Review Papers

SAKK Young Oncology Academy 2021: Highlights of EHA, ESTRO, ESMO & ASCO

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 2021, 10 mentees successfully concluded the program. As part of the program, the participants write a short review paper about an abstract in 2021.

ESTRO Highlights 2021 – Gastrointestinal Tumors

In this summary, we highlight some of the important gastrointestinal abstracts from the ESTRO 2021 conference.

Surgical tolerability after chemo-radiotherapy: preliminary data of phase III OPERA in rectal cancer

Jean Pierre Gerard from Centre Antoine-Lacassagne, in France, presented the preliminary data of the OPERA trial, a phase III study evaluating the benefit of the addition of a contact brachytherapy boost (CXB) to standard chemoradiotherapy (CRT) on organ preservation rate in rectal adenocarcinoma.[1] 142 patients with distal-middle rectal cancers, T2/T3a-b <5 cm, N0-1 (8 mm), M0, were included over a five-year period starting in mid-2015. All the patients received CRT (45 Gy in 25 fractions) with concurrent capecitabine (825 mg/m^2 BID). Randomization was between boost with either external beam radiotherapy (EBRT), 9 Gy in 5 fractions (standard arm) or CXB, 90 Gy in 3 fractions (experimental arm). In the experimental arm, CXB was administered either before or after CRT for tumor <3 cm and ≥3 cm, respectively. Those who achieved partial response, had total mesorectal excision (TME) while those with complete response were offered watch-and-wait strategy. Patients were assessed at week 14, 20 and 24 using palpation, proctoscopy and MRI. Thirty out of 142 patients received TME, 70% of which had anterior resection; median hospital stay was 9.5 days. Second surgery was performed in 3 patients (10%) and medical toxicity was observed in 4 patients (13%). No death was observed at day 30. Clinical complete response (cCR) at 24 week was 81% in all the 142 patients and 91% in the subset of patients with tumor <3 cm. Overall, 85% of patients scored less than 30 at the «Low Anterior Resection Syndrome» (LARS) score. In conclusion, surgical tolerability after CRT +/- CXB was acceptable with no excess toxicity. For early T2/T3a-b<3 cm, organ preservation was possible in more than 90% of cases. Therefore, non-operative modality should be considered for this subset of patients.

Dose-escalated chemoradiotherapy in esophageal cancer: randomized phase II/III CONCORDE trial

The CONCORDE trial was presented by Giles Crehange.[2] It addresses the question of dose escalation in locally advanced esophageal cancer unsuitable for surgery. 217 patients with stage I-III biopsy-proven esophageal carcinoma were included. All patients received 40 Gy in 20 fractions elective nodal irradiation with concomitant chemotherapy by FOLFOX-4 for 3 courses followed by 3 adjuvant courses. Randomization was between boost with either 10 Gy in 5 fractions (standard arm) or 26 Gy in 13 fractions (experimental arm). Patients were essentially male (81.6%) with stage III (74% vs 26% for stage I-II) squamous cell carcinoma (88.4%), mostly treated with IMRT/VMAT (80.1%). There was no difference in acute (p=0.390), although there were more patientswith grade 3 dysphagia (63% vs. 48.8%) in the experimental arm, and late toxicities (p=0.253), between the two groups. Planned radiotherapy dose per protocol was not delivered in 15.3% in the standard arm and in 23.1% in the experimental arm (p=0.27). No significant differences in the causes of deaths were observed between the 2 groups (p=0.78). Median overall survival was 25.2 months (95% CI: 17.8-NR) in the in the standard arm and 23.5 months (95% CI: 14.5–32.2) in the experimental arm (HR: 1.14, 95% CI: 0.82–1.59; p=0.44). Median overall survival was 19.7 months with 3D conformal (95% CI: 12.4–27.3) and 25.5 months (95% CI: 18.5-NR) with IMRT (p=0.07).

Investigators concluded that dose escalated chemoradiotherapy delivering 66 Gy could be delivered without significant increase in acute and late toxicity and no significant differences in the causes of death between the 2 study arms. Overall

survival was similar between the 2 treatment arms with a trend toward better survival with IMRT. ■

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Highlights of 2021 EHA Congress – Multiple Myeloma

We summarize three studies focusing on immunotherapies in multiple myeloma (MM).

Daratumumab (Dara) plus lenalidomide (R) and dexamethasone (d)

Dara is a monoclonal antibody directed against CD38, an antigen overexpressed in MM cells. Updated results of an interim overall survival (OS) analysis from the phase III MAIA trial were presented.

Newly diagnosed MM (NDMM) patients (pts) ineligible for high-dose chemotherapy and autologous stem cell transplant were randomized 1:1 to Dara-Rd or Rd alone and treated until disease progression or unacceptable safety events. 737 pts with a median age of 73 years (yrs) were enrolled. Baseline characteristics were well balanced. After a median follow-up of 56.2 months, an estimated 5-year OS rate of 66.3% versus 53.1% for Dara-Rd versus Rd was observed (HR: 0.68; p=0.0013). No new safety signals were identified at longer follow-up.

In conclusion, after almost 5 yrs of follow-up, the use of Dara-Rd in NDMM pts ineligible for transplant showed a significant improvement in survival and a favorable benefit-risk profile.

Ciltacabtagene autoleucel (ciltacel), a B-cell maturation antigen (BCMA)-targeted CAR T-cell therapy

The CARTITUDE-2 trial is an ongoing, multicohort, phase II study of cilta-cel, in pts with MM. First results of cohort A, which included MM pts with disease progression after 1–3 prior therapy lines including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), were presented. Treatment consisted of a single infusion of cilta-cel.

The primary objective of this cohort was to assess negativity of residual disease at 10^{-5}. Secondary endpoints included overall response rates (ORR), duration of response (DOR), duration of measurable residual disease (MRD) negativity and safety.

At data cut-off, 20 pts with a median age of 60 yrs and a median of 2 prior therapy lines had received cilta-cel. All pts were exposed to a PI, an IMiD, 95% to alkylating agents, and 65% to Dara before.

ORR was 95%, with 75% or 85% achieving at least a complete (CR) or a very good partial remission (VGPR), respectively. Median time to first response (TTR) was 1 month and median DOR was not reached. All pts with MRD-evaluable samples (n=4) at the time of data cut-off were negative. Regarding adverse events (AEs), cytopenias were very frequent. Cytokine release syndrome (CRS) occurred in 85% of patients (10%≥ grade 3) and immune effector cell-associated neurotoxicity (ICANS) in 20% (all grade 1–2). Both CRS and ICANS were transient.

In summary, a single cilta-cel infusion led to deep and early responses with a manageable safety profile in pretreated MM pts.

Talquetamab (Tal), a novel bispecific antibody

The G protein-coupled receptor family C group 5 member D (GPRC5D) is an orphan receptor that is expressed on malignant plasma cells. Tal is a bispecific antibody that redirects T-cell killing to MM cells by binding to GPRC5D and CD3.

Updated safety and response phase I study results were presented for the patient cohort treated with the recommended phase II dose (RP2D, 405 μg/kgBW s.c.). The cohort consisted of 28 pts with a median age of 61.5 yrs and a median of 5.5 prior therapy lines. The median follow-up was 6.2 months. The ORR at the RP2D was 63%, with 50% reaching at least VGPR, with a median TTR of 1 month that was durable and deepened over time. The most common AEs were cytopenias, CRS (79%; 4% grade 3), and low-grade skin-related AEs.

To sum up, Tal appears to be well tolerated, safe, and effective in heavily pretreated MM pts and a promising new agent. ■

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Highlights of the Virtual ESMO Congress 2021 – Head & Neck Cancer

Immunotherapy is reshaping the way we treat patients in oncology, and has already a firmly established place for multiple indications in cancer. Here we discuss 2 abstracts presented at ESMO 2021, evaluating the possible additional role of immunotherapy for head and neck cancers.

Avelumab-cetuximab-radiotherapy versus standard of care in patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN): randomized phase III GORTEC-REACH trial

This abstract[1] presented by Jean Bourhis evaluates the adjunction of avelumab concomitantly to radiotherapy (RT) and cetuximab and followed for 12 months of avelumab maintenance for LA-SCCHN. Control groups where standard of care cisplatin and RT for cisplatin eligible patients, or cetuximab and RT for cisplatin ineligible patients. The primary endpoint was progression-free survival (PFS) and one of the secondary endpoints was distant metastasis progression (DMP). For the cisplatin-eligible patients, the futility boundary was crossed at 1 year of PFS with a hazard ratio (HR) of 1.27. For the cisplatin-ineligible patients no differences where noted as the 2 years PFS was 31 % in the experimental group versus 44 % in the control group with a p-value of 0.14. On the other hand, the cumulative incidence of DMP at 42 months of follow-up was 5.4 % for the avelumab group versus 14.3 % in the control group (p = 0.007). In summary, this trial is negative and did not show any benefit of adding avelumab in combination to cetuximab and radiotherapy, followed by a 12-months maintenance. We can question the choice of the cisplatin-ineligible control group for which carboplatin is often preferred to cetuximab in daily practice. Moreover, the JAVELIN 100 H&N study recently published,[2] was also negative for the same indication, but a subgroup analysis could identify that patients with a high PD-L1 expression (≥ 25 %) tend to benefit more from the addition of avelumab. This subgroup analysis was not available in this trial.

Nivolumab + ipilimumab vs. EXTREME as first-line treatment for recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): final results of CheckMate 651

In this abstract[3] presented by Athanassios Argiris, the authors studied the efficacy of ipilimumab and nivolumab (IPI NIVO) for 2 years in R/M SCCHN patients, compared to the standard of care EXTREME chemotherapy regiment (5FU, cisplatin/carboplatin and cetuximab). Two primary endpoint were pre-specified: overall survival (OS) and OS for patients with a PD-L1 combined positive score (CPS) ≥ 20. In the full cohort, no benefit of IPI NIVO was found on OS, but in the CPS ≥ 20 group, IPI NIVO performed better with a median OS of 17.6 months compared to 14.6 months in the EXTREME group (p = 0.0469). Careful analysis of the data shows a crossover of 46 % from EXTREME to immunotherapy that may have decreased the benefit of IPI NIVO, but better represents the real world situation. Moreover, as usual for clinical trials evaluating chemotherapy versus immunotherapy, we note an early crossing of the curves. Notably, the IPI NIVO patients seem to have a better self-rated health status as evaluated with patient-reported outcomes, and the treatment-related adverse events (TRAE) were comparable, except for serious TRAE, which were more frequent in the chemotherapy cohort (16 vs 28 %). In the end this study confirms what was known from the KEYNOTE-048 study,[4] as pembrolizumab was also superior to EXTREME for CPS ≥ 20 patients. Of note, in the KEYNOTE-048 study, a combination of pembrolizumab with carboplatin and 5FU was also superior to chemotherapy alone for CPS > 1 patients, but no chemotherapy combination group was present in this abstract.

Conclusion

Both abstracts are not practice changing, but strengthen the position of immune checkpoint inhibitors especially for R/M SCCHN patients, with a new option of IPI NIVO in patients with PD-L1 CPS ≥ 20, even though pembrolizumab monotherapy is already approved, and is expected to be tolerated better. ■

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ESMO/E-AHPBA: Highlights Lower Gastrointestinal Cancer

At the 2021 ESMO and E-AHPBA meetings novel therapeutic approaches for metastatic colorectal cancer (mCRC) have been presented. This short summary will explore the potential advances in interventional and surgical treatment options of this condition.

Transarterial radioembolization (TARE) in non resectable mCRC

Mary F. Mulcahy presented results from the EPOCH-trial.[1] In this phase III trial 428 patients with progression under first-line chemotherapy (CTX) were randomized to receive either Y^{90} glass microspheres (Y^{90}) TARE and CTX, or CTX alone.[2] A biological agent was added individually. The most important inclusion criteria were unresectable unilobar or bilobar disease, the ability to receive irinotecan- or oxaliplatin-based CTX and absent extrahepatic metastases. Primary endpoints were progression-free survival (PFS) and hepatic PFS (hPFS). PFS (8.0 vs. 7.2 months, p=0.0013) and hPFS (9.1 vs. 7.2 months, p<0.0001) were significantly longer with Y^{90}+CTX compared to CTX alone. Key characteristics of interest associated with a PFS and hPFS benefit were resected primary, *KRAS* mutation status, addition of a biologic agent, low hepatic tumour burden (<3 lesions; PFS ≥10 to <25% and hPFS <25%), as well as the origin of the primary tumour (both sides in hPFS and left sided in PFS). However, there was no improvement of the secondary endpoint overall survival (OS) after addition of Y^{90}. Therefore, despite the promising improvement of PFS, the addition of Y^{90} to CTX does not bear any clinical relevance at this point and is unlikely to affect everyday medical practice.

This report is largely in line with previous randomized controlled trials that explored the role of TARE or the analogous selective internal radiotherapy (SIRT) in the treatment of patients with liver metastases from colorectal cancer.[3–5] In those three studies that included a total of 1677 patients, TACE/SIRT were applied in addition to CTX using both older and modern therapeutic regimes in a first- or second-line setting. All showed an improved hPFS but failed to demonstrate a significant effect on OS.

Despite these results, it may be possible that through careful selection, the concept of Y^{90}+CTX can be further refined. Therefore, studies investigating the role of TARE/SIRT on OS in individuals who are most likely to benefit from their addition to modern oncological treatment regimens should be encouraged.

Simultaneous portal and hepatic vein embolization (PVE/HVE) in mCRC

Remon Korenblik presented the results from the DRAGON Collaborative.[6] Seven centres retrospectively contributed their cases of major liver resection after PVE/HVE or PVE in initially unresectable mCRC patients because of inadequate future liver remnant (FLR). The co-primary endpoints were resectability, FLR hypertrophy and major complications (Clavien-Dindo >IIIA). 39 PVE/HVE and 160 PVE cases were included. Resectability after PVE/HVE (90% vs. 68%, p=0.007) and FLR hypertrophy (59% vs. 48%, p=0.02) were higher than in PVE alone. There was no significance in 90-day-mortality (3% vs. 16%, p=0.15) and major complications (26% vs. 34%, p=0.55). Conclusively, these results suggest that PVE/HVE leads to increased liver growth and resectability compared to the PVE alone group.

PVE is shown to be an already established therapy preparation for tumours to be resected with initially insufficient FLR.[7] HVE was shown to have comparable morbidity and mortality peri- and postoperatively.[8] The aim of combining PVE and HVE is to achieve hypertrophy more quickly and thus enable early surgery. In the DRAGON 1 trial, the feasibility and safety of combined PVE/HVE will be investigated and the 25 centres will be trained to create optimal conditions for the DRAGON 2 trial (randomized comparative prospective trial).

Taken together, PVE/HVE shows promise as a therapeutic option in the curative setting of hepatic mCRC. In the upcoming prospective trials of the DRAGON Collaborative, the potential superiority of combined PVE/HVE over PVE alone will be investigated. ■

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ESMO 2021 Highlights – Genitourinary Cancer

This is a summary of studies presented at this year's ESMO Congress focussing on genitourinary cancer.

PEACE-1

Karim Fizazi presented this phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer (mCSPC).[1] 1173 Patients with mCSPC were randomized to either standard of care (SOC) or SOC and abiraterone and/or local radiotherapy. The SOC changed during recruitment from ADT alone to ADT and Docetaxel by the results of STAMPEDE and LATITUDE. There was no interaction between abiraterone and radiotherapy regarding overall survival (OS). Therefore, the two abiraterone arms were pooled. Coprimary endpoints were radiographic progression-free survival (rPFS) and OS. The results of 710 patients who received ADT and Docetaxel as SOC were presented. The data for radiotherapy are still immature. In the triple therapy group mOS was not reached vs. 4.4 years (HR: 0.75, 95% CI: 0.59–0.96, p=0.021) in the ADT and docetaxel group. The subgroup analyses in patients with high volume disease showed a significant and clinical meaningful prolongation of OS with an improvement from 3.5 to 5.1 years (HR: 0.72, 95% CI: 0.55–0.95) when adding abiraterone to ADT and docetaxel. Notable is that the difference remains even when 81% of the patients in the SOC group received a next hormonal agent in a later line, emphasizing the benefit of a more intensive therapy at an earlier stage even more.

The results of the PEACE1 trial are practice changing regarding the triple therapy of ADT, Docetaxel and abiraterone in men with de novo mCSPC with high volume disease.

Vesper Trial

In this open label phase III trial by the French Study Group, 500 patients with muscle-invasive bladder cancer were randomized to receive 6 cycles of dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) every 2 weeks or 4 cycles of gemcitabine and cisplatin (GC) every 3 weeks before or after cystectomy. The primary endpoint was PFS after 3 years.

A trend towards improved PFS in the dd-MVAC arm was found in the overall population. In the neoadjuvant treatment group, the 3-year PFS rate was significantly higher for dd-MVAC vs GC with 66% vs. 56% (HR: 0.70 (95% CI: 0.51–0.96) p=0.025). The secondary endpoint OS is not yet mature but preliminary data point towards a benefit with a HR: 0.66. Notable is the higher rate of side effects with only 60% in the ddMVAC group completing the 6 cycles.

In conclusion, ddMVAC is an option for very fit and highly motivated patients as a neoadjuvant treatment of muscle invasive bladder cancer.

SAKK 01/10

The current standard of care in seminoma IIA/B is 3–4 cycles platin-based chemotherapy or radiotherapy of the paraaortal/pelvic lymph nodes, with cure rates exceeding 90%. The high cure rates come at the price of a higher rate of short- and long-term toxicity like mucositis, febrile neutropenia, renal impairment, polyneuropathy, secondary malignancies.[2]

The investigators intended to lower the risk of short- and long-term toxicity but preserve the high efficacy. This phase II trial treated 116 patients with 1 cycle of carboplatin AUC 7, followed by involved-node RT (IIA: 30 Gy; IIB: 36 Gy).[3] Primary endpoint was 3-years PFS rate with a target of 95% (lower limit CI 90%). 3-year PFS rate is 93.7% (90% CI [88.5%, 96.6%]), IIA: 95.2% (90% CI [85.5%, 98.5%]), IIB: 92.6% (90% CI [85.1%, 96.4%]). During treatment, only 8,4% grade 3 or grade 4 adverse events occurred, mainly neutro- and thrombocytopenia, and 51,7% had no adverse event at all. No adverse event of any stage was present after treatment was completed.

The regime is less toxic than the standard of care, while still providing very high cure rates. In case of recurrence, chemotherapy as a curative option is still feasible.

In conclusion, especially in the seminoma stage IIA, the the de-escalated treatment regimen used in this trial appears as a good treatment option. ■

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Literature:

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Highlights of ESMO & ASCO 2021 on Upper Gastrointestinal Malignancies

The worldwide burden of upper gastrointestinal malignancies is substantial. In 2020 gastric cancer (GC) was the 5th most frequently diagnosed cancer and the 4th leading cause of cancer death.[1] Similarly esophageal cancer (EC) ranked 7th in terms of incidence and 6th in terms of mortality.[1]

Adenocarcinomas (ADC) and squamous cell carcinomas (SCC) are the most frequent histologies; 90 % of GC are ADC, and the incidence of gastro-esophageal junction (GEJ) ADC has been rising in westernized societies.[2,3] Platinum-based chemotherapy has been the standard of care for the past decade for patients with metastatic, HER2-negative GC/GEJ ADC.[3,4] However, survival has remained dismal, with a median OS of less than 12 months.[4,5] Likewise, outcomes of patients with stage II/III EC/GEJC and non-complete pathologic remission after tri-modality therapy (i. e. chemoradiation & surgery) are poor with high recurrence rates.[6–8] Until last year there were no established adjuvant treatments for the 70–75 % of patients that present with incomplete pathologic response, and close observation is the only alternative.[6–9] CM-649 and CM-577 have addressed these relevant unmet medical needs and were presented at the Annual Conferences of ESMO & ASCO 2021, respectively.

CheckMate 649

CM-649 is a phase III, 1st-line, 3-arm RCT that randomized patients with locally advanced, unresectable or metastatic GC/GEJ ADC to standard chemotherapy with CAPOX or FOLFOX versus chemo plus nivolumab (NIVO) versus double immunotherapy with NIVO plus ipilimumab (IPI).[5] The study met both its primary endpoints demonstrating superiority for the NIVO/chemotherapy arm vs chemotherapy alone in terms of OS (HR: 0.7, 95 % CI: 0.61–0.81) and PFS (HR: 0.79, 95 % CI: 0.71–0.88) for patients with CPS ≥ 5. However, the addition of NIVO did not improve OS or PFS for patients with CPS < 5. The NIVO & IPI arm was closed early due to high toxicity and lack of efficacy. NIVO & IPI did not provide any meaningful improvement in OS and was inferior to chemotherapy in terms of PFS. However, MSI-high patients demonstrated superior OS, PFS and ORR, both with NIVO/chemo and NIVO & IPI vs. chemotherapy alone.

CheckMate 577

CM-577 is a phase III trial randomizing patients with stage II/III E/GEJ ADC (71 %) or SCC (29 %) who underwent neoadjuvant chemoradiation and R0 resection, but with incomplete pathologic response, to receive 1 year of adjuvant NIVO or placebo. CM-577 met its primary endpoint demonstrating a DFS benefit (HR: 0.69, 95 % CI: 0.56–0.86) for adjuvant NIVO, and a distant metastases-free survival benefit (HR: 0.74, 95 % CI: 0.6–0.92). DFS was improved both for patients with ADC and SCC, however, the benefit was more pronounced for SCC. Similarly, the benefit of adjuvant NIVO was more important in patients with esophageal tumors compared to those with GEJ cancer. In contrary, DFS was not improved for patients with CPS < 5. OS data are not mature yet, however, it is hoped that adjuvant NIVO results in an improvement of the cure rate and does not just postpone recurrence.

Conclusion

In conclusion, 1st-line NIVO/chemotherapy provided superior OS and PFS in patients with locally advanced unresectable or metastatic GC/GEJ ADC and a CPS ≥ 5. Also, adjuvant NIVO is effective for patients with EC/GEJC who have an incomplete pathologic response after tri-modality therapy, especially for those with CPC ≥ 5 and SCCs. ■

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Review Paper ESMO 2021 Highlights: Gynecological Cancer

In the last decades, we experienced a dramatic change in the evolution of cervical cancer (CC) history. Due to screening and more recently vaccination, the incidence of the disease decreased dramatically in the western world and early stages diagnosis is often preventable and curable.[1,2] Nevertheless, the prognosis at late stages remains desolate with a 5-years overall survival (OS) of less than 20 %[3] and around one third of the patients die from their cancer in Switzerland.[4]

For patients with recurrent or metastatic (RM) disease, chemotherapy with platinum-based regimens was until recently the only treatment option, with a median OS of 13.3 months.[5–7]

Since 2014, the addition of the antiangiogenic bevacizumab allowed the improvement of the median OS up to 17 months.[8]

The data presented at ESMO Congress 2021 claim to be a new milestone in the management of this aggressive disease by the introduction of the immunotherapy in 1st and 2nd line treatment of RMCC. We selected two studies whose significant results are going to determine a change in the clinical practice.

KEYNOTE-826[9]

In this phase III study, 617 patients with RMCC, chemo-naive, were randomized to receive pembrolizumab vs. placebo in addition to the standard 1st-line paclitaxel-platinum chemotherapy with or without bevacizumab.

Patients treated with pembrolizumab had a statistically significant improvement in OS when compared to placebo (24.4 months vs. 16.5 months, respectively) and a significantly longer progression-free survival (PFS) (10.4 vs. 8.2 months, respectively). The benefit was observed in PD-L1+ population, but also in all comers. The response rate and duration were improved. Immune-related adverse events rate of grade ≥3 was 11.4 %.

This is the first randomized phase III study demonstrating an OS benefit by the addition of immunotherapy to the 1L chemotherapy in RMCC. The addition of pembrolizumab to chemotherapy will probably be new standard of care.

EMPOWER-Cervical 1/GOG-3016/ ENGOT-cx9[10]

This phase III trial investigated the anti-programmed cell death (PD)-1 cemiplimab vs. investigator's choice single-agent chemotherapy (IC chemo) in 608 patients with CC resistant to platinum-based chemotherapy.

The study met its co-primary endpoints with a significant improvement of median OS in the squamous cell carcinoma and in total population, in whom cemiplimab reached 12.0 months vs. 8.5 months in the control arm.

The benefit was especially obvious in cancers expressing PD-L1. Immune-related adverse events rate of grade ≥3 was 6 %.

This study and the previously presented phase II KEYNOTE-158 trial[11] reinforce the role of PD-1 inhibitors as monotherapy in the treatment of pretreated patients.

Conclusions

The results of these two randomized phase III trials introduce definitely immunotherapy as a key player in the treatment of RMCC. Several other trials are ongoing. PD-L1 expression allows selecting the CC patients, who benefit most from immune checkpoint inhibitors. ■

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Highlights of EHA Congress 2021: Acute Leukemia

While new and immediately practice-changing clinical studies were scarce at this year's EHA meeting, we are presenting three interesting, yet diverse abstracts aiming to improve therapy today, tomorrow and thereafter.

Home-based intensive chemotherapy in patients with acute myeloid leukemia (AML)

Intensive chemotherapy remains the mainstay of induction therapy in acute myeloid leukemia. Traditionally, patients are hospitalized for weeks until blood count recovery. In this Danish multi-center study by Nørskov et al.[1] 104 patients received this therapy at home via a CADD pump after undergoing an educational program and combined with visits in the outpatient clinic every 2–3 days during neutropenia.

264 treatments were started as an outpatient therapy with patients being at home in 67 % (1069 days). 64 treatment cycles were solely managed in the outpatient clinic (24 %). Although patients had to come to clinic for non-serious adverse events correlated with the pump system 18 times, no serious adverse events occurred. Patients felt safe and reported improved quality of life and wellbeing.

In conclusion, this study shows that induction chemotherapy is safe and feasible in the setting of a selective patient population with adequate teaching as well as a trained team of nurses and doctors.

Interim results of a phase II study of blinatumomab plus ponatinib for philadelphia positive acute lymphoblastic leukemia (Ph+ ALL)

The combination of the bispecific anti-CD19/CD3 antibody blinatumomab with the tyrosine kinase inhibitor (TKI) dasatinib shows impressive response rates in newly diagnosed patients with Ph+ ALL.[2] In this study, Short et al.[3] investigate the efficacy of a combination of blinatumomab and ponatinib in the frontline and relapsed/refractory setting for patients Ph+ ALL and CML in blast phase.

A complete remission (CR) was achieved in 96 % (partially with incomplete platelet recovery) and 79 % had a complete molecular response. 19 out of 20 patients in the frontline setting are in ongoing response without hematopoietic stem-cell transplantation with a median complete CR of 6 month (1–33 month).

In summary, this study is a proof of concept for the combination of blinatumomab with available TKI as induction therapy in Ph+ ALL, which is likely to be practice-changing soon.

Phase Ib results of the first-in-class anti-CD47 antibody magrolimab with azazitidine in AML

With still limited therapeutic options for elderly or unfit patients with AML, improvement is urgently needed. Magrolimab is an antibody blocking the «do not eat me» CD47 signal overexpressed in AML and several other cancers, thereby leading to increased phagocytosis. This is especially interesting as targeted therapies have almost exclusively involved cells of the adaptive immune system so far.

Sallman et al. presented first data of a combination therapy of magrolimab with azazitidine in patients with AML and high risk myelodysplastic syndrome (MDS) at ASH last year,[4] with an ongoing phase III trial in higher risk MDS presented at EHA this year.[5]

The preliminary data of 64 patients shows an overall response rate of 63 % with a CR rate of 42 %. The median time to response was only ~ 2 months and, importantly, not negatively affected by *TP53* mutations.

Although this is still early phase data, magrolimab is a promising new option for elderly/unfit AML/MDS patients in the future. ■

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Oncology Highlights of the Year 2021 – Lung Cancer

One of the highlights of this year's congresses was the presentation of the IMpower 010 trial.

IMpower 010 is an ongoing phase III trial with a randomised, multicentre, open-label design, investigating the role of atezolizumab after adjuvant cisplatinum-based chemotherapy (chemo) in patients who underwent complete resection of a stage IB-IIIA non-small-cell lung cancer (NSCLC).[1,2]

1005 patients were randomised 1 : 1 into to receiving atezolizumab versus surveillance following 1–4 cycles of chemo after curatively intended resection. The primary endpoint was disease-free survival (DFS), which was tested hierarchically:

1. in the stage II-IIIA population with PD-L1 expression of ≥ 1 % (on tumour cells (TC)
2. in all stage II-IIIA patients
3. in the intention to treat population (ITT), i. e. all patients stage IB-IIIA.

Secondary endpoints include overall survival (OS) in the ITT and DFS in the PD-L1 TC ≥ 50 % stage II-IIIA population.

In the planned interim analysis DFS was significantly and meaningfully improved in stage II-IIIA PD-L1 ≥ 1 % cases and all randomised stage II-IIIA cases resulting in a 34 % and 21 % risk reduction in the risk of disease recurrence or death (table 1). The required significance level for a DFS benefit was not reached in the ITT population (alpha spending for hierarchical testing). DFS and OS data collection are ongoing.

The effect of adjuvant atezolizumab seemed to depend on the expression of PD-L1: for stage II-IIIA patients, whose tumours showed a PD-L1 expression of ≥ 50 % the unstratified HR was 0.43 (95 % CI: 0.27–0.68). In an exploratory post-hoc analysis on the stage II-IIIA population with PD-L1 expression of 1–49 % the unstratified HR was 0.87 (95 % CI: 0.60–1.26), whereas a HR of 0.97 was found for patients with stage II-IIIA disease and PD-L1 < 1 % (95 % CI: 0.72–1.31).

Further exploratory endpoints were reported, such as the disease-relapse pattern (locoregional only vs. distant only vs. locoregional and distant): there seemed to be no effect of atezolizumab on the relapse pattern.

A small cohort of *EGFR* mutated cases (n = 43) were included in the trial: in stage II-IIIA patients, whose tumours showed a PD-L1 expression ≥ 1 %, DFS appeared to be similar in patients with *EGFR*-positive, *EGFR*-negative and *EGFR*-unknown status. However, at this time – following the results of the ADAURA trial 3 – Osimertinib remains the first treatment choice for *EGFR*-positive NSCLC.

Conclusion

The IMpower 010 trial is the first positive phase III trial of adjuvant immunotherapy after surgical resection and adjuvant chemo in patients with stage IB-IIIA NSCLC. This effect seems to be predominantly carried by the stage II-IIIA cases with a PD-L1 expression ≥ 50 %, atezolizumab could become standard of care in this setting. For patients with tumours expressing PD-L1 in 1–49 % of TC, however, the role of PD-L1 will remain a topic of discussion and more mature data will be needed to use this biomarker to tailor individual treatment approaches for NSCLC patients. Furthermore, although DFS can facilitate a timely implementation of new therapies, it has not been established as a reliable surrogate marker for OS in NSCLC; OS remains the gold standard for establishing new standards of care in the adjuvant setting. ■

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	stage II-IIIA, PD-L1 ≥ 1% (median follow-up 32.8 mo)		stage II-IIIA, all-randomised (median follow-up 32.2 mo)		stage IB-IIIA, ITT (median follow-up 32.2 mo)	
	atezolizumab (n=248)	control (n=228)	atezolizumab (n=442)	control (n=440)	atezolizumab (n=507)	control (n=498)
median DFS	NE (36.1, NE)	35.3 (29.0, NE)	42.3 (36.0, NE)	35.3 (30.4, 46.4)	NE (36.1, NE)	37.2 (31.6, NE)
stratified HR (95 % CI)	0.66 (0.50, 0.88)		0.79 (0.64, 0.96)		0.81 (0.67, 0.99)	
P value	0.004		0.02		0.04	

Tab. 1: Disease-free survival in the atezolizumab and control group. Data cut-off 21/01/2021. NE, not estimable. ITT, intention to treat