SAKK Kompetenzzentrum
Effingerstrasse 33
CH-3008 Bern
communication@sakk.ch

Young Oncology Academy 2022
Review Papers

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, radio-oncology, urology, gynecology or dermatology, who would like to actively contribute to clinical and translational research.

For almost one year, the participants of the academy are under the guidance of a renowned faculty member. A particular focus lies on providing the young talents with insights into the successful development, management, execution and publication of a clinical trial. As part of the academy, participants also attend the ESMO congress, or the EHA (for hematologists) or ESTRO (for radio-oncologists) congresses, respectively.

In 2022, 9 mentees successfully concluded the program. As part of the program, the participants wrote a short review paper about an abstract in 2022.

Contents

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ESMO 2022 highlights on prostate and urothelial cancer

In the following summary we present two of the most relevant abstracts on prostate and urothelial cancer presented at the ESMO 2022 congress.

Duration of androgen deprivation therapy after radical prostatectomy and radiation therapy: results from the RADICALS-HD study

Radicals HD was a phase III trial enrolling patients with prostate cancer (PCa) at high risk of relapse after radical prostatectomy.[1] Patients were initially randomized 1:1 to either adjuvant or salvage radiation therapy (RT), and subsequently 1:1:1 to either no androgen deprivation therapy (ADT), 6 months of ADT or 24 months of ADT. For several reasons, this complex randomization was soon replaced by a 2 arm 1:1 randomization (*figure 1*) [2]. Patients were either randomized to no ADT vs 6 months ADT, or 6 months ADT vs 24 months ADT. The primary endpoint was metastasis-free survival (MFS). In the part of the study evaluating no vs 6 months ADT, 1480 patients were enrolled; around 60% of patients had ypT3/4, 3% ypN1 and 11% Gleason score (GS)≥8 PCa. 10-years MFS was 79% in the no ADT vs 80% in the 6 months ADT arm (HR 0.89, 95% CI 0.69-1.14, p-value 0.35). In the part of the study evaluating 6 months ADT vs 24 months ADT, 1523 patients were enrolled; approximately 72% of patients had ypT3/4, 8% ypN1 and 29% GS≥8 PCa. 10-years MFS was 72% in the 6 months ADT vs 78% in the 24 months ADT arm (HR 0.77, 95% CI 0.61-0.97, p-value 0.03). The authors concluded that 24 months ADT increases MFS in PCa patients with risk factors for relapse receiving either adjuvant or salvage RT in comparison with 6 months ADT. Data on overall survival are still immature and awaited to draw definitive conclusions.

Enfortumab Vedotin (EV) in combination with pembrolizumab in locally advanced or metastatic urothelial cancer: the EV-103 Cohort K study

The first line treatment for patients with cisplatin-ineligible, locally advanced or metastatic urothelial cancer (la/mUC) is represented by carboplatin-gemcitabine or, in selected cases, immunotherapy (atezolizumab or pembrolizumab).[3] However, modest overall response rates (ORR) and overall survival (OS) from both therapies urge the need for new treatments.[3] EV-103 Cohort K was a phase 2 randomized non-comparative trial evaluating the efficacy of EV monotherapy or in combination with pembrolizumab (pembro) in cisplatin ineligible la/mUC.[4] A total of 149 patients were randomized 1:1 to EV (1.25 mg/kg) as monotherapy on days 1 and 8 every 3 weeks or EV with pembro (200 mg day 1) (*figure 2*). The primary endpoint was ORR by blinded independent central review. The confirmed ORR was 64.5% for EV/pembro combination compared to 45% for EV monotherapy. Moreover, 85.7% of the ORRs from EV/pembro were recorded in the first 9 weeks from the beginning of therapy and 97% of patients receiving EV/pembro had some reduction in tumor volume. The ORR was independent from PD-L1 expression. Most common treatment related adverse events (TRAEs) were fatigue, peripheral sensory neuropathy and skin reactions. Serious and lethal TRAEs occurred in 23.7% and 3.9% patients in the EV/pembro arm vs 15% and 2.7% in the EV monotherapy group,

respectively. Nonetheless, the main reason for suspending treatment was disease progression and not TRAEs. The authors concluded that the combination of EV and pembro leads to a high ORR and rapid responses in patients with cisplatin-ineligible la/mUC. Therefore, this combination treatment has the potential to become the first line therapy of choice in this patients' population. Definitive results are expected to derive soon from an ongoing phase III trial (EV-302) assessing the combination of EV and pembro compared to platinum-based chemotherapy.

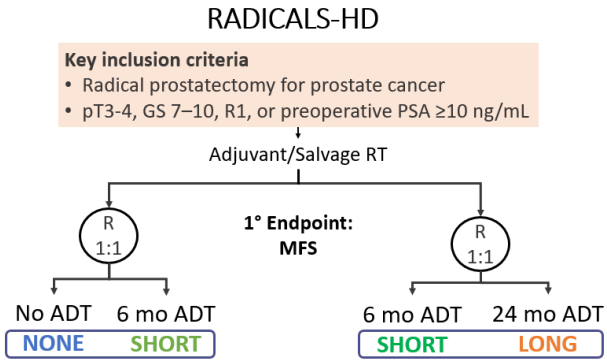

Figure 1: Trial design of the RADICALS HD study, adapted from Park et al. ESMO 2022, LBA 9. R1 = positive surgical margins; GS = Gleason score; ADT = androgen deprivation therapy; PSA prostate-specific antigen; MFS = metastastis-free survival.

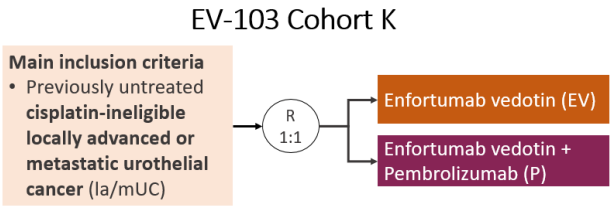

Figure 2: Trial design of the EV-103 Cohort K, adapted from Rosenberg et al. ESMO 2022, LBA 73.

Authors

Author: Dr. med. **Luca Afferi**, Department of Urology, Cantonal Hospital Lucerne LUKS
Mentor: PD Dr. med. **Richard Cathomas**, Division of Oncology/Hematology, Cantonal Hospital Graubünden

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Highlights of EHA 2022 regarding aggressive Lymphoma

In this summary, we highlight four important abstracts on aggressive lymphomas presented at the EHA conference 2022 in Vienna.

Two new bispecific antibodies in the treatment of R/R aggressive B- cell lymphoma: Epcoritamab and Glofitamab

Catherine Thieblemont and Michael Dickinson each presented phase II studies of two new bispecific antibodies: epcoritamab, an anti-CD20xCD3 1:1 IgG1 antibody and glofitamab, an anti-CD20xCD3 2:1 IgG1 antibody (1 and 2). These two trials are very similar in the design and studied a comparable population of heavily pretreated R/R aggressive B-cell lymphoma, including CAR-T cell pretreatment in one third of the cases.

The results are very similar in both studies: overall response rate (ORR) 63 % for epcoritamab and ORR 51.6 % for glofitamab, and a complete remission (CR) rate of 39 % in both studies. Concerning the side effects, cytokine release syndrome (CRS) was the most common adverse event (49.7 % for epcoritamab and 63 % for glofitamab), but mostly grade 1 and 2.

The main difference between the two substances was the way of administration: while epcoritamab is administered subcutaneously and given until progression, glofitamab is given intravenously in a fixed duration of twelve cycles. To reduce the CRS induced by glofitamab, a pretreatment with obinutuzumab and a step-up dosing during the first cycle is used.

In summary, these two phase II studies with the bispecific antibodies glofitamab and epcoritamab show promising results in heavily pretreated patients with R/R aggressive B-cell lymphoma. Studies with bispecific antibodies in early lineages and in combination with chemoimmunotherapy are ongoing.

DA-EPOCH-R appears to have similar efficacy compared to R-CODOX-M/R-IVAC, with a better toxicity profile in Burkitt lymphoma

Two different chemotherapies, R-CODOX-M/R-IVAC and DA-EPOCH-R were compared in a phase III academic trial in patients with newly diagnosed Burkitt lymphoma (3). Only high risk cases were included defined as elevated levels of LDH, WHO Performance Score (PS) ≥ 2, stage III/IV or mass ≥ 10 cm. Patients received either two cycles of R-CODOX-M & R-IVAC or 6 cycles of DA-EPOCH-R. After randomization of cumulative 84 patients, the study had to be closed prematurely due to slow recruitment. After a median observation time of 19.1 months, a similar complete metabolic remission (CMR) was achieved in both arms (66 vs 65%), so the study failed to show an improved outcome by using DA-EPOCH-R. However, this regimen was better tolerated with lower incidence of infections, transfusion rates and hospitalization days.

The SHINE study: The addition of Ibrutinib to standard chemotherapy results in prolonged Progression-free survival (PFS) in elderly patients with de novo Mantle Cell Lymphoma

Michael Wang presented a randomized phase III trial, investigating whether the addition of the bruton's tyrosine kinase inhibitor ibrutinib to standard chemotherapy with bendamustine and rituximab leads to an improvement in PFS in an elderly population with newly diagnosed mantle cell lymphoma (4).

The primary endpoint of this study was met, ibrutinib in combination with standard chemoimmunotherapy significantly prolonged PFS (80.6 months versus 52.9 months, HR 0.75, p=0.01), whereby OS was similar in both groups, with median OS not to be reached yet.

Ibrutinib is an established medication in the second line treatment of mantle cell lymphoma. Whether a PFS benefit in the absence of demonstrated OS difference justifies the addition of ibrutinib in first line, is questionable.

Authors

Author: Dr. med. **Martina Bertschinger**, Cantonal Hospital Winterthur
Mentor: Prof. Dr. med. **Urban Novak**, Inselspital / University Hospital of Bern

Literature

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ESMO 2022 highlights: Immunotherapy

Despite the multiples success of immunotherapy in the treatment of various solid tumors, their efficacies vary, and only subsets of cancer patients can benefit from them. Therefore, new therapeutic modalities are urgently needed. Among them, active immunotherapy (cancer vaccine) is very promising as advances in biotechnology provide tools to craft innovative approaches. Here we discuss, the Maxi-Vax study presented at the ESMO annual meeting 2022 poster session.

MaxiVax: phase I study testing the feasibility, safety and efficacy of cell-based vaccine using encapsulation cell technology

Preclinical data have showed that sustained, local delivery of low doses of Granulocyte macrophage-colony stimulating factor (GM-CSF) by irradiated, genetically engineered tumor cells at the immunization site leads to potent, specific, long-lasting anti-tumor immunity in several tumor types (1).

The MaxiVax technology (MVX-ONCO-1) is a combination product of a human cell line genetically engineered in vitro to secrete GM-CSF protected within a biocompatible microcapsule (cell encapsulation technology) and lethally irradiated autologous tumor cells. These three components are already well known and clinically tested. However, the combination of the three elements as an active, personalized cancer immunotherapy is novel and has not yet been investigated in patients.

The objective of the study (2) was to assess the safety and tolerability of 6 vaccine doses of MVX-ONCO-1, administered subcutaneously (injections and capsule implantations), in patients with a progressive advanced metastatic solid tumor who are not or not any longer amenable to any standard therapy of their tumor disease. The primary endpoints were safety and feasibility and secondary endpoints to measure anti-tumor responses and immune monitoring.

The vaccine was manufactured individually for each patient. One treatment consisted in the subcutaneous implantation of two capsules and the injection of 4 millions of autologous tumor cells (previously harvested with a biopsy or minimally invasive surgery). In total, patients received 6 administrations over 8 weeks.

34 patients were enrolled and treated in the study, most of them had sacral chordoma and serous ovarian carcinoma. Preparation of irradiated autologous tumor cells and encapsulated MVX cells was achieved in 30/34 pts (88%). Of the 34 enrolled patients, 29 (85.3 %) completed the full course of study treatment, consisting of six administrations of MVX-ONCO-1. 5 patients did not complete the study treatment because of death or disease progression. All 34 patients experienced at least one adverse event (AE). The most frequently reported AE was defect of the device (in 15 patients, 44.1%; bent capsule at explantation or broken suture string) followed by hematoma at the implant site in 11 patients (32.4%) and fatigue in ten patients (29.4%). No patients experienced any G3 or G4 treatment-related toxicities.

Disease control was observed in 20/34 patients (18/34 stable disease and 1/34 partial response, 1/34 complete response). Prolonged survival in 2/2 recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) patients was observed and correlated with an increase of IFN-y secretion (measuring by ELISPOT) during treatment compared to baseline.

In conclusion, production and application of MVX-ONCO is feasible, safe, and well-tolerated. Preliminary efficacy data showed immune stimulation, intriguing prolonged survival, and tumor control including partial and complete response. Single-agent efficacy Phase II study is ongoing in patients with recurrent/metastatic HNSCC.

Author

Author: Dr. med. **Natacha Bordry**, University Hospital Geneva HUG
Mentor: Prof. Dr. med. Dr. phil. nat. **Sacha Rothschild**, Cantonal Hospital Baden AG

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ESMO 2022 Highlights: Lower GI

NICHE-2 study

Immune checkpoint inhibition (ICI) constitutes standard of care for metastatic colorectal cancer (CRC) with microsatellite instability (MSI) [1, 2]. We learned from the phase I NICHE-1 study published in 2020, that in the neoadjuvant setting, a short course of ICI with ipilimumab and nivolumab leads to profound pathological responses in a majority of patients with MSI CRC.

NICHE-2 study, presented at ESMO 2022 in a Presidential Symposium (LB abstract 7), is a phase II study based on NICHE-1 findings. NICHE-2 treated 112 patients with locally advanced colorectal MSI tumors with a single dose ipilumumab and two doses nivolumab followed by surgery within 6 weeks. Co-primary endpoint was safety and 3 year disease-free survival (DFS). Only 4% of patients experienced grade ≥3 adverse events and 98% of patients underwent timely surgery with 100% R0 resections. Three year DFS is expected next year but at a 13.1 month median follow-up, no recurrence was observed so far. Impressively, major pathological response was observed in 95% of patients (!), and 67% had a complete pathological response, with even higher rates in patients with MSI related to Lynch syndrome compared to sporadic mismatch-repair deficiency.

In conclusion, NICHE-2 showed that with a short course of ICI, a large fraction of patients achieve major and complete pathological responses with low toxicity, even with locally advanced tumors. Response rates are higher than what is observed in the metastatic setting, and confirms impression that using ICI in the neoadjuvant setting, with tumor in place, constitutes a unique opportunity. This study will be practice changing and opens the question if a fraction of these patients still need surgery or can benefit from a follow-up has seen in rectal cancer [3]. It also demonstrates the incredible power of immunotherapy if used at the right time, in the correct population, and with a robust biomarker to predict response.

FRESCO-2 trial

Options for treatment of patients with advanced and refractory CRC are limited and this population constitutes an unmet medical need. In the third line setting, treatment with regorafenib and TAS-102 provides only modest clinical benefit at the cost of a relatively high toxicity[4, 5]. Patients are often fit enough and willing to receive other lines of treatment but options are limited.

In this context, the FRESCO-2 study was presented at ESMO 2022 (LB abstract 25), opening new options in this clinical setting. FRESCO-2 is a phase III randomized trial evaluation the efficacy and safety of fruquintinib, a potent VEGF1-3 inhibitor, in heavily pre-treated patients with metastatic CRC. Treatment with fruquintinib showed a statistically and clinically relevant gain in both PFS (1.9 months, HR 0.321) and OS (2.6 months, HR 0.662). Toxicity profile was acceptable and as expected from a VEGF inhibitor, with mainly hypertension and abdominal symptoms such as diarrhea and anorexia.

In conclusion, fruquintinib constitutes a novel treatment option, in patients with advanced and heavily pretreated metastatic CRC (including with TAS-102 and regorafenib), with a typical and acceptable TKI toxicity profile.

Authors

Mentee: Dr. med. **Nils Degrauwe**, Department of Oncology, Lausanne University Hospital CHUV

Mentor: Prof. Dr. med. **Ulrich Güller**, Klinik für Medizinische Onkologie und Hämatologie, Spital STS AG Thun

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Highlights of 2022 EHA Congress – Myeloproliferative Neoplasms

Myeloproliferative Neoplasms (MPNs) are clonal hematopoietic stem cell disorders that have a proliferative nature and a variable tendency to transform into myelofibrosis and acute leukemia. In addition to symptom relief and prevention of thromboembolic as well as bleeding events, the treatment goal of disease modification has become increasingly important in recent years. We summarize two abstracts focusing on the treatment of Polycythemia vera (PV) and Primary Myelofibrosis (PMF).

Ropeginterferon alfa-2b (Ropeg-IFNα2b) versus hydroxyurea (HU) in patients with PV

The randomized, phase 3, open-label PROUD-PV trial and its extension phase 3b CONTINUATION-trial compared Ropeg-IFNα2b to HU in patients with early-stage PV. While the positive results after 3 years led to the approval of Ropeg-IFNα2b (Besremi®) for PV (in CH: PV without symptomatic splenomegaly), the final analysis after 6 years focused on longer-term benefits. With Ropeg-IFNα2b a significantly higher number of patients achieved a complete hematologic response (p=0.02) and molecular response (p<0.0001). Importantly, the median JAK2V617F allele burden declined continuously and 20.7% of patients achieved an allele burden <1% compared to only one patient with HU, indicating a disease modifying potential. Moreover, survival in the abscence of disease progression or thromboembolic events was significantly higher with Ropeg-IFNα2b (5.3%) compared to HU (16.2%). More patients treated with Ropeg-IFNα2b (81.4%) did not require phlebotomies to maintain a hematocrit <45% compared to HU (60%) and fewer disease-related symptoms were reported with Ropeg-IFNα2b. In addition, the rate of adverse events was balanced between the study arms.

In summary: Long-term Ropeg-IFNα2b fulfills treatment goals important to patients, has the potential to influence disease progression and a higher probability of event-free survival.

Pelabresib combined with Ruxolitinib in patients with primary myelofibrosis (PMF)

Through its inhibition of bromodomain and extra-terminal domain (BET) proteins the small molecule Pelabresib (CPI-0610) reduces transcription of abnormally expressed genes in PMF.
The preliminary data from the Manifest Trial (arm 2: prior JAK-inhibitor treatment, arm 3: first-line treatment) – an ongoing, global, open-label phase 2 study – focused on efficacy and safety of pelabresib in combination with ruxolitinib in patients with PMF (DIPSS int2/high). 68% of treatment-naive and 20% of pretreated patients achieved at least a 35% reduction in spleen volume at week 24. Furthermore, 56% and 30% respectively reported a reduction in total symptom score (TTS50) of at least 50% at week 24. Pelabresib seems to have the potential to modify disease-activity described as lowering levels of inflammatory cytokines and improving bone marrow fibrosis, inducing megakaryocyte declustering and increasing erythrocytes. The

most common AEs grade 3-4 were thrombocytopenia, anemia, GI events and respiratory tract infections.

In conclusion: Pelabresib + Ruxolitinib was well tolerated, effective in reducing spleen volume and symptom burden and seems to alter disease activity.

Authors

Author: Dr. med. **Eva M. Heilmann**, Department of Hematology, University Hospital Basel
Mentor: Prof. Dr. med. **Gabriela M. Baerlocher**, University of Bern

Literature

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ESMO Highlights of the Year 2022 – Lung cancer

We selected two studies in the field of lung cancer presented at this year's ESMO congress as highlights of the year. Both studies deal with targeted therapies in metastatic non-small cell-lung cancer (NSCLC).

CodeBreaK 200 phase 3 study

The CodeBreaK 200 phase 3 study compared sotorasib versus docetaxel in patients with previously treated metastatic NSCLC that harbour a *KRAS G12C* mutation[1]. In the previous phase 1/2 CodeBreaK 100 study in metastatic *KRAS G12C* mutated NSCLC sotorasib used in 2nd - 4th line showed an impressive objective response rate (ORR) of 37.1% (95% confidence interval [CI]: 28.6 – 46.2), and a progression-free survival (PFS) and overall survival (OS) of 6.8 months (95% CI 5.1 – 8.2) and 12.5 months (95% CI 10.0 – could not be evaluated), respectively[2]. CodeBreaK 200 is the confirmatory phase 3 trial, comparing sotorasib to docetaxel, the standard of care in 2nd line, after progression to platinum and/or immunotherapy-based chemotherapy[1]. The study met its primary endpoint of PFS by blinded independent central review (BICR) with a hazard ratio (HR) of 0.66 (95% CI 0.51 – 0.86) for sotorasib in comparison to docetaxel (p=0.002). The median PFS for sotorasib is 5.6 months (95% CI 4.3 – 7.8) versus 4.5 months (95% CI 3.0 – 5.7) for docetaxel. The tumour response by BICR is also superior for sotorasib with an ORR of 28.1% (95% CI 21.5 – 35.4) versus 13.2% (95% CI 8.6 – 19.2) for docetaxel (p<0.001). Although a significant PFS benefit was reported, no OS benefit could be demonstrated (HR 1.01, 95% CI 0.77 – 1.33, p=0.53), however, the study was not powered to detect a statistically significant difference. The lack of OS benefit might be partly explained by crossover: 34% of patients in the docetaxel arm received a subsequent KRAS G12C inhibitor. The safety profile of both drugs is in the known range and revealed no new safety issues. The additionally presented patient-reported outcomes global health status, physical functioning and dyspnoea were superior for sotorasib, whereas there was no significant difference regarding cough and chest pain. In our conclusion, sotorasib is a well-tolerated treatment alternative in previously treated *KRAS* G12C mutated NSCLC demonstrating a PFS benefit, better ORR and less toxicity, but one has to bear in mind that no OS benefit could be demonstrated.

INSIGHT 2 phase 2 study

Secondly, we would like to present the first results of the INSIGHT 2 phase 2 study, investigating the combination of osimertinib and tepotinib in *EGFR* mutated NSCLC with acquired resistance to 1st line osimertinib and harbouring a *MET* amplification as mechanism of resistance[3]. The primary objective of this study was ORR by an independent review committee (IRC). A confirmed ORR of 54.5% (95% CI 32.2 – 75.6) was reported in patients with *MET* amplification detected by central FISH on tumour biopsy with ≥ 9 months' follow-up. In comparison, an ORR of 8.3% (95% CI 0.2 – 38.5) was reported in the tepotinib monotherapy arm with *MET* amplification detected by central FISH on tumour biopsy and ≥ 6 months' follow-up. In this study, no new safety issues have been raised regarding the two substances. In our conclusion, the combination of osimertinib and tepotinib seems to be

very active in *EGFR* mutated NSCLC progressing on 1st line osimertinib with *MET* amplification as mechanism of action. Furthermore, this study addresses a high unmet need, as there are no clear recommendations on how to treat patients progressing on osimertinib.

Authors

Author: Dr. med. **Kira-Lee Koster**, Department of Medical Oncology and Haematology, Cantonal Hospital St.Gallen
Mentor: Prof. Dr. med. **Miklos Pless**, Department of Medical Oncology, Cantonal Hospital Winterthur

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Highlights of ESMO Congress 2022 in Paris – Upper Gastrointestinal Cancer

HER2 (human epidermal growth factor receptor 2) represents one of the most clinically relevant biomarkers for patients with stage IV gastric or gastroesophageal junction (GEJ) cancer. The expression of HER2 plays a crucial role in the treatment protocol to be followed.

HER2-positive disease: DESTINY-Gastric02

G. Y. Ku presented the updated results of this nonrandomized phase II single-arm trial. Trastuzumab[1] is a monoclonal antibody against HER2 and represents the standard of care for patients with HER2-positive advanced gastric or GEJ cancer when combined with chemotherapy[2]. However, in the case of progression under this therapy, the available treatment options are limited.

After the promising results of the randomized, phase 2 DESTINY-Gastric01[3] trial, which demonstrated that the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) led to significant improvements in response and overall survival (OS) when compared to chemotherapy alone in patients from Asia (median OS; 12.5 vs. 8.4 months; P=0.01), the DESTINY-Gastric02 trial investigated the role of T-DXd in a western population. 79 patients from the United States and Europe with pathologically confirmed HER2-positive (IHC3+ or IHC2+/ISH+) unresectable or metastatic disease after progression on a first-line Trastuzumab-containing regimen were enrolled in this study.

After a median follow-up of 10.2 months, the confirmed objective response rate (ORR) was 41.8% (95% CI, 30.8-53.4). The median OS was 12.1 months (95% CI, 9.4-15.4), in line with the results of the DESTINY-Gastric01 trial, and a median progression-free survival (PFS) of 5.6 months (95% CI, 4.2-8.3) was reported. Treatment-emergent adverse events (TEAEs) grade ≥1 were reported for all patients, and 55.7% reported grade ≥3. The most common TEAEs being nausea (67.1%), vomiting (44.3%) and fatigue (57.0%), which was consistent with the established safety profile of T-DXd. Patient-reported outcomes were assessed utilizing general (EQ-5D) and gastric cancer-specific (FACT-Ga) scores, suggesting that quality of life did not worsen during the treatment.

Limitations of DESTINY-Gastric02 include the relatively small sample size and the single-group design. To overcome these limitations, DESTINY-Gastric04[4], a global, multicenter, open-label, 2-arm, randomized, phase 3 trial is actively enrolling patients from 24 different countries.

HER2-negative disease: Moonlight trial

S. Lorenzen presented the results of two arms (A1/A2) of this four-arm investigator-initiated phase II trial that enrolled 90 treatment-naïve patients with HER2-negative advanced or metastatic adenocarcinoma of the stomach or GEJ. The aim of this trial was to evaluate whether the administration of FOLFOX chemotherapy plus nivolumab (nivo)[5] and ipilimumab (ipi) in parallel (arm A1) is more effective than FOLFOX induction followed by nivo and ipi (arm A2) with the primary endpoint progression-free survival (PFS) at 6 months.

90 patients were randomized 1:2 to arm A1 (60 patients; FOLFOX plus nivo 240 mg; q2w and ipi 1 mg/kg; q6w administered in parallel) or arm A2 (30 patients; three cycles of mFOLFOX induction treatment followed by nivo and ipi). With a median follow-up of 7.3 months PFS at 6 months was significantly higher (57%) in arm A1 than in A2 (28%; p=0.012) with a median PFS of 8.4 vs 4.0 mo, respectively (p=0.006). Median overall survival was not reached in A1 and was reported at 9.1 months in A2. The objective response rate was 47% vs 30%, respectively. Treatment-related adverse events (AE) were less common in the sequential arm. Specifically, grade ≥3 AE were observed in 93% of the patients enrolled in arm A1 and 73% in arm A2, serious AE were 70% in arm A1 and 62% in A2.

In conclusion, the study suggests that the parallel administration of FOLFOX chemotherapy plus nivolumab and ipilimumab is more effective than the sequential administration of the treatment and should be considered the first-line approach for patients with HER2-negative disease despite the association with higher toxicity.

Authors

Author: Dr. med. **Alexandros Lalos,** Clarunis Visceral Surgery, University Hospital of Basel
Mentor: PD Dr. med. **Lukasz Filip Grochola**, Department of Visceral and Thoracic Surgery, Cantonal Hospital Winterthur

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Pathology Highlights of the Year 2022 - Breast Cancer

One of the highlights of this year's congresses was the presentation of the results of the study by Dr. Blaye et al. on an immunological signature to predict outcome in patients with triple-negative breast cancer (TNBC) with residual disease after neoadjuvant chemotherapy (NACT)[i].

Background

TNBC accounts for 10-15% of all breast cancers[ii]. After treatment with neoadjuvant chemotherapy, pathological response is an important prognostic factor that inversely correlates with the risk of relapse[iii]. Response is quantified through residual cancer burden (RCB), which classifies tumors in four categories[iv]. Although RCB 0-I are associated with very good prognosis and RCB III with poor prognosis, RCB II is a very heterogeneous group that need to be further investigated. In this regard, in 2019, it was shown that tumor-infiltrating lymphocytes (TILs) are an independent prognostic factor[v]. However, their quantification is pathologist-specific and TILs alone does not capture the full immunological microenvironment picture.

The aim of the study was to analyze the immunological microenvironment in residual TNBC after NACT and describe an immunological transcriptomic prognostic signature.

Study

RNA [from both tumor cells and tumor microenvironment (TME)] of 115 cases of TNBC from post-treatment formalin-fixed paraffin embedded (FFPE) tumor-samples was extracted and analyzed on the NanoString PanCancer Immuno-Oncology panel (IO360) containing 770 genes related to immune response in cancer.

Analysis of TME through unsupervised hierarchical clustering allowed the identification of five clinical cluster (C1-C5): C2, C3, C4 were enriched in immunity genes (interferon-γ-related and lymphoid compartment) and had a significantly better survival than C1 and C5 (log-rank p=0.04), which were enriched in genes implicated in cell proliferation pathways and were poor in immune-related gene.

Then, the composition of immune infiltrates of residual disease was evaluated. An enrichment in B-lymphocytes, in total T cells, in CD8+ T cells on cytotoxic and natural killer cells were observed in patients who did not experiences metastatic relapse.

Finally, eight genes whose expression was significantly associated with better survival (*BLK, GZMM, CXCR6, LILRA1, SPIB, CCL4, CXCR4, SLAMF7*) were selected through univariate Cox proportional hazards regression model. Thus, an eight-gene signature was developed, which accurately predicts distant-relapse-free-interval (DRFI), having patients with 8-gene signature "high" a significantly longer DRFI than patients with 8-gene signature "low" [HR 0.18 95% (CI 0.09-0.35), $p < 0.001$]. Moreover, this signature could also separate high-risk from low-risk patients in the RCB II group [HR 0.15 (95% CI 0.06-0.4), $P < 0.001$], which contains patients with very heterogeneous outcomes.

Conclusions

The results are of great importance since they allow a better understanding of the transcriptomic profile of immune infiltrates in TNBC. This may help to identify patients with increased risk of relapsing, improving follow-up and therapy strategies and prognosis in TNBC, especially in the RCB II group, characterized by highly heterogeneous prognosis.

A limitation is that RNA expression range values vary between platforms and patient cohorts, thus preventing the definition of a common threshold. For that reason, the signatures identified should be determined in a dedicated validation study to allow the utilization of these signatures in clinical practice.

Authors

Author: Dr. med. **Umberto Maccio**, Institut für Pathologie und Molekularpathologie, University Hospital Zurich USZ

Mentor: Prof. Dr. med. **Laurence De Leval**, Pathologie, Lausanne University Hospital CHUV

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ESMO Highlights 2022 in Gynecological Cancer: Are we curing ovarian cancer patients?

This year's congress provided overall survival (OS) results from the SOLO-1/GOG 3004 and PAOLA-1/ENGOT-ov25 trials investigating olaparib (ola) alone and in combination with bevacizumab (bev) as maintenance therapy in patients with advanced ovarian cancer (AOC).
Based on the results of randomized phase 3 trials, Poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) have been approved as a new standard of care in AOC and have revolutionized the way patients are treated in the front-line[1–4] and recurrent setting [5–7]. Currently, ola, niraparib, ola plus bev and bev demonstrated significant improvements in progression-free survival (PFS) and are approved for first-line maintenance therapy [1,3,4,8].

SOLO-1/GOG 3004 trial

The results of SOLO-1 at 5 years showed that first-line maintenance therapy with ola substantially extended PFS in patients with newly diagnosed AOC with BRCA mutation (BRCAm) [1]. OS analysis after 7-years of follow-up (FU) is a clinically relevant time point and the longest FU for any PARPi in the first-line setting. Patients with newly diagnosed AOC with BRCAm who had a clinical response to platinum-based chemotherapy were randomized to receive either ola (n=260) or placebo (n=131) for 2 years or until disease progression. The hazard ratio for OS was 0.55 (95% CI, 0.40 to 0.76), not achieving statistical significance (P= .0004[P< .0001 required]). It is worth acknowledging that 90% of patients stopped ola treatment at 2 years and that in the subsequent 5 years only 33% of patients died in the ola arm versus 53.5% in the placebo cohort. Importantly, 45.3% versus 20.6%, respectively, had not received a first subsequent treatment suggesting that there might be cure for some AOC patients.

PAOLA-1/ ENGOT-ov25 trial

This phase 3 trial compared maintenance ola + bev with placebo + bev in patients with newly diagnosed AOC who had received first-line standard-of-care treatment including bev regardless of BRCAm. In the primary analysis, ola + bev demonstrated a significant PFS benefit over placebo + bev (HR 0.59, 95% CI 0.49–0.72; P<0.001), mainly in patients with HRD+ tumors (HR 0.33, 95%CI 0.25–0.45). The final analysis investigated whether this translated into an OS advantage at 5 years. After a median FU of 61.7 months in the ola+ bev arm and 61.9 months in the placebo+ bev arm, median OS was 56.5 months vs 51.6 months, respectively (HR, 0.92; 95% CI, 0.76-1.12; P = .4118). OS rates at 5 years were 47.3% with the addition of ola compared to 41.5% with placebo.
The power of this study is shown in patients with HRD+ tumors where the addition of ola to bev reduced the risk for death by 38% (HR, 0.62; 95% CI, 0.45-0.85), with a 5-year OS of 65.5% with the combination regimen and 48.4% with placebo. This benefit was consistent in patients harboring a BRCAm (5-year OS, 73.2% vs 53.8%, respectively; HR, 0.60; 95% CI, 0.39-0.93). However, no statistically significant benefit was seen in patients without BRCAm (5-year OS, 54.7% vs 44.2%; HR, 0.71; 95% CI, 0.45-1.13), nor in HRD- patients (5-year OS, 32.3% vs 25.7%, respectively; HR, 1.19; 95% CI, 0.88-1.63).

Conclusion

Ola (+/- bev) led to a clinically meaningful benefit in OS in patients with AOC and HRD+ (with and without BRCAm). The authors in both trials support the use of ola (and bev) in BRCAm (and HRD+) AOC. The survival data confirm the value of biomarker directed first-line maintenance therapy with ola.

Authors

Author: Dr. med. **Bich Doan Nguyen-Sträuli**, Gynecologic Oncology, University Hospital Zurich USZ
Mentor: Dr. med. **Francesca Caparrotti**, Radio-Oncology, Clinique Générale Beaulieu - Swiss Medical Network, Geneva

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