V710 - Untersuchung von HLA Verlust Rezidiven nach Allogener Stammzelltransplantion in einer Globalen Multizentrischen Studie (HLALOSS Consortium) / Investigation of HLA loss relapse after allogeneic stem cell transplantation in a global multicentric cohort (HLALOSS Consortium)

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Introduction: Genomic loss of the patient-specific HLA has been described in previous single-center studies as a frequent immune escape mechanism leading to relapse after allogeneic stem cell transplantation (SCT). HLA loss accounts for up to 30% of relapses after HLA-haploidentical SCT, but its frequency and clinical relevance in other transplantation settings is unknown. Here we present the first global collaborative study to investigate the incidence of this phenomenon across transplant platforms.

Methods: Twenty-seven transplant centers from across the globe (Europe n=22, North America n=4, Asia n=1) joined to form the HLALOSS consortium. To date, we collected a total of 634 cases of relapse from adult patients with acute leukemias, myelodysplastic syndromes or myeloproliferative neoplasms after allogeneic HSCT from HLA-haploidentical relatives (29.3%), HLA-mismatched unrelated donors (MMUD, 25.9%), 10/10-matched unrelated donors (MUD, 35.8%), or unrelated cord blood units (UCB, 9.0%). HLA Chimerism was analyzed by conventional HLA typing, qPCR or a novel next-generation-sequencing (NGS) platform, the latter allowing us to quantify patient-specific, donor-specific and shared HLA alleles by direct counting.

Results: To date, we analyzed 222 cases of post-transplantation relapse after haploidentical (n=104), MMUD (n=61), 10/10-matched, HLA-DPB1 mismatched MUD (n=49), or UCB (n=8) HSCTs. Of these, 127 cases were analyzed by NGS, which showed a sensitivity of 0.5% and high concordance with conventional HLA typing or qPCR (R^2=0.86, p< 0.0001). In the total 222 cases analyzed to date by the different methods, we detected 35 HLA loss post-transplantation relapses, 27 of which after haploidentical HSCT (26.0% of relapses in this setting), 7 after MMUD HSCT (11.5%), 1 after 10/10 MUD HSCT (2%) and none after UCB HSCT. Analysis of the remaining 412 collected samples is ongoing.

Conclusion: The present data, obtained from the largest collaborative study on the immunobiology of relapse to date, confirm the clinical relevance of HLA loss as a major mechanism of immune evasion and post-transplantation relapse, including after HSCT from partially HLA-incompatible unrelated donors.

V711 - Die Rolle der RAS Pfad Überaktivierung bei Progression und Transformation der chronisch myelomonozytären Leukämie / The role of RAS pathway hyperactivation in the progression and transformation of chronic myelomonocytic leukemia

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Introduction: Although mutations in RAS signaling genes have been previously reported in individual patients with transformed chronic myelomonocytic leukemia (CMML) a comprehensive (molecular and functional) analysis of the role of RAS pathway activation in the progression/transformation of CMML in a large patient cohort has not been performed. A close correlation between RASopathy mutations (*NRAS, KRAS, NF-1, PTPN11 and CBL*) and spontaneous in vitro myeloid colony (CFU-GM) growth in CMML has been described (Geissler et al. Leukemia 2016).

Methods: In the "Austrian Biodatabase for Chronic Myelomonocytic Leukemia" (ABCMML) we retrospectively and prospectively collect hematological, clinical, molecular and biologic informations of patients with CMML from different centers in a real life setting. Molecular aberrations are determined by targeted next generation sequencing (NGS) and spontaneous myeloid colony formation is assessed by semisolid in vitro cultures as described previously

(Geissler K et al, J Exp Med 1996). Using data (molecular, N=288; CFU-GM, N=207) from 225 CMML patients we compared the frequencies of RASopathy gene mutations and of high CFU-GM growth (>100/10^5PBMNCs) in patients without (cohort A) and with (cohort B) transformation and/or progression related death during follow-up, and in patients already transformed at the time of sampling (cohort C).

Results: The frequencies of RAS pathway mutations in groups A, B, and C were 32%, 54% (B vs A; p=0.002111), and 74% (C vs A, p< 0.00001), and of high colony growth 17%, 31% (B vs A; p=0.039418), and 86% (C vs A, p< 0.00001), respectively. Increases in allele burden of RAS pathway mutations and increases in spontaneously formed CFU-GM numbers before and after transformation could be shown in individual patients.

Conclusions: We find at the molecular and functional level indications for RAS pathway hyperactivation in the majority of patients with transforming CMML which may be relevant for targeted treatment strategies.

V712 - Strahlentherapie bei Bulk (B) und extra-lymphatischem (E) Befall in Kombination mit 6xR-CHOP-14 oder R-CHOP-21 bei jungen DLBCL Patienten mit guter Prognose: Ergebnisse der 2x2 randomisierten UNFOLDER Studie der DSHNHL/GLA / Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: Results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA

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Introduction: The role of RT to B and E for young patients with good-prognosis DLBCL is ill-defined.

Methods: 18-60 year-old patients (aaIPI=0 with B [≥7.5 cm], aaIPI 1) qualifying for radiotherapy to B or E were randomized to 6xR-CHOP-14 or 6x-R-CHOP-21 followed by RT (39.6 Gy) to B and E sites or observation in a 2x2 factorial design. Primary endpoint was event-free survival.

Results: A planned interim analysis of the first 285 patients had revealed a significantly better EFS of patients assigned to RT (p=0.004) resulting in the pre-defined closing of the non-RT arms. 305 pts (R-CHOP-21: 155; R-CHOP-14: 150) assigned to RT and 162 (R-CHOP-21: 81, R-CHOP-14: 81) assigned to observation were evaluable for this final analysis. There were no relevant differences in protocol adherence and toxicity between the two chemotherapy regimens. EFS, PFS and OS after R-CHOP-14 and R-CHOP-21 were not

different. After 66 months median observation 3-year EFS was worse in pts not assigned to RT (68% vs. 84%; p=0.001), due to a higher rate of PR (11% vs. 2%) triggering additional treatment (mostly RT) as an EFS event. 3-year PFS of pts assigned to RT was not significantly better (89% vs. 81%; p=0.221) and 3-year OS (93% vs. 93%, p=0.506) was not different, which was confirmed in a multivariate analysis adjusting for elevated LDH, stage III/IV, B and E involvement (HR_{EFS}=0.5 [95%CI: 0.4-0.8], p=0.001; HR_{PFS}=0.7 [0.5-11], p=0.174; HR_{OS}=1.2 [0.6-2.2], p=0.674). Results were not different when the analysis was restricted to patients with bulky disease only.

Conclusion: There were no differences in outcome between R-CHOP-14 and R-CHOP-21. Patients assigned to observation had a worse EFS because of more events largely due to a higher PR rate triggering additional treatment with no differences in PFS and OS. These results highlight the difficulties in interpreting residual masses in DLBCL without a PET which has been shown to identify (elderly) patients with B who can be spared from radiotherapy without compromising their outcome [Pfreundschuh et al., ASCO 2017, #7506].

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V713 - Prävalenz und Kinetik BCR-ABL-unabhängiger Genmutationen bei CML Patienten in der chronischen Phase / Prevalence and dynamics of BCR-ABL independent gene mutations in chronic phase CML patients

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Introduction: Living without treatment has become a realistic aim for patients with chronic myeloid leukemia (CML) who achieved durable deep molecular remission under treatment with tyrosine kinase inhibitors (TKI). Recently, we have identified novel BCR-ABL independent gene mutations in newly diagnosed CML patients whereby mutations in epigenetic modifier genes were most common. However, prevalence, kinetics and prognostic significance of such mutations in a clinically well-characterized patient population need to be investigated systematically.

Methods: A total of 100 chronic phase CML patients from the German CML-V (TIGER) trial were investigated by targeted deep next-generation sequencing (NGS) covering 54 genes frequently mutated in myeloid malignancies. Paired samples at diagnosis and after 12 months of therapy were investigated to study mutation dynamics. If available, follow-up samples after 24 month (87/100 patients) and 36 months (39/100 patients) of therapy were also investigated.

Results: Thirty-five different mutations were detected in 32/100 patients (32%) affecting the genes ASXL1, BCOR, CALR, CUX1, DNMT3A, FBXW7, GATA2, IKZF1, JAK2, NOTCH1, RUNX1, STAG2, TET2, TP53, U2AF1 and WT1. ASXL1 (n=13) and DNMT3A (n=5) were the most common mutations. In five patients more than one mutation was identified. 26/100 patients (26%) showed at least one mutation at diagnosis. Analysis of follow-up samples revealed that in 20 patients the mutations disappeared during TKI treatment. In 6 patients the mutation persisted indicating that the mutation preceded the BCR-ABL translocation. In 2/87 patients (2%) the initial mutation re-emerged at month 24 after disappearance at month 12. In 8/100 patients (8%) a new mutation occurred at month 12; four of these mutations vanished and 8 persisted in further follow-up samples. So far, only one patient showed a mutation first to emerge at month 24.

Conclusions: BCR-ABL independent gene mutations were frequently identified in chronic phase CML patients at diagnosis. In a minority of patients such mutations seem to precede the BCR-ABL translocation indicating a multistep pathogenesis in CML. BCR-ABL

independent gene mutations were found to vary in their dynamics during TKI treatment and may function as important cofactors in the evolution and persistence of the disease.

V714 - IMpower150: Atezolizumab (Atezo) plus Bevacizumab (Bev) und Chemotherapie (Chemo) zeigt Wirksamkeit bei der Erstlinienbehandlung entscheidender Subgruppen bei metastasierendem nicht-squamösen NSCLC (mNSCLC) / IMpower150: Efficacy of atezolizumab (atezo) plus bevacizumab (bev) and chemotherapy (chemo) in 1L metastatic nonsquamous NSCLC (mNSCLC) across key subgroups

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Introduction: Atezo (anti-PD-L1) + bev + chemo prolonged PFS vs bev + chemo in patients with 1L non-squamous mNSCLC in the randomized Ph 3 IMpower150 study regardless of PD-L1 expression. This analysis aims to further understand the efficacy of atezo + bev + chemo in key subgroups: PD-L1 expression subgroups defined by the SP142 and SP263 IHC assays, patients with EGFR/ALK genetic alterations and patients with liver metastases at baseline.

Methods: Patients received atezo 1200 mg + bev 15 mg/kg + carboplatin (C) AUC 6 + paclitaxel (P) 200 mg/m^2 (Arm B) or bev + C + P (Arm C) IV q3w. A co-primary endpoint (EP) was PFS in the ITT-WT (EGFR or ALK wild-type patients); a secondary EP was PFS in subgroups defined by PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC) with SP142. Retrospective analysis with SP263 was a pre-specified exploratory EP.

Results: In Arms B and C of the ITT-WT (n = 692), 503 patients had available tumor sections for SP263 testing (biomarker-evaluable population, BEP). Patient characteristics in the ITT-WT and BEP were similar. A similar PFS benefit was observed for Arm B vs C across all PD-L1 expression subgroups defined by either assay, including patients with PD-L1-negative and PD-L1-low tumors (Table). PFS benefit with Arm B vs C was also observed in patients with EGFR or ALK genomic alterations, including patients with actionable EGFR mutations, and in patients with liver metastases at baseline (Table).

Conclusions: PFS benefit with atezo + bev + chemo was observed across all PD-L1 subgroups, regardless of the IHC assay used. Additionally, clinically meaningful PFS benefit was observed in patients with EGFR/ALK genomic alterations, and in patients with liver metastases with this combination.

Table. PFS in Biomarker Subgroups and Other Subgroups of Interest in IMpower150

				Median PFS, mo	
PFS[a]	**n (%)**	**HR[b] (95% CI)**	***P* Value**	**Arm B**	**Arm C**
ITT-WT	692 (100%)	0.62 (0.52, 0.74)	<0.0001	8.3	6.8
BEP with SP263 results in ITT-WT	503 (73%)	0.62 (0.50, 0.76)	<0.0001	8.3	6.8
PD-L1 Expression Subgroups Defined by the VENTANA SP142 Assay (BEP, n = 503)					
PD-L1 negative TC0 and IC0	235 (47%)	0.77 (0.57, 1.04)	0.0836	8.2	7.0
PD-L1 low TC1/2 or IC1/2	167 (33%)	0.53 (0.37, 0.76)	0.0005	8.3	6.1
PD-L1 high TC3 or IC3	101 (20%)	0.49 (0.30, 0.79)	0.0032	11.1	6.9
PD-L1 Expression Subgroups Defined by the VENTANA SP263 IHC Assay (BEP, n = 503)					
PD-L1 negative TC < 1%	237 (47%)	0.72 (0.53, 0.97)	0.0298	7.2	7.0
PD-L1 low TC < 50% and ≥ 1%	140 (28%)	0.57 (0.38, 0.84)	0.0041	9.7	6.9
PD-L1 high TC ≥ 50%	126 (25%)	0.50 (0.33, 0.77)	0.0015	9.1	6.2
Other Subgroups of Interest (ITT, n = 800)					
ITT	800 (100%)	0.61 (0.52, 0.72)	<0.0001	8.3	6.8
EGFR/ALK+[c]	108 (14%)	0.59 (0.37, 0.94)	0.0253	9.7	6.1
EGFR exon 19 deletion or L858R[d]	59 (7%)	0.41 (0.22, 0.78)	0.0050	10.2	6.1
Liver metastases	110 (14%)	0.40 (0.26, 0.62)	<0.0001	8.2	5.4
No liver metastases	690 (86%)	0.64 (0.53, 0.76)	<0.0001	8.3	7.0

BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cell; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TC, tumor cell; WT, wild-type.
TC0 and IC0 = PD-L1 expression on < 1% of TC or IC; TC1/2 or IC1/2 = PD-L1 expression on < 50% and ≥ 1% of TC or < 10% of and ≥ 1% of IC; TC3 or IC3 = PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC.
[a] Investigator-assessed
[b] Stratified HR for ITT-WT and ITT; unstratified HR for all other subgroups.
[c] Patients with a sensitizing *EGFR* mutation or *ALK* rearrangement must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[d] Other *EGFR* mutations include L861Q, G719X, S7681, exon 20 insertion, T790M and other.
(NCT02366143)

[Table 1]

V715 - Die Bestimmung von HER2 beim Magenkarzinom ist eine Herausforderung: hohe Abweichungen zwischen zentraler und lokalen Pathologien und deren Auswirkung auf die Lebenserwartung / Determination of HER2 in Gastric Cancer (GC) is still challenging: high deviation rates between local and central pathologies and its impact on survival

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Background: Trastuzumab is an approved targeted therapy in GC. It addresses HER2, a membrane-bound receptor tyrosine kinase which belongs to the epidermal growth factor receptor family. According to current guidelines, indication for trastuzumab is determined by immunohistochemistry HER2 score 3+ or in case of an intermediate score (2+) additional amplification (HER2/CEP17 ratio ≥2) by in situ hybridization. While trastuzumab is used for 1st-line treatment of stage IV HER2+ GC, not all patients respond and almost all initial responders eventually experience progression. Resistance mechanisms against trastuzumab in GC are poorly understood. The VARIANZ study aims to assess the biological background of resistance to anti-HER2 therapy in GC.

Methods: This academic network study funded by the German Federal Ministry of Education and Research (BMBF 01ZX1610E) recruited patients (pts) who received medical treatment for stage IV GC in 34 sites. HER2 expression was verified centrally by two dedicated GI pathologists using immunohistochemistry (DCS, HI608C0I) and chromogenic-in-situ hybridization (Zytomed Systems, C-3022-40). Treatment and survival outcomes were reported by investigators.

Results: 549 pts were enrolled from May 2014 to Jan 2018. At present, 501 samples were fully characterized for HER2. According to predefined criteria as used in the ToGA study, 87 of 501 samples were found HER2+ in central testing. In 66 samples with a HER2+ status diagnosed by local pathologists, HER2 positivity could not be confirmed centrally. The deviation rate between local and central testing was 22.4%. Centrally confirmed HER2-positive GC displayed a higher percentage of tumor cells staining positive for HER2 (58.3 ± 30.4% [SD] vs. 13.8 ± 20.7% [SD]; p< 0.001) and a higher HER2/CEP17 ratio (6.8 ± 5.5 [SD] vs. 1.4 ± 0.3 [SD]; p< 0.001). Survival outcomes indicate that only pts with centrally confirmed HER2+ status benefit from trastuzumab with an overall survival of 29.9 months (95%-CI 20.2 - 39.6; n=36) versus 10.8 months (95%-CI 7.7 - 13.7, n=42); HR for death was 3.1 in pts with unconfirmed vs. confirmed HER2+ GC receiving trastuzumab plus chemotherapy; p< 0.001.

Conclusions: Variability between local and central HER2 assessment in GC is significant. Pts with centrally unconfirmed HER2+ status have no benefit from anti-HER2 therapy. HER2 status should be assessed in highly qualified laboratories and cut-offs for defining HER2+ should be reconsidered.