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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Subunit-Specific Analysis of Cohesin-Mutant Myeloid Malignancies Reveals Distinct Ontogeny and Outcomes

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Introduction:Loss of function mutations in the cohesin complex ring components and modulators *STAG2, RAD21, SMC1A, SMC3,* and *PDS5B* are recurrent genetic drivers in myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and MDS/myeloproliferative neoplasm (MPN) overlap syndromes. However, whether different cohesin subunit mutations share disease characteristics and prognostic impact is not well understood.
Methods: We assembled a cohort of 4,439 patients with hematologic neoplasms at the Dana-Farber Cancer Institute (DFCI) and the Munich Leukemia Laboratory (MLL), and identified a subset of 790 cohesin-mutant patients, the largest cohesin-mutant cohort to date. We performed a retrospective analysis of the incidence, clinical presentation, genomic landscape, and clinical outcomes in a cohesin subunit-specific way.
Results: *STAG2* mutations were most common and present in 610 cases (diagnosed as MDS (50%), AML (36%), MDS/MPN (10%)), followed by *RAD21* in 104 (20% MDS, 64% AML, 2% MDS/MPN), *SMC3* in 26 (35% MDS, 42% AML, no MDS/MPN), *SMC1A* in 22 (27% MDS, 55% AML, 5% MDS/MPN), *PDS5B* in 16 (13% MDS, 38% AML and 6% MDS/MPN), and 12 cases with more than one mutated cohesin gene (50% MDS, 33% AML, 8% MDS/MPN). Within the DFCI cohort, 256 (82%) patients were diagnosed with a myeloid malignancy and 55 (18%) patients with a non-myeloid hematologic malignancy. We focused our subsequent analysis on 735 patients diagnosed with MDS, MDS/MPN or AML, and compared them to 3,649 cohesin-wildtype (WT) patients in the DFCI and MLL cohorts.
We found that *STAG2* mutations were acquired at the MDS stage and were associated with MDS with increased blasts (75% cases with MDS-IB1 or IB2) and secondary AML. We also noted their co-occurrence with secondary AML-type mutations, such as *ASXL1* (64%, OR=5.5, FDR=5e-29), *SRSF2* (45%, OR=7.4, FDR=5-e31) and *RUNX1* (37%, OR=3.5, FDR=2e-13), and trisomy 8 (OR=10.6, FDR= 2.2e-50). In contrast, mutations in *RAD21*, *SMC1A*, *SMC3* and *PDS5B* shared features with *de novo* AML, including co-occurrence with *NPM1* (32%, OR 4.3, FDR=1e-6) and *FLT3* (23%, OR= 2.8, FDR= 0.01), and association of *RAD21* and *SMC1A* with t(8;21) AML (OR= 131;134; FDR= 3.8e-5;4.1e-19). Of note, both *STAG2* and *RAD21* mutations shared a mutational exclusivity with *TP53* mutations (OR=0.04-0.06, FDR < 0.001, **Figure 1A)**.
We next assessed the impact of different cohesin mutations on clinical outcomes. We conducted independent analyses of overall survival (OS) and progression free survival (PFS) in MDS and AML. Given our observations that cohesin mutations were mutually exclusive with *TP53* mutations, and the established prognostic impact of *TP53* mutations, we compared the overall survival (OS) and AML-free survival (PFS) of patients with *STAG2*-mutant MDS (n=119) to *TP53*-mutant MDS (n=280) and cohesin/ *TP53*-WT MDS (n=1,023). With a median follow-up (FU) of 51.1 months we observed a significantly worse OS of *STAG2*-mutant MDS compared to cohesin and *TP53*-WT MDS (HR 1.44, CI= 1.10-1.89, p=0.007) and a similar risk of leukemic transformation as *TP53*-mutant MDS cases (median AML-PFS of 15.4 months for *STAG2*, and 12.1 months for *TP53*, p=0.3). Furthermore, *STAG2*-mutant AML (n=148) had significantly worse OS than AML without myelodysplasia related changes (MR)

(n=1384) (HR= 0.62, 95% CI=0.5-0.76, p<0.001, median FU 42.8 months), and similar outcomes as AML-MR without *TP53* mutations (n=567), (HR=1.25, 95% CI= 1.01-1.55, p=0.04). Importantly, this pattern was distinct from outcomes of *RAD21*-mutant AML (n=39), which was almost identical to AML-non-MR and significantly better than *STAG2*-mutant AML OS (HR= 0.56, 95% CI= 0.34-0.93, p=0.024) (**Figure 1B)**. The effects of *STAG2* and *RAD21* mutations on OS remained significant when censored for allogeneic stem cell transplantation. Our findings suggest that only *STAG2* mutations confer a negative impact on MDS and AML, and this is attributed to secondary ontogeny.

Conclusions: In summary, our study establishes a role for different cohesin subunit mutations in distinct subtypes of MDS and AML, which has significant prognostic implications and expands our current understanding of this important group of driver genes. The findings from our subunit-specific analysis demonstrate that while *STAG2* mutations are characterized by secondary AML ontogeny arising from MDS and associated with a worse prognosis, *RAD21* mutations are associated with *de novo* AML and better survival.

Disclosures Meggendorfer: *MLL Munich Leukemia Laboratory:* Current Employment. **Winer:** *Curis Inc:* Consultancy; *Abbvie:* Consultancy. **Stone:** *Jazz:* Consultancy; *Takeda:* Other: DSMB; *Kura One:* Consultancy; *BerGenBio:* Consultancy; *Amgen:* Consultancy; *Ligand Pharma:* Consultancy; *Rigel:* Consultancy; *Cellularity:* Consultancy; *AvenCell:* Consultancy; *Lava Therapeutics:* Consultancy; *Syntrix:* Other: DSMB; *Hermavant:* Consultancy; *GSK:* Consultancy; *Epizyme:* Other: DSMB; *Aptevo:* Other: DSMB; *CTI Biopharma:* Consultancy; *Abbvie:* Consultancy. **DeAngelo:** *Incyte:* Honoraria; *Blueprint:* Research Funding; *Jazz:* Honoraria; *AbbVie:* Research Funding; *Novartis:* Research Funding; *Autolus:* Honoraria; *Takeda:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *GlycoMimetics:* Research Funding; *Servier:* Honoraria; *Amgen:* Honoraria; *Blueprint:* Honoraria; *Gilead:* Honoraria; *Kite:* Honoraria. **Garcia:** *Genentech:* Consultancy, Research Funding; *Astellas:* Consultancy; *Bristol Myers Squibb:* Consultancy; *AstraZeneca:* Research Funding; *Prelude:* Research Funding; *Pfizer:* Research Funding; *New Wave:* Research Funding; *Servier:* Consultancy; *Gilead:* Consultancy; *AbbVie:* Consultancy, Research Funding. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Lindsley:** *Takeda Pharmaceuticals:* Consultancy; *Bluebird bio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Qiagen:* Consultancy; *Sarepta Therapeutics:* Consultancy; *Verve Therapeutics:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Vertex Pharmaceuticals:* Consultancy. **Luskin:** *AbbVie:* Research Funding; *Jazz:* Honoraria; *Pfizer:* Honoraria; *Novartis:* Honoraria, Research Funding. **Stahl:** *GSK:* Membership on an entity's Board of Directors or advisory committees; *Dedham group:* Consultancy; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Other: GME activity ; *Boston Consulting:* Consultancy; *Rigel:* Membership on an entity's Board of Directors or advisory committees; *Curis Oncology:* Other: GME activity ; *Haymarket Media:* Other: GME activity ; *Clinical care options:* Other: GME activity ; *Sierra Oncology:* Membership on an entity's Board of Directors or advisory committees; *Kymera:* Membership on an entity's Board of Directors or advisory committees.

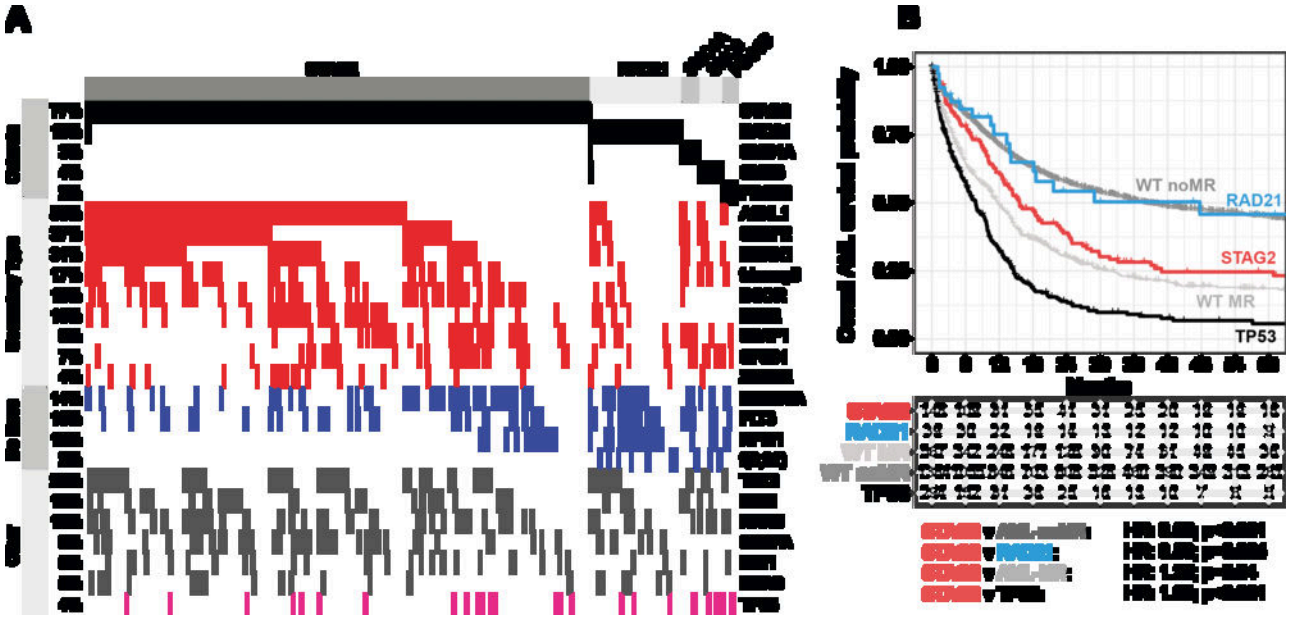

Figure 1

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