Young Oncology Academy 2022 – Teil 2

Der onkologische Nachwuchs resümiert

Das Kernstück in der Nachwuchsförderung der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) ist die Young Oncology Academy (YOA), ein Förderungs- und Mentor*innenprogramm für junge Onkolog*innen. Als Teil der Academy besuchen die teilnehmenden Assistenzärzt*innen einen grossen Kongress. Hier nun drei weitere dieser dabei entstandenen Berichte.

Highlights of 2022 EHA Congress – Myeloproliferative Neoplasms

Eva M. Heilmann (35) arbeitet am Universitätsspital Basel in der Abteilung Hämatologie. Sie ist Fachärztin für allgemeine innere Medizin und aktuell in Facharztausbildung zur Hämatologin. Sie ist überzeugt: «Eine optimale Patient*innenbetreuung setzt unter anderem Kenntnisse neuer Studiendaten sowie eine aktive Teilnahme an Studienplanung und -umsetzung voraus. Die Young Oncology Academy bietet hierfür eine sehr gute Grundlage. Zudem ermöglicht sie die Vernetzung von erfahrenen Expert*innen mit jungen, motivierten Ärzt*innen verschiedenster Fachdisziplinen über die ganze Schweiz hinweg.»

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 versus hydroxyurea in patients with PV

The randomized, phase III, open-label PROUD-PV trial and its extension phase IIIb CONTINUATION-trial compared Ropeginterferon alfa-2b (ropeg-IFNα2b) to hydroxyurea (HU) in patients with early-stage PV.[1] 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 *JAK2*V617F 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.

To sum it up, 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 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-II-study – focused on efficacy and safety of pelabresib in combination with ruxolitinib in patients with PMF (DIPSS int2/high).[2]

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 adverse events grade 3–4 were thrombocytopenia, anemia, grastointestinal 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:
Dr. med. **Eva M. Heilmann**[1]
Prof. Dr. med. **Gabriela M. Baerlocher**[2]
[1] Department of Hematology
University Hospital Basel
[2] University of Bern

Literature:

1 Gisslinger H et al.: Ropeginterferon alfa-2b achieves patient-specific treatment goals in polycythe-mia vera. Final results from the PROUD-PV/CONTINUATION-PV studies. EHA 2022; Abstr. #S196 **2** Mascarenhas J et al.: BET-inhibitor pelabresib (CPI-0610) combined with ruxolitinib in patients with myelofibrosis – JAK-inhibitor naive or with suboptimal response to ruxolitinib – preliminary data from the MANIFEST-study. EHA 2022; Abstr. #S198

Highlights of EHA 2022 Regarding Aggressive Lymphoma

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Martina Bertschinger (35) ist im Kantonsspital Winterthur auf dem Gebiet der hämatoonkologischen Erkrankungen tätig. Für sie ist die Young Oncology Academy «eine ausgezeichnete Gelegenheit, sich in ein Gebiet zu vertiefen und sein Netzwerk zu verbessern».

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:[1, 2] epcoritamab, an anti-CD20xCD3 1:1 IgG1 antibody, and glofitamab, an anti-CD20xCD3 2:1 IgG1 antibody. These two trials are very similar in design and studied a comparable population of heavily pretreated R/R aggressive B-cell lymphoma, including CAR(chimeric antigen receptor)-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 PFS in elderly patients with de novo MCL

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 progression-free survival (PFS) in an elderly population with newly diagnosed mantle cell lymphoma (MCL).[4] The primary endpoint of this study was met, ibrutinib in combination with standard chemo-immunotherapy 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 MCL. Whether a PFS benefit in the absence of demonstrated OS difference justifies the addition of ibrutinib in first line, is questionable. ■

Authors:
Dr. med. **Martina Bertschinger**[1]
Prof. Dr. med. **Urban Novak**[2]
[1] Kantonsspital Winterthur
[2] Inselspital/Universitätsspital Bern

Literature:

1 Thieblemont C et al.: Subcutaneous epcoritamab in patients with relapsed or refractory large B-cell lymphoma (EPCORE NHL-1): Pivotal results from a phase 2 study, EHA 2022; Abstr. #LB2364 **2** Dickinson M et al.: Glofitamab induces durable complete remissions and has favorable safety in patients with relapsed/refractory diffuse large B-cell lymphoma and ≥2 prior therapies: pivotal phase II expansion results. EHA 2022; Abstr. #S220 **3** Chamuleau M et al.: R-CODOX-M/R-IVAC versus dose-adjusted (DA)-EPOCH-R in patients with newly diagnosed high-risk Burkitt lymphoma; first results of a multi-center randomized HOVON/SAKK TRIAL. EHA 2022; Abstr. #LB2370 **4** Wang M et al.: Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. N Engl J Med 2022; 386: 2482-94

ESMO 2022 Highlights: Lower GI

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Nils Degrauwe (34) arbeitet am CHUV in Lausanne auf dem Spezialgebiet medizinische Onkologie. Er nahm an der Young Oncology Academy teil, um «mein Wissen in der klinischen Krebsforschung zu erweitern und um mit jungen wie mit erfahrenen Ärzt*innen zu arbeiten, die auf verschiedenen Gebieten der Krebsbehandlung tätig sind».

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.

The 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 were 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 this confirms the 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 as 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 (LBA 25), opening new options in this clinical setting. FRESCO-2 is a phase III randomized trial evaluating the efficacy and safety of fruquintinib, a potent VEGF(vascular endothelial growth factor) 1-3 inhibitor, in heavily pretreated patients with metastatic CRC. Treatment with fruquintinib showed a statistically and clinically relevant gain in both PFS (1.9 months, HR :0.321) and overall survival (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 tyrosine kinase inhibitor toxicity profile. ■

Authors:
Dr. med. **Nils Degrauwe**[1]
Prof. Dr. med. **Ulrich Güller**[2]
[1] Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne
[2] Klinik für Medizinische Onkologie und Hämatologie, Spital STS AG Thun

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1 Andre T et al.: Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 2020; 383: 2207-18 **2** Lenz HJ et al.: First-Line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: The phase II CheckMate 142 study. J Clin Oncol 2022; 40: 161-70 **3** Cercek A et al.: PD-1 Blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022; 386: 2363-76 **4** Mayer RJ et al.: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015; 372: 1909-19 **5** Grothey A et al.: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381(9863): 303-12