follow-up of 20,7 months. PFS had not been reached in the Isa-Kd group and was 19.2 months in the Kd group. This benefit was seen across nearly every subgroup.

Grade ≥3 adverse events (AEs) were reported in 76.8% of the Isa-Kd group versus 67.2% in the Kd group. Grade ≥3 cardiac failure was seen in 4.0% of the Isa-Kd–treated patients and in 4.1% of the Kd-treated patients.

In summary, we observe a clear improvement in PFS with a manageable safety profile when adding Isa to Kd in RRMM.

Idecabtagene Vicleucel, a BCMA-Targeted CAR T-Cell Therapy

The KarMMa trial is a phase II study of idecabtagene vicleucel, a B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cell therapy, in patients with RRMM who had exposure to at least 3 prior regimens and were refractory to their last regimen.[2] The aim of the study was to assess the efficacy and safety with a primary end point of overall response rate (ORR).

A total of 128 patients received idecabtagene vicleucel infusion (at 3 targeted doses) following lymphodepletion with cyclophosphamide plus fludarabine. Around 88% of patients required bridging therapy during CAR T-cell manufacturing. The median age of patients was 61 years,

with a median of 6 prior lines of treatment, and 35 % had high-risk cytogenetics. With a median follow-up of 13.3 months, the ORR was 82 % in patients receiving 450 x 106 CAR+ T-cells and with an ORR of 73 % in the total population. This was seen across all subgroups. The time to first response was rapid and within 1 month. The median PFS was 8.8 months and even up to 20,2 months in patients achieving a CR.

Regarding AEs, cytopenia was very frequent and cytokine release syndrome (CRS) occurred in 84 % of patients with only 5 (9 %) patients experiencing grade 3 or more. In conclusion, in highly refractory RRMM, idecabtagene vicleucel demonstrated a tolerable safety profile with frequent and deep responses, which are also durable especially in patients achieving a CR.

Teclistamab, a Novel Bispecific Antibody

In the ongoing, 2-part, phase I trial the safety and anti-myeloma activity of Teclistamab, a combined humanized B-cell maturation antigen (BCMA) with CD3 bispecific antibody, is investigated in patients with RRMM.[3] The study included so far 78 patients (30 % with high-risk cytogenetics), who had a median of 6 prior lines of therapy. Teclistamab was administered at doses ranging from 38.4 mg/kg to 720 mg/kg.

Only 26 patients are continuing the treatment, 21 of them have achieved at least a partial response (16 still have ongoing response). The other 52 patients discontinued treatment due to progressive disease (41 patients) or AEs (5 patients). The most common AEs were CRS (56 %, no grade ≥ 3) and cytopenias (one third were grade ≥ 3).

The ORR was 30 % and the very good partial response (VGPR) was 25 %. At the 270 mg/kg dose level, ORR was up to 67 % and the VGPR was 50 %. Four of 5 patients were minimal residual disease (MRD)-negative at a 10^{-6} level of sensitivity.

Overall, teclistamab seems to be safe across all doses, with higher response rates upon higher doses.

Authors:
Dr. med. **Carmen de Ramón Ortiz**
Hôpitaux Universitaires de Genève
Prof. Dr. med. **Gabriela M. Baerlocher**
Universitätsklinik für Hämatologie und Hämatologisches Zentrallabor
Universitätsspital/Inselspital und Universität Bern

Literature:

1 Moreau P et al.: Isatuximab plus carfilzomib and dexamethasone in relapsed/refractory multiple myeloma (IKEMA) interim analysis of a phase III, randomized, open-label study. EHA 2020, Abstr. #LB2603 **2** San Miguel J et al.: Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T cell therapy, in patients with relapsed and refractory multiple myeloma: initial KarMMa results. EHA 2020, Abstr. #S209 **3** Mateos MV et al.: A phase I study of teclistamab, a humanized B cell maturation antigen (BCMA) x CD3 bispecific antibody, for the treatment of relapsed and/or refractory multiple myeloma (RRMM). EHA 2020, Abstr. #S206

Highlights of ESMO 2020 – Genitourinary Cancer

This is a summary of studies on prostate cancer and renal cell carcinoma presented at the ESMO 2020 Virtual Congress.

Improved OS in a subset of mCRPC patients treated with Olaparib

De Bono et al presented abstract 610 O: Final overall survival (OS) analysis of PROfound: Olaparib vs. physician's choice of enzalutamide or abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations.

PROfound is a randomized, open-label, phase III trial evaluating the PARP inhibitor Olaparib in men with mCRPC who had disease progression while receiving a novel hormonal agent (NHA) (e. g., enzalutamide or abiraterone). The requirement for inclusion was a mutation in an HRR DNA-damage repair pathway-related gene (NGS by Foundation One). It is the first randomized phase III trial evaluating a therapy targeting a molecularly identified alteration in prostate cancer and the first application of the concept of synthetic lethality in genitourinary cancer. The primary endpoint rPFS has benn reported in 2019[1], the authors now presented the final OS results.

© iStockPhoto.com/Mohammed Haneefa Nizamudeen

OS was significantly improved with olaparib for patients in cohort A, i.e., patients with *BRCA1/2* or *ATM* mutation. Median OS benefit was 19.1 vs. 14.7 months, HR: 0.69 (95% CI: 0.50–0.97; p=0.0175). Patients with other HRR associated gene mutations did not show a survival benefit. The main side effects of olaparib were anemia, mild nausea and fatigue.

Key points regarding this trial are a high rate of cross over from the control arm to the intervention arm (66 %), and a possible undertreatment in the control group: Patients in the control group received another NHA, which is known to have impaired efficacy after prior progression to an NHA2. However, Olaparib appears to be a valid therapy option for mCRPC patients with *BRCA2* or *BRCA1* mutations.

Effective new first-line therapy option in advanced renal cell carcinoma (RCC)

Choueiri et al presented abstract 696 O: Nivolumab + cabozantinib (NIVO + CABO) vs. sunitinib in first-line treatment for aRCC: first results from the randomized phase 3 CheckMate 9ER trial.

Patients included had previously untreated advanced or metastatic clear cell RCC. All IMDC prognostic risk groups were included. Around 70 % of patients underwent prior nephrectomy. Of note, the CABO dosage was 40 mg/day (60 mg/d are standard).

PFS and OS were both significantly better in the intervention arm. Median PFS: 16.6 vs. 8.3 months, HR: 0.51 (95 %CI: 0.41 – 0.64; p = 0.0001). All subgroups benefited. OS: not reached (both arms), HR: 0.60 (95% CI: 0.40–0.89; p = 0.001). Objective response and best overall response were also superior in the combination arm. Adverse events were similar in both groups, with a slightly increased hepatic-toxicity in the intervention arm. Nevertheless, > 50 % of patients had further CABO dose reduction.

These results show a clear, well tolerable, benefit of NIVO + CABO vs. sunitinib. Yet, the exact impact on the change of practice remains unclear. Recently published studies showed similar results comparing combinations of immunotherapeutic agents vs. sunitinib.[3,4] The three studies differ in patient characteristics, especially regarding prognostic risk groups. Moreover, the OS follow-up interval ranges from 10 to 42 months. Despite a current direct comparison being immature, the following therapy options appear to emerge:

1. IO-TKI combination: for aggressive, quickly progressing symptomatic high volume disease
2. IO-IO combination: QoL improves, no TKI-related long-term toxicity
3. TKI mono or active surveillance remain options for IMDC favorable patients.

Author:
Dr. med. **David C. Müller**
Clinic for Urology
University Hospital Basel

Mentor:
PD Dr. med. **Richard Cathomas**
Department of Oncology
Cantonal Hospital Graubünden, Chur

Literature:

1 de Bono J et al.: Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020; 382(22): 2091-102 **2** Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019; 20(12): 1730-9 **3** Motzer RJ et al.: Nivolumab plus Ipilimumab versus Sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018; 378(14): 1277-90 **4** Rini BI et al.: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019; 380(12): 1116-27

EMSO 2020 Highlights – Radiation Oncology

For Radiation Oncology, selected topics were presented at ESMO 2020. I will hereby summarise two presentations.

JAVELIN Head & Neck 100 trial

The JAVELIN trial was presented by Ezra Cohen from the Moore Cancer Center in La Jolla: Avelumab plus chemoradiotherapy (CRT) followed by Avelumab maintenance vs CRT in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). Avelumab is an anti-PD-1 immune checkpoint inhibitor that has proven antitumor activity in the treatment of recurrent and/or metastatic SCCHN with an acceptable safety profile.[1–3]

The randomized, placebo-controlled, double-blind phase III trial included newly histologically diagnosed treatment naïve patients with high-risk LA SCCHN (N = 697). Patients were randomized 1:1 to an experimental arm (N = 350) receiving Avelumab (10 mg/kg) for 1-week in a lead-in phase followed by the CRT phase, delivering IMRT (70 Gy in 35 fractions over 7 weeks applying 1 fraction/day and 5 fractions/weeks) with 3 cycles of concomitant cisplatin (100 mg/m^3) and the addition of Avelumab (10 mg/kg Q2W), followed by a maintenance phase of 12 months with Avelumab (10 mg/kg Q2W). The other half (N = 347), included in the standard arm, received the standard of care,[4] meaning the same procedure as above but replacing Avelumab by placebo. In the interims analysis the results crossed the futility criteria and the trial was therefore stopped early. PFS as primary endpoint was not reached in both arms but the results of the experimental arm could not improve PFS (HR: 1.21; CI: 0.93–1.57; p = 0.92) as well as the secondary endpoint OS (HR: 1.31; CI: 0.9-1.85; p = 0.94). Exploratory analyses favored Avelumab only in patients with high PD-L1. Baseline characteristics were balanced between the groups and overall response rates did not differ (ORR: 0.95; CI: 0.66-1.35; p = 0.62). In the experimental arm grade 3/4 AE were slightly increased (N = 66/14 vs. N = 63/11) as well as infusion and immuno-related AEs (N = 22 vs. N = 3 respectively N = 35 vs. N = 26) with thyroid disorders as main immuno-related AE. The discontinuation rates though were comparable as the safety overview in total.

Conclusion

Avelumab could not improve PFS and OS. High-dose cisplatin-based CRT remains the standard of care for LA SCCHN. Subgroup data shows that Avelumab is of benefit in high PD-L1 tumors, but this needs to be further explored and validated.

EPIC-OPC Study

THE EPIC-OPC study was presented by Miren Taberna from the Catalan Institute

of Oncology in Barcelona and analyzed the performance of dual p16 and HPV testing for determining prognosis in cancer of the oropharynx.

Patients with HPV-related OPC are known to have better outcome and 59% reduction of death.[5] For HPV detection, the expression of the surrogate marker p16 by IHC is most often used, as recommended by the guidelines from the College of American Pathologists, and defines the OPC TNM staging.[6–8] However, double testing of p16 and HPV-DNA via PCR has a better diagnostic accuracy and prognostic value. So far, the subset of p16+/HPV- OPC patients and their prognosis remains unclear. The aim was to clarify the proportion, determinants and prognosis of OPC patients that are p16+/HPV- in an international, multicentric study. Thirteen cohorts of OPC patients were retrospectively analyzed for OPC-specific, overall and disease-free survival as well as the distribution of p16+/HPV- discordance.

About 1/3 in the p16+/HPV+ group were non-smokers. In Toronto, Canada, more than 2/3 of p16+ patients were also HPV+, while in Barcelona, Spain, only 1/3 of p16+ patients were also HPV+. The 5-year overall survival was significantly better for p16+/HPV+ patients (HR: 0.25; CI: 0.22–0.28) compared to both p16+/HPV- (HR: 0.65; CI: 0.53–0.79) and p16-/HPV+ patients (HR: 0.64; CI: 0.54–0.76), whose outcome was similar. OPC patients with double negative p16 and HPV had the worst outcome, as expected. The 5-year disease-free survival and the 5-year OPC-specific cumulative hazard of death were likewise.

Conclusion

p16-/HPV+ and p16+/HPV- patients have significantly worse survival than p16+/HPV+ OPC patients. Up to 1/3 of OPC patients would be incorrectly classified in the 8th edition of the TNM by using p16 IHC staining alone. This subset of patients would be potentially undertreated if CRT was de-escalated.

Authors:
Dr. med. Dr. rer. nat. **Galina F. Fischer**
Kantonsspital St. Gallen
Dr. med. **Francesca Caparrotti**
Geneva University Hospital

Literature:

1 Gulley JL et al.: Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. Lancet Oncol 2017; 18: 599-610 **2** Keilholz U et al.: Avelumab in patients with previously treated metastatic melanoma: phase 1b results from the JAVELIN Solid Tumor trial. J Immunother Cancer 2019; 7: 12 **3** Hassan R et al.: Efficacy and Safety of Avelumab Treatment in Patients With Advanced Unresectable Mesothelioma: Phase 1b Results From the JAVELIN Solid Tumor Trial. JAMA Oncol 2019; 5: 351-7 **4** Pfister DG et al.: Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020; 18: 873-98 **5** Gillison ML et al.: Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000; 92: 709-20 **6** Rietbergen MM et al.: Human papillomavirus detection and comorbidity: critical issues in selection of patients with oropharyngeal cancer for treatment De-escalation trials. Ann Oncol 2013; 24: 2740-5 **7** Lewis JS Jr et al.: Human Papillomavirus Testing in Head and Neck Carcinomas: Guideline From the College of American Pathologists. Arch Pathol Lab Med. 2018; 142: 559-97 **8** Prigge ES et al.: Diagnostic accuracy of p16(INK4a) immunohistochemistry in oropharyngeal squamous cell carcinomas: A systematic review and meta-analysis. Int J Cancer 2017; 140: 1186-98.

Acknowledgements

I would like to thank SAKK YOA for the opportunity of the scholarship and my mentor, Francesca Caparrotti, for her support.

ESMO Highlights 2020 – Breast cancer

This year's ESMO meeting brought new data regarding the treatment of breast cancer. Several chosen abstracts will be discussed in this short review.

Metastatic Breast Cancer

Aditya Bardia presented first results of the ASCENT trial in this year's ESMO meeting.[1] In this phase III trial, pretreated patients with metastatic triple negative breast cancer (mTNBC) were randomized to receive either Sacituzumab Govitecan (SG), an anti-Trop-2 antibody coupled to SN-38, or single agent chemotherapy of physician's choice. Eligible patients should have received at least 2 prior lines of standard chemotherapy. The trial met its primary endpoint, progression free survival (PFS), in patients without brain metastases (5.6 vs 1.7 months). A benefit on overall survival (OS), predefined as a secondary endpoint, was also observed (mOS 12.1 months with SG vs. 6.7 months with TPC (HR: 0.48; p<0.0001). In conclusion, this

is the first phase III trial to demonstrate significant improvement efficacy with the first in class antibody conjugated drug, SG versus chemotherapy, in patients with pretreated mTNBC. SG is approved as a third-line treatment for patients with mTNBC under the FDA›s Accelerated Approval Program.

Early and locally advanced Breast Cancer

Nadia Harbeck presented the primary results of the IMpassion 031 trial.[2] In this phase III trial, patients with previously untreated stage II–III histologically documented TNBC were randomly assigned to receive neoadjuvant nab-paclitaxel and anthracycline-based chemotherapy plus atezolizumab or placebo. Co-primary endpoints were

pathological complete response (pCR) in the intention to treat (ITT) and PD-L1-positive populations. The addition of atezolizumab was related with a significant increase in the rate of pCR in the ITT population (57.6% vs. 41.1%). The pCR benefit was observed in all clinically important subgroups, including patients with PD-L1-negative status. These results are in alignment with KEYNOTE-522[3], which showed improvement in pCR with pembrolizumab plus chemotherapy in both PD-L1-positive and PD-L1-negative patients. However, two smaller studies, NeoTRIPaPDL1.[4] and GeparNuevo[5], failed to show significant pCR improvements with the addition of PD-L1 inhibitors to chemotherapy in patients with early TNBC. These differences are probably related to different trial designs.

Based on the activity of CDK4/6 inhibitors in the metastatic setting, monarchE[6] and PALLAS[7] trials of adjuvant abemaciclib and palbociclib, respectively, in hormone receptor-positive (HR+), HER2-negative (HER2-), early-stage breast cancer, were presented in this year's ESMO meeting, showing contrasting results. Both used invasive disease-free survival (iDFS) as the primary endpoint. The PALLAS study compared palbociclib plus standard adjuvant endocrine therapy (ET) to standard adjuvant ET alone in 5794 patients with HR+/HER2- early breast cancer stage II-III. At a median follow-up of 23.7 months, no significant difference in 3-year iDFS was observed between the arms.

The international phase III monarchE study included 5637 patients with HR+/HER2– early breast cancer with clinical and/or pathological risk factors putting them at high risk for relapse. The trial met its primary endpoint with 25% reduction in recurrence with the first two years, when abemaciclib was added to ET versus ET alone. The different outcomes could be related either to the different patient populations or to the high rate of discontinuation in PALLAS.

Conclusion

This year's ESMO brought SG, a new powerful drug into play for mTNBC, and neodadjuvant atezolizumab has clear activity in TNBC. Further follow-up will clarify the role of CDK4/6 inhibitors as an adjuvant treatment in patients with HR+/HER2- breast cancer.

Authors:
Dr. **Aikaterini Liapi**
Oncology Department, CHUV, Lausanne
Prof. Dr. med. **Miklos Pless**
Tumorzentrum
Kantonsspital Winterthur.

Literature:

1 Bardia A et al.: ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). ESMO 2020, Abstr. #LBA17 **2** Mittendorf EA et al.: Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomized, double-blind, phase 3 trial. Lancet 2020; 396(10257): 1090-100 **3** Schmid P et al.: Pembrolizumab for early triple negative breast cancer. N Engl J Med 2020; 382: 810-21 **4** Bianchini G et al.: Tumour infiltrating lymphocytes (TILs), PD-L1 expression and their dynamics in the NeoTRIPaPDL1 trial. ESMO 2020, Abstr. #LBA 13 **5** Loibl S et al.: A randomized phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol 2019; 30(8): 1279-88 **6** Johnston S et al.: Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2–, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020: doi: 10.1200/JCO.20.02514 **7** Mayer E et al.: PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. ESMO 2020, Abstr. #LBA12

ESMO Highlights 2020: Head and Neck Cancer

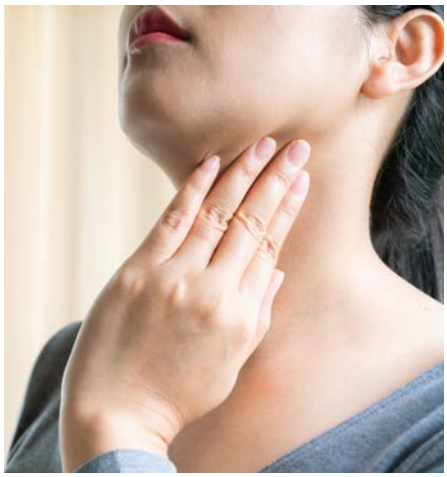
Immune checkpoint inhibitors (ICIs) have shown efficacy in the treatment of recurrent and metastatic squamous cell carcinoma of the head and neck (SCCHN) and are a new standard of care (SOC).[1,2] Numerous studies investigate the benefit of ICI in the curative setting in the context of definitive combined radio-chemotherapy (RCT) as well as in the neoadjuvant and adjuvant situation. The results of these studies are awaited with great hope. Unfortunately, these expectations were not met in ESMO 2020 with the presentation of two randomized studies.

JAVELIN Head & Neck 100

In the JAVELIN Head & Neck 100 trial[3] 697 patients with previously untreated high-risk locally advanced (LA) SCCHN were randomized to avelumab or placebo in combination with SOC cisplatin-based RCT. RCT consisted of intensity-modulated radiotherapy (IMRT, 70 Gy/35 fractions) and 3 cycles of cisplatin 100 mg/m^2 q3w followed by 12 months of avelumab or placebo. The primary endpoint progression free survival (PFS) was not met. Median PFS was not reached in both arms with a hazard ratio (HR) of 1.21 (p=0.92). The trial was unblinded at the first planned interim analysis due to futility. The secondary endpoint overall survival (OS) showed no benefit from avelumab, either. The reason for this unexpected result is not clear. Patients with PD-L1 expression ≥25% had a trend towards better PFS. This might be a population worthwhile focusing on in future trials with ICIs in the curative setting.

PembroRad

The PembroRad trial[4] compared pembrolizumab (200 mg q3w, 3 cycles) to cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) administered concomitantly with IMRT (69.96 Gy/33 fractions) in 133 patients with unresected


© iStockPhoto.com/PORNCHAI SODA

LA-SCCHN unfit to receive high-dose cisplatin. Unlike the JAVELIN 100 study patients did not receive adjuvant pembrolizumab. The primary endpoint of loco-regional control (LRC) at 15 months did not show a statistically significant difference (cetuximab-RT 59%, pembrolizumab-RT 60%, OR: 1.05, p=0.91). The secondary endpoint OS did not show a significant difference either (OS at 2 years: cetuximab-RT 55%, pembrolizumab-RT 62%). There were significantly more adverse events(AE) ≥ grade 3 in the cetuximab arm, mainly skin and mucosal toxicites. Even though LRC and OS did not differ significantly, the conclusion that pembrolizumab is non-inferior to cetuximab cannot be drawn, as the trial was designed to show superiority for pembrolizumab. So far, no data for PD-L1 expression have been presented. As with the JAVELIN trial, the reasons for the disappointing results are unclear. It was speculated that concomitant RT could play a detrimental role by destructing tumor-specific T cells and changing the tumor microenvironment. It remains unclear, whether biomarker selection might improve the outcome.

IMCISION

While the results of ICIs combined with definitive (chemo-)RT were disappointing, the phase I/IIa IMCISION trial[5] showed promising data for neoadjuvant ICIs. Of 32 patients with T2-4 N0-3 SCCHN, 6 received nivolumab 240mg at week 1 and 3 and 26 received nivolumab 240mg plus ipilimumab 1mg/kg at week 1 and Nivolumab 240mg at week 3 followed by tumor resection at week 5. 31% of patients had a (near) complete pathological response in the surgical specimen. SOC surgery was never delayed due to immune-related AE. After a median follow-up of 14 months, none of the patients had a relapse. As this is a phase I/IIa study, it remains to be seen, whether these promising results can be confirmed in a phase III study.

Authors:
Dr. med. **Angela Fischer Maranta**
Department of Oncology and Hematology
Cantonal Hospital Graubünden, Chur
PD Dr. med. Dr. phil. **Sacha Rothschild**
Department of Oncology
University Hospital Basel

Literature:

1 Ferris RL et al.: Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016; 375: 1856-67 **2** Burtness B et al.: Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019; 394: 1915-28 **3** Cohen EE et al.: 9100 Primary results of the phase III JAVELIN head & neck 100 trial: Avelumab plus chemoradiotherapy (CRT) followed by avelumab maintenance vs CRT in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). Ann Oncol 2020; 31: S658 **4** Bourhis J et al.: LBA38 Pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC): Results of the GORTEC 2015-01 «PembroRad» randomized trial. Ann Oncol 2020; 31: S1168 **5** Zuur L et al.: LBA40 Neoadjuvant nivolumab and nivolumab plus ipilimumab induce (near-) complete responses in patients with head and neck squamous cell carcinoma: The IMCISION trial. Ann Oncol 2020; 31: S1169

Review paper ESMO 2020 Highlights: Gynecological Cancer

This year's ESMO congress provided eagerly anticipated results of new therapies in gynecological cancer. Here, we will present you three relevant studies focused on innovative treatment.

Endometrial Cancer (EC): NSGO PALEO/ENGOT-EN3 Trial

Currently, there is no standard second line treatment for EC according to ESMO-ESGO-ESTRO EC Guidelines 2017. Endocrine therapy is a reasonable alternative, however, objective response rate (ORR) in aromatase inhibitor monotherapy was <10% in phase II studies. In ER+/HER2- breast cancer the combination of letrozole (L) with the CDK4/6 inhibitor palbociclib (PC) was superior to L alone in terms of progression-free survival (PFS) and overall survival (OS).[1] The majority of EC express estrogenic receptor (ER) and have a high Cyclin A expression, both targets of PC.

In this phase II trial the combination of PC with L was compared to L + placebo in patients with advanced or recurrent EC expressing ER ≥10%. Overall, 73 patients were randomised 1:1. The primary endpoint (PE) was achieved with a clinically meaningful improvement in PFS of 5.3 months in the PC + L arm (3.0 vs. 8.3 months). Despite a similar quality of life in both arms, there was a relatively high rate of PC dose reduction in 36% and treatment interruptions in 25%. A possible explanation may be the age of the population (median 68.5 years) and prior lines of therapy (53%=1 and 33%>2).

These promising results are already appealing for the clinic, even if a phase III validation trial should be considered. Other alternatives for the cutoff of ER expression and the choice of the endocrine therapy (aromatase inhibitors vs. progestin or tamoxifen) merit future investigations.

Cervical Cancer (CC): innovaTV 204/ GOG-3023/ENGOT-cx6 Trial

Standard therapies for previously treated and recurrent/metastatic CC generally result in limited ORR, barely reaching 20% with a median OS ranging from 6.0 to 9.4 months.[2–9] Tisotumab vedotin (TV) is a new generation antibody-drug conjugate (ADC) targeting tissue factor (TF), which is expressed on CC and can promote tumor growth, angiogenesis, and metastases.[10–12] Membrane TF expression is associated with metastasis formation and the FIGO clinical stage of CC.[12]

In this phase II trial, 101 patients with previously treated recurrent or metastatic CC were given TV 2 mg/kg i.v q3w (as 2nd or 3rd line). TV showed an ORR of 24% (7% complete response), a median PFS of 4.2 months and OS of 12.1 months. The median duration of response (mDOR) was 8.3 months. Membrane TF expression level had no impact on the response rate.

In conclusion, TV showed promising results in CC, especially with a relatively long mDOR. This treatment is part of a new generation of treatments, ADCs, that already demonstrated some impressive results in other cancers, as trastuzumab-emtansine, trastuzumab-deruxtecan, sacituzumab govitecan in breast cancer or mirvetuximab soravtansine in ovarian cancer.

Ovarian Cancer: IMagyn050/GOG 3015/ENGOT-OV39

ORR to anti PD1/PD-L1 monotherapy is limited (8–20%) in recurrent ovarian cancer (OC). OC is a VEGF-driven tumor, susceptible to both the anti-angiogenic and immunomodulatory properties of bevacizumab (Bev). VEGF inhibition may promote T-cell infiltration into the tumor and trigger an anti-tumor immune response.[13,14] Chemotherapy (CT) can also be immunogenic. This provided the rational for combining atezolizumab (AZ), a PD-L1 inhibitor with Bev and CT. The efficacy of this combined approach has been demonstrated in non-small-cell lung cancer, advanced EC and hepatocellular cancer.[15–17]

In this phase III trial the addition of AZ to a first-line platinum-taxane chemotherapy and Bev did not meet its PE. The mPFS was not improved in the intention to treat population or the PD-L1+ subgroup. Additionally, no signal of benefit in terms of OS was observed in this first interim analysis. Exploratory analyses in the subgroup with immune cells (IC) expressing PD-L1 ≥5% showed a trend favouring AZ.

The negative results of this trial were a surprise and disappointing. Further analyses of the immune biomarkers are needed to better qualify the sub-groups that could potentially benefit from the addition of AZ. The role of *BRCA* mutations and Homologous recombination deficiency also need to be clarified in this setting.

Conclusion

In addition to chemotherapy, endocrine therapy and bevacizumab, new therapies are arriving in gynecological cancer with promising results. Following the data presented above, we can observe that more in depth subpopulation analyses and exploration of biomarkers are needed to find the correct population for a suitable drug. This shows a trend towards personalized medicine in gynaecological cancer.

Authors:
Dr. med. **Tibor Zwimpfer**
University Hospital Basel
Dr. med. **Khalil Zaman**
University Hospital Lausanne

Literature:

1 Finn RS et al.: Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375(20): 1925-36 **2** Van den Berg YW et al.: The relationship between tissue factor and cancer progression: insights from bench and bedside. Blood 2012; 119(4): 924-32 **3** Lorusso D et al.: Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol 2010; 21(1): 61-6 **4** Schilder RJ et al.: Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2005; 96(1): 103-7 **5** Miller DS et al:. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2008; 110(1): 65-70 **6** Bookman MA et al.: Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2000; 77(3): 446-9 **7** Garcia AA et al.: Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Am J Clin Oncol 2007; 30(4): 428-31 **8** Monk BJ et al.: Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2009; 27(7): 1069-74 **9** Chung HC et al.: Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2019; 37(17): 1470-78 **10** Pan L et al.: Expression of flTF and asTF splice variants in various cell strains and tissues. Mol Med Rep 2019; 19(3): 2077-86 **11** Cocco E et al.: Expression of tissue factor in adenocarcinoma and squamous cell carcinoma of the uterine cervix: implications for immunotherapy with hI-con1, a factor VII-IgGFc chimeric protein targeting tissue factor. BMC Cancer 2011; 11: 263 **12** Zhao X et al.: Expression of tissue factor in human cervical carcinoma tissue. Exp Ther Med 2018; 16(5): 4075-81 **13** Perren TJ et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365(26): 2484-96. Erratum in: N Engl J Med 2012; 366(3): 284 **14** Motz GT et al.: Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nat Med 2014; 20(6): 607-15 **15** Socinski MA et al.: Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018; 378(24): 2288-301 **16** Finn RS et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382(20): 1894-905 **17** Makker V et al.: Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol 2020; 38(26): 2981-92

■15