V1021 - Gilteritinib verlängert das Überleben bei Patienten mit rezidivierter oder refraktärer, FLT-3-mutierter akuter myeloischer Leukämie: Ergebnisse der Admiral-Phase-3-Studie / Gilteritinib significantly prolongs overall survival in patients with FLT3-mutated relapsed/refractory acute myeloid leukemia: results from the phase 3 ADMIRAL trial

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Introduction: Gilteritinib is a potent/selective oral FLT3 inhibitor. Based upon interim analysis response rates from the ADMIRAL phase 3 study of gilteritinib vs salvage chemotherapy (SC) in patients (pts) with relapsed/refractory (R/R) *FLT3*-mutated (*FLT3*$^{mut+}$) AML (NCT02421939), gilteritinib was approved as single-agent therapy in this population. We present the final results of this pivotal trial.

Methods: Adults with confirmed *FLT3*$^{mut+}$ AML (*FLT3*-ITD or *FLT3*-TKD D835/I836 mutations) refractory to induction chemotherapy, or in untreated first relapse, were randomized (2:1) to receive continuous 28-day cycles of 120-mg/day gilteritinib or prerandomization-selected SC: low-dose cytarabine (LoDAC), azacitidine (AZA), mitoxantrone/etoposide/cytarabine (MEC), or fludarabine/cytarabine/granulocyte colony-stimulating factor/idarubicin (FLAG-IDA). Prior FLT3 inhibitor use, other than midostaurin or sorafenib, was excluded. Overall survival (OS) and the combined rate of complete remission/complete remission with partial hematologic recovery (CR/CRh) were co-primary endpoints. Safety/tolerability was also examined.

Results: A total of 371 pts were randomized: 247 to gilteritinib and 124 to SC (MEC, 25.7%; FLAG-IDA, 36.7%; LoDAC, 14.7%; AZA, 22.9%). Median age was 62 years (range, 19-85). Baseline *FLT3* mutations were: *FLT3*-ITD, 88.4%; *FLT3*-TKD, 8.4%; both *FLT3*-ITD and *FLT3*-TKD, 1.9%; unconfirmed, 1.3%. Overall, 39.4% of pts had refractory AML and 60.6% had relapsed AML. Patients assigned to gilteritinib had significantly longer OS (9.3 months) than SC (5.6 months; hazard ratio for death=0.637; *P*=0.0007); 1-year survival rates were 37.1% and 16.7%, respectively. The CR/CRh rates for gilteritinib and SC were 34.0% and 15.3%, respectively (nominal *P*=0.0001); CR rates were 21.1% and 10.5%. Common adverse events (AEs) in all randomized pts were febrile neutropenia (43.7%), anemia (43.4%), and pyrexia (38.6%). Common grade ≥3 AEs related to gilteritinib were anemia (19.5%), febrile neutropenia (15.4%), thrombocytopenia (12.2%), and decreased platelet count (12.2%). Exposure-adjusted serious treatment-emergent AEs were less common with gilteritinib (7.1/patient-year) than SC (9.2/patient-year).

Conclusions: In pts with R/R *FLT3*$^{mut+}$ AML, gilteritinib demonstrated superior efficacy compared with SC and had a favorable safety profile. These results change the treatment paradigm for R/R *FLT3*$^{mut+}$ AML and establish gilteritinib as the new standard of care.

V1022 - Einfluss von IDH 1 und 2 Mutationen bei AML Patienten - Analyse von 5213 erwachsenen AML Patienten / Clinical characteristics and outcome in IDH1/2mutant AML patients - analysis of 5213 newly diagnosed patients with Acute Myeloid Leukemia

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Purpose: Mutations of the *IDH1* and *IDH2* genes are frequent alterations in AML. Previous analyses have reported differential impact on outcome, depending on the *IDH*-mutation type.

Patients and methods: AML pts. consecutively enrolled into intensive AML treatment protocols of the SAL, AMLCG or into the SAL registry were included in this analysis. Screening for mutations was performed either by NGS based sequencing of exon 4 for IDH1 and 2 or DHPLC, followed by NGS.

Results: Samples of 5213 pts. were analyzed. Median FU was 87 months. Pts.' Characteristics are shown in Table 1. 446 pts. (8.6%) had *IDH1* and 608 (11,7%) had *IDH2*mutations.
Of the *IDH1* variants, the most common ones were the R132C found in 195 pts. (44%) and R132H in 182 pts. (41%). For *IDH2*, 463 pts. had the R140Q (77%) and 116 pts. the R172K

(19%) variant.
In *IDH1*-mutated pts., we observed significant differences in baseline characteristics between the two most common mutation types. Pts. carrying the R132C mutation were older (61 vs. 55 years, $p < .001$), had lower WBC (3.6 vs. 21 Gpt/L, $p < .001$) and were less likely to have *NPM1* (25% vs. 70%, $p < .001$), and *FLT3*-ITD mutations (10% vs. 25%, $p < .001$) than those with the R132H variant.
In univariate cox regression, the CR rate (54% vs 74%, $p \leq .001$) and OS (12.9 months vs. 21.8 months) was significantly lower in pts. with *IDH1* R132C compared to those with the R132H variant. In multivariate analysis including age, WBC, *NPM1* and *FLT3*-ITD status, and ELN2017 risk, the CR rate was also significantly lower ($p = .038$).
For IDH2, OS was in trend more favourable for pts. with *IDH2* R172K (26 vs. 18 months) as compared to those with R140Q. In Pts. w/o *NPM1*/*FLT3*-ITD mutation, those with *IDH2*R172K (n=51) had a highly significant better OS than pts. (n=84) with *IDH2* R140Q (52 vs. 17 months, $p = .017$).

Conclusion: In this large cohort of AML pts. with *IDH1*/2 mutations, we found significant and so far not reported differences for the most prominent mutations types of *IDH1*. In case of *IDH2* we confirmed findings on co-mutations and showed a favorable outcome for intensively treated pts. without *NPM1/FLT3*-ITD mutation and *IDH2* R172K.

Parameter	IDH WT	IDH1 R132C	IDH1 R132H	IDH1 other	IDH2 R172	IDH2 R140	p-value
Number of pts., n (%)	4176 (100)	195 (100)	182 (100)	68 (100)	116 (100)	470 (100)	
Age (years), median	57	63	54	61	61	60	<0.001
WBC in Gpt/l, median	15.2	3.8	20.7	15	2.3	16.7	<0.001
NPM1 mut; n (%)	1145 (28)	48 (25)	127 (70)	44 (65)	2 (2)	229 (49)	<0.001
FLT3-ITD; n (%)	917 (22)	19 (10)	46 (25)	17 (25)	5 (4)	113 (24)	<0.001

[Table 1. Baseline characteristics]

V1023 - Behandlungsrealität des Mammakarzinoms: die prospektive, intersektorale Registerplattform OPAL für Patienten mit metastasiertem oder inoperablem Mammakarzinom in Deutschland / Routine care of advanced breast cancer: the prospective, national research platform OPAL for patients with advanced breast cancer in Germany

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Introduction: The Tumor Registry Breast Cancer (TMK) has prospectively documented treatment and outcome of patients (pts) with breast cancer (BC) by oncologists in Germany since 2007 and provided insight into treatment in routine practice where pts' sociodemographic and medical characteristics often differ from those treated in clinical trials. OPAL continues this successful work focusing on changes in treatment reality of advanced BC (ABC), patient-reported outcomes (PROs) and representation of all specialists (medical and gynecologic oncologists) treating ABC in Germany.

Methods: OPAL like the TMK is a prospective, observational, open, multicentre clinical registry. In addition to the 4500 pts from the TMK, at least 2000 pts will be recruited in OPAL, stratified into 3 cohorts: 1000 pts with hormone receptor positive, HER2-negative, 500 pts with HER2-positive and 500 pts with triple-negative ABC. In total, up to 200 sites (comprehensive cancer centres, clinics and office-based gynaecologic and medical oncologists) will be participating. All pts are recruited at start of their first palliative systemic treatment (≤6 weeks after start of treatment, PRO-Module: before/at start of treatment), to avoid an overestimation of outcome data. There is no treatment specification.
OPAL collects detailed information on all (sequential) treatments, patient and tumor characteristics, physician-reported factors potentially influencing treatment decision, biomarker testing and additional treatments (surgery, radiotherapy, osteoprotective therapy). Follow-Up is until death or up to 5 years.
Associated satellite projects are a decentralized biobank for future investigational translational research and the collection of PROs in clinical routine (every 3 months for 3.5 years). The data remain in Germany.

Results: By April 2019, a total of 5076 pts had been recruited, 434 since the start of OPAL in December 2017. 2105 pts with ABC recruited by 116 sites are now available for analyses of the combined TMK/OPAL database. First results from the interim analysis 2019 will be presented.

Conclusions: OPAL will show how pts with ABC in Germany are treated and how the choice of treatment changes over time, which sequential treatments are applied and what the effectiveness (e.g. best response, progression-free and overall survival) and PROs are in a “real world” setting. It will reveal the impact of new treatments in pts in routine care and allow to identify areas for improvement of care.

V1024 - Risikofaktor PET-Positivität nach zwei Zyklen ABVD - Ergebnisse der GHSG-Studie HD16 für frühe Stadien des Hodgkin-Lymphoms / Pet positivity after 2 cycles of abvd is a risk factor in patients with early-stage favorable Hodgkin lymphoma treated in the phase 3 GHSG HD16 study

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Background: PET-adapted therapy is the standard treatment for advanced-stage Hodgkin lymphoma (HL). The role of interim PET in early-stage favorable disease is still unclear.

Aims: In our HD16 study (NCT00736320) for early-stage favorable HL, we evaluated the use of PET after 2 cycles of ABVD (PET-2) to guide involved-field radiotherapy (IFRT). Furthermore we investigated if a positive PET-2 is a risk factor for progression-free survival (PFS) in these patients.

Methods: From 2009-2015, we recruited 1150 patients with newly diagnosed early-stage favorable HL aged 18-75. Patients were randomly assigned to receive standard combined-modality treatment (CMT) with 2xABVD and 20 Gy IFRT or PET-guided treatment, where IFRT was restricted to patients with DS ≥3 after 2xABVD. A central objective of the trial was to test whether a Deauville score (DS) ≥3 was associated with PFS impairment among patients treated with CMT (i.e. those randomized to the standard group and those from the PET-guided randomization group with DS ≥3). We also explored the association of DS with baseline characteristics and treatment outcomes considering different cutoffs for positivity.

Results: Among 1007 randomized patients with regular PET, 667 (66%), 218 (22%) and 122 (12%) had DS 1-2, 3 and 4, respectively. Of those, 693 were assigned to treatment with CMT (353, 218 and 122 with DS 1-2, 3 and 4, respectively). Clinical stage II and bulky disease at initial staging were associated with an unfavorable DS after 2xABVD. With median follow-up

of 46 months, estimated 5-year PFS was 93.2% (90.2-96.2) among patients with DS1-2, 92.8% (88.8-96.9) for those with DS3 and only 80.9% (72.2-89.7) in the DS4 subgroup. Considering DS ≥3 as cutoff, the PFS difference missed statistical significance (HR adjusted for baseline factors 1.73 [0.99-3.02], p=0.055). With DS4 as cutoff, the difference became more pronounced, indicating a threefold risk for treatment failure in patients with DS4 after chemotherapy (adjusted HR 2.94 [1.63-5.31], p=0.0004). Overall survival was on a high level with no differences between any subgroups defined by DS.

Conclusions: In early-stage favorable HL, a positive PET after 2xABVD is associated with a larger tumor volume and represents a risk factor for PFS among patients treated with standard CMT, particularly when DS4 is considered as cutoff for positivity. PET-guided treatment intensification in this high-risk subgroup might help to reduce the frequency of relapses.

V1025 - Ein-Jahres-Daten zur Wirksamkeit von Ravulizumab (ALXN1210) in erwachsenen, komplementinhibitor-naiven Patienten mit Paroxysmaler Nächtlicher Hämoglobinurie / One-Year Efficacy of Ravulizumab (ALXN1210) in adult patients with paroxysmal Nocturnal hemoglobinuria naive to complement inhibitors

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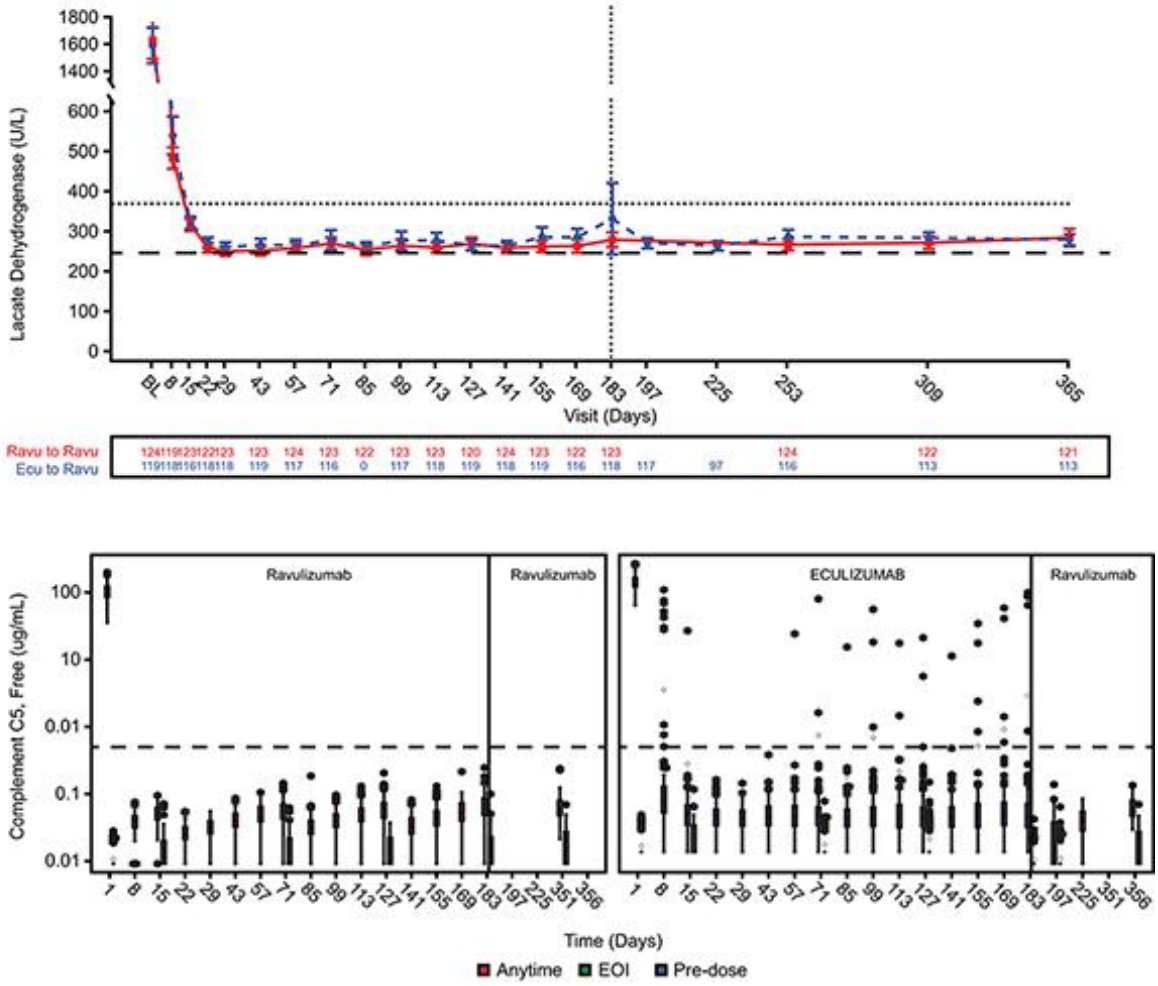
Introduction: Ravulizumab is a novel C5 complement inhibitor for treating paroxysmal nocturnal hemoglobinuria (PNH). In a phase 3 study in complement inhibitor-naive PNH patients (pts), qw8 ravulizumab was non-inferior to qw2 eculizumab for all endpoints after 26 wks. The efficacy profile of ravulizumab after switching from eculizumab in adult PNH pts was characterized in an extension study (NCT02946463).

Methods: In this phase 3, active-controlled, open-label study (123 centers, 25 countries) pts were randomized to eculizumab (n=121) or ravulizumab (n=125) for 26 wks. Then, pts on ravulizumab continued ravulizumab maintenance (R-R arm), and pts on eculizumab switched to ravulizumab (E-R arm). Data for lactate dehydrogenase normalization (LDH-N), transfusion avoidance, breakthrough hemolysis (BTH), LDH levels and plasma free C5 levels were obtained through 52 wks

Results: In the R-R-arm, 74% (26 wks) vs 77% (27-52 wks) of pts avoided transfusion. Over 90% (n=83) of pts avoiding transfusion in wks 0-26 maintained this response through 52 wks; 38% (n=12) requiring transfusion in wks 0-26 avoided it in wks 27-52. In E-R, 66% (26 wks) vs 67% (52 wks) avoided transfusion; 87% (n=69) avoiding transfusion for 26 wks maintained this response through 52 wks and 28% (n=11) (E-R) requiring transfusion in wks 0-26 avoided it in wks 27-52. LDH-N occurred in 48% (R-R)/42% (E-R) of pts at 26 wks and 44%/40% at 52 wks. Pts on ravulizumab had a 77% mean LDH reduction from baseline at 26 and 52 wks. All R-R pts (n=119) maintained free C5 < 0.5mg/mL through 52 wks (Figure). No E-R pts had free C5 >0.5mg/ml after the switch. BTH occurred in 4% (R-R)/11% (E-R) of pts at wks 0-26 and 3%/2% at wks 27-52. No BTH event (wks 27-52) was associated with free C5 >0.5mg/ml. This demonstrates maintenance of free C5 control in pts on ravulizumab. The drug was well tolerated and the most common treatment-related adverse events decreased in frequency during treatment.

Conclusions: Ravulizumab showed consistent and durable efficacy over 52 wks. All pts with suboptimal free C5 control on eculizumab achieved complete free C5 inhibition after switch to ravulizumab, associated with a decreased BTH incidence.



[LDH and free C5 concentration in the R-R and E-R arm]

V1026 - GADD45b spielt eine essentielle Rolle in der G-CSF-vermittelten Differenzierung hämato-poetischer Stammzellen zu Granulozyten / GADD45b plays an essential role in the G-CSF triggered granulocytic differentiation of hemato-poietic stem cells

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The mechanism of maturation arrest of myeloid progenitors in severe congenital neutropenia (CN) patients is not fully elucidated. We identified GADD45b as a stress sensor downstream of G-CSF signaling which was shown to be essential in stress-induced murine myelopoiesis. In CN patients G-CSF fails to activate GADD45b expression which might be a reason of diminished granulopoiesis in CN patients. To test this hypothesis, we inhibited GADD45b expression in $CD34^+$ cells and iPSCs of healthy donors using specific CRISPR/Cas9 RNP. We evaluated G-CSF-triggered myeloid differentiation of GADD45b-deficient iPSCs using embryoid body (EB)-based method and found that iPSCs present with severely diminished granulocytic differentiation upon *GADD45B* knockout, as assessed by FACS, CFU assay and morphological examination of cytospin slides. We also observed reduced G-CSF-mediated granulocytic differentiation of GADD45b-deficient $CD34^+$ cells of healthy individuals in CFU assay and liquid culture differentiation. Importantly, rescue of GADD45b in HSPCs of CN patients (n = 2) by lentivirus-based transduction of *GADD45B* cDNA restored defective granulocytic differentiation, as compared to control transduced cells. To determine the role of GADD45b *in vivo*, we performed transient gadd45bb knockout in zebrafish and found that gadd45bb-deficiency in zebrafish embryos resulted in drastically reduced numbers of mpo-expressing myeloid cells. These data strongly support the essential role of GADD45b in G-CSF-mediated granulocytic differentiation.

In silico analysis of *GADD45B* promoter revealed putative binding sites for C/EBP transcription factors. Reporter gene assay and ChIP confirmed C/EBPα binding to the *GADD45B*promoter. Intriguingly, C/EBPα expression is severely diminished in myeloid cells of CN patients. To study the mechanism by which GADD45b mediates myeloid differentiation, we performed RNA sequencing and EPIC methylation array of WT or GADD45b-deficient $CD34^+$ HSPCs treated or not with G-CSF. Interestingly, in GADD45b-deficient cells, G-CSF failed to induce hypomethylation and mRNA expression of genes important in granulocyte differentiation and functions, such as *RXRA*, *MEFV*, *CXCR1*, *FPR2*, *SERPINA1*.

In summary, our data suggest that GADD45b plays an essential role in granulocytic differentiation and inability of G-CSF to induce *GADD45B* expression in CN patient cells might be a reason for the defective granulopoiesis.