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ORAL ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Results of the Phase II of Epirchop Study, Evaluating the Efficacy of Tazemetostat in Combination with R-CHOP in Elderly Newly Diagnosed Diffuse Large B Cell Lymphoma (DLBCL): A Lysa Study

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Introduction:
Tazemetostat (TAZ) is a selective oral EZH2 inhibitor with a favorable safety profile and activity in pts with either *EZH2*wild type or mutant B-cell NHL. In the phase I part of Epi-RCHOP study, we reported that R-CHOP plus TAZ (Taz-RCHOP) was well tolerated with safety and PK results comparable to R-CHOP alone, and the RP2D of TAZ in combination with RCHOP was consistent with TAZ monotherapy (800mg BID). We report here the efficacy results of the phase II TAZ R-CHOP study (Epi-RCHOP, NCT02889523), in pts 60-80y with newly diagnosed DLBCL.
Methods:
Pts received 6 R-CHOP every 21 days in combination with continuous TAZ at 800 mg BID, plus 2 cycles of TAZ and R (cycle 7 and 8). Prophylaxis with G-CSF, valaciclovir and trimethoprim sulfamethoxazole were strongly recommended. Primary endpoint was PET-based complete metabolic response rate (CR, Lugano 2014) at end of study treatment (EOT, i.e 8 cycles or at time of permanent treatment discontinuation) (data cut-off was January 30, 2023). Sample size calculation was made with the expectation of an increase of 10% in CR, with an H0 hypothesis of 70% and an H1 assumption of 80%, leading to a theorical sample size of 122 pts, assuming a drop out of 5%. The efficacy set correspond to pts who signed an informed consent and received at least one dose of TAZ. Pts without response assessment (no matter the reason) were considered non-responders. Key secondary objectives were progression free and overall survival. A sensitivity analysis was performed excluding pts who withdrawn their consent (N=112). Analyses were conducted using SAS® version 9.3.
Results:

From July 31, 2020 to July 18, 2022, 122 pts were enrolled in 27 LYSA centers. Median age was 70 years (60-80), 57% were female, 12% had an ECOG-PS2+, 70.5% a stage IV disease and 19.7% stage III, 66% elevated LDH, 73.8% an IPI of 3-5. Mutational profile was available for 76 pts, of whom 10 (13%) had an *EZH2* mutations and 26 (34%) and EZB profile as assessed with LymphGen classifier. One hundred pts (82%) received 8 cycles and 22 had a premature treatment discontinuation (PTD), 12 (9.8%) during the first 2 cycles and 10 (8.2%) between cycle 3 and 8. Reasons for PTD were: consent withdrawal (N=10, including 7 during cycle 1 & 2), adverse events (AE, N=6, including 2 treatment related), death (N=2, both due to septic shock), protocol deviation (N=2), progressive disease (N=1) or physician decision (N=1). Overall, the median percentage of TAZ dose received was 98.4% (mean 77.2%, Q1: 61%; Q3: 100%), and AE led to TAZ interruption in 4.1%, discontinuation in 2.8% and dose reduction in 2.4% of the cases. Mean time between cycles was 21.5 days. In oct 2020, after the inclusion of 22 pts, recommendation to cap vincristine at 1mg was done, due to an excess of constipation. At end of treatment or PTD, 92/122 pts (75.4%, IC95: 66.8-82.8%) achieved CR, 8 (6.6%) PR, 5 (4.1%) had a PD, 2 (1.6%) had died (septic shock) and 15 (12.3%) were not evaluated and considered as non-responders. The primary objective was not met in this efficacy set, with a CR of 75.4% (lower than the H1 at 80%). The sensitivity analysis, excluding the 10 pts that withdrawn their consent (all non-evaluated), showed a CR rate of 82.1% (92/112, IC95: 73.8-88.7%) and PR rate of 7.1%. After a median follow-up of 18.5 months (Range = [0.2; 28.1]), 17/122 pts had a relapse/progression (13.9%) and 12 had died: 4 due to lymphoma, 3 to COVID-19, 4 to AE (2 septic shock, 1 acute myeloid leukemia and 1 heart failure), 1 unknown cause (in CMR). The estimated 18m PFS and OS were 77.7% (IC95: 67.5-85.1%) and 88.8% (IC95: 79.9-93.9%) respectively. Most frequent AE were: neutropenia (53%), anemia (51%), nausea (47%), asthenia (42%), peripheral neuropathy (37%), gastro-intestinal hypomotility (35%), weight loss (28%), vomiting (24%), thrombocytopenia (24%). AE of grade 3 or more occurred in 73% of the pts and were mainly hematological AE with neutropenia (48%, including 6% of febrile neutropenia), anemia (23%), thrombocytopenia (17%) and gastro-intestinal disorder (overall 10.7%). Red blood cell and platelets transfusions were administered in 31% and 11.5% of the pts respectively.
Conclusion:
R-CHOP plus TAZ is doable. Efficacy results in this trial conducted during the COVID pandemic in a particularly challenging population, suggest that the combination warrant further investigation including correlative studies with molecular subclassification that will be presented.

Disclosures Sarkozy: *Incyte Bioscience:* Consultancy, Other: Travel, Accommodations, Expenses; *BMS:* Consultancy; *Janssen:* Consultancy; *AbbVie:* Honoraria; *GSK:* Consultancy; *Gilead:* Other: Congress fees; *Roche:* Other: Travel, Accommodations, Expenses, Research Funding; *Prelude Therapeutics:* Consultancy; *Beigene:* Consultancy; *Lilly:* Honoraria; *Gilead:* Other: Travel, Accommodations, Expenses; *Takeda:* Other: Travel, Accommodations, Expenses. **Molina:** *Janssen:* Other: Travel and congress fees. **Houot:** *Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda, F. Hoffmann-La Roche Ltd:* Honoraria; *Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte, Miltenyi:* Consultancy. **Herbaux:** *AbbVie, F. Hoffmann-La Roche Ltd, AstraZeneca, Janssen:* Honoraria; *AbbVie, F. Hoffmann-La Roche Ltd, AstraZeneca, Janssen:* Consultancy; *AbbVie, Takeda:* Research Funding; *Physician and professor of Hematology at academic center (CHU Montpellier France):* Current Employment. **Ysebaert:** *Beigene:* Honoraria, Research Funding, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Gilead/Kite:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria, Research Funding; *BMS/Celgene:* Consultancy, Honoraria; *Abbvie:* Honoraria, Research Funding, Speakers Bureau. **Bachy:** *Takeda:* Honoraria; *Pfizer:* Honoraria, Other: Personal Fees; *Incyte:* Honoraria; *Novartis:* Honoraria, Other: Personal Fees; *Bristol Myers Squibb:* Honoraria, Other: Personal Fees, Research Funding; *Amgen:* Research Funding; *Kite, a Gilead Company:* Honoraria, Other: Personal Fees; *Roche:* Consultancy, Honoraria; *Hospices Civils de Lyon Claude Bernard Lyon 1 University:* Current Employment. **Jardin:** *Janssen, Gilead, AbbVie, F. Hoffmann-La Roche Ltd, BMS, Takeda:* Honoraria. **Morschhauser:** *F. Hoffmann-La Roche Ltd, AbbVie, BMS, Genmab, Gilead, Novartis:* Consultancy; *F. Hoffmann-La Roche Ltd, Gilead, AbbVie:* Membership on an entity's Board of Directors or advisory committees. **Ribrag:** *Incyte:* Consultancy; *NanoString:* Consultancy; *Roche:* Consultancy; *Argenx:* Research Funding; *Astex Pharmaceuticals:* Research Funding; *GSK:* Research Funding; *Gilead:* Consultancy; *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees.

OffLabel Disclosure: Tazemetostat in first line DLBCL in combination with R-CHOP

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