EVERSANA TO PRESENT FIVE POSTER ABSTRACTS AT THE 61ST AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING AND EXPOSITION IN ORLANDO, FLORIDA

3893 Improved Overall Survival with Enasidenib Compared with Standard of Care Among Patients with Relapsed or Refractory Acute Myeloid Leukemia and IDH2 Mutations: A Propensity Score Matching Analysis Using Data from the AG221-C-001 Trial and Two Data Sources from France and Germany

Program: Oral and Poster Abstracts

Session: 615. Acute Myeloid Leukemia: Commercially Available Therapy, excluding Transplantation: Poster III

Hematology Disease Topics & Pathways:

Diseases, AML, Myeloid Malignancies

Monday, December 9, 2019, 6:00 PM-8:00 PM

Hall B, Level 2 (Orange County Convention Center)

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Introduction: Enasidenib is approved for the treatment of patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 mutation (m*IDH2*+) in the USA. To compare the relative effectiveness of enasidenib with standard of care (SoC) in terms of overall survival (OS) among patients with

m*IDH2*+ R/R AML who are ineligible for hematopoietic cell transplantation (HCT), a propensity score matching (PSM) analysis was performed using data from the phase 1/2 AG221-C-001 single-arm trial and a real-world chart review study of patients from France (France chart review [FCR] study) and historical data from the AML Study Group (AMLSG) database.

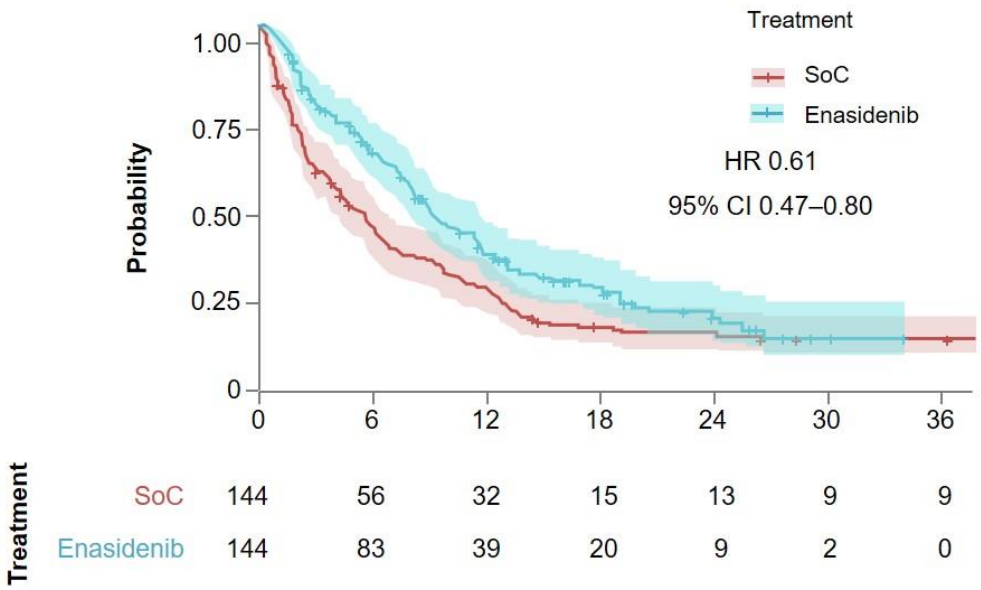
*Method*s: Individual patient data (IPD) were obtained from the phase 1/2 AG221-C-001 trial for enasidenib (100 mg/day) and from the FCR study and AMLSG database for SoC. Data from the FCR study and AMLSG database were combined to create a single pooled SoC group. Based on clinician feedback and data availability, 6 clinically important covariates (history of HCT before baseline, age, number of prior lines of AML therapy at baseline, cytogenetic risk at baseline, history of myelodysplastic syndromes [MDS], Eastern Cooperative Oncology Group performance status) were used for propensity score calculation and matching. Patients from the 2 groups were matched using nearest neighbor 1:1 matching with a caliper of 0.2 standard deviations (SDs) of the logit transform of the propensity score. A comparison of means, SDs, and standardized mean differences (SMDs) between treatment groups was conducted for each covariate to assess the balance between the pre- and post-match populations. Hazard ratios (HRs) were estimated using doubly robust Cox proportional hazard models that adjusted for the aforementioned covariates. Sensitivity analyses were conducted using alternative matching algorithms, weighting methods, and covariates. Additional sensitivity analyses excluding patients with early events (landmark analyses) were conducted.

Results: Before matching, considerable differences existed between the enasidenib (N = 195) and SoC (N = 258) groups (i.e. SMDs > 0.10 were observed for nearly all covariates), and OS was numerically in favor of enasidenib (HR 0.82, 95% confidence interval [CI] 0.66–1.01). After matching, the enasidenib and SoC groups (N = 144 per group) were mostly well balanced (SMDs for all covariates except for prior MDS were < 0.10), and enasidenib was associated with significantly longer OS than SoC (HR 0.61, 95% CI 0.47–0.80). The median OS was 8.8 months (95% CI 7.5–10.7) for enasidenib and 4.4 months (95% CI 3.5–6.1) for SoC (Figure). Sensitivity analyses (i.e., analyses using alternative matching algorithms, weighting methods and covariates, and landmark analyses) delivered results consistent with the primary analysis.

Conclusions: The results of this study suggest that enasidenib may prolong survival compared with SoC for patients with m*IDH2*+ R/R AML who are ineligible for HCT. The incorporation of 2 separate data sources (i.e. the FCR study and AMLSG database) into a combined SoC group increases the generalizability and robustness of these findings. Additional studies should aim to validate these findings using data sources from other countries and assess the comparative efficacy of enasidenib with SoC for other clinically important

outcomes.

Figure. Kaplan–Meier Estimated OS, 1:1 Nearest Neighbor-Matched Sample of Enasidenib (AG221-C-001) and SoC (FCR Study and AMLSG Database)



The reported HR and 95% CI were estimated from a Cox proportional hazards analysis of the matched sample using a robust variance estimator to account for the presence of matching. The shaded area in the Kaplan–Meier curve represents the 95% CI.
AML, acute myeloid leukemia; AMLSG, AML Study Group; CI, confidence interval; FCR, France chart review; HR, hazard ratio; OS, overall survival; SoC, standard of care.

Disclosures: De

Botton: *Syros:* Consultancy; *Servier:* Consultancy; *Janssen:* Consultancy; *Daiichi:* Consultancy; *AbbVie:* Consultancy; *Agios:* Consultancy, Research Funding; *Celgene Corporation:* Consultancy, Speakers Bureau; *Forma:* Consultancy, Research Funding; *Novartis:* Consultancy; *Pfizer:* Consultancy; *Pierre Fabre:* Consultancy; *Bayer:* Consultancy; *Astellas:* Consultancy. **Brandwein:** *Roche:* Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria; *Jazz Pharma:* Consultancy, Honoraria; *Otsuka:* Honoraria. **Stein:** *Agios:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Daiichi Sankyo, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Bioline:* Membership on an entity's Board of Directors or advisory committees; *Genentech:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *PTC Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Syros:* Membership on an

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3066 Outcomes of Patients with t(11;14) Multiple Myeloma: An International Myeloma Working Group Multicenter Study

Program: Oral and Poster Abstracts

Session: 651. Myeloma: Biology and Pathophysiology, excluding Therapy: Poster II

Hematology Disease Topics & Pathways:

Diseases

Sunday, December 8, 2019, 6:00 PM-8:00 PM

Hall B, Level 2 (Orange County Convention Center)

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Background: Multiple myeloma (MM) is a heterogeneous disease with varying survival outcomes depending on the presence of certain genetic abnormalities. Common abnormalities include trisomies, translocations involving the chromosome 14, and amplifications or deletions of chromosomes 1, 13, and 17. t(11;14), occurring in 15% of patients with myeloma, had been considered a standard risk abnormality, but recent data suggest inferior outcome. This is important as new therapeutic options such as the BCL-2 inhibitor venetoclax has been shown to be particularly effective in t(11;14) patients.

Methods: This was a multicenter study to identify the outcomes of patients with t(11;14), using a retrospectively assembled cohort. Patients with MM diagnosed between 2005 and 2015 with t(11;14) identified on FISH performed within six months of diagnosis, and with treatment details available and if alive, a minimum of 12 months of follow up, were enrolled.

Results: The current analysis includes 1216 patients; median age of 62.56 years; 58.7% male. The median follow-up from diagnosis for the entire cohort was 51.9 months; 69.1% of the patients were alive at the last follow up. ISS stage distribution included: Stage I (35.7%), Stage II (34.0%) and Stage III (15.1%), data was missing for the rest. The distribution of concurrent FISH abnormalities included: trisomies (3.5%), del 13q (13.3%), 1q amp (8.8%), and del 17p or monosomy 17 (5.8%). Initial regimen included: 27.2% had an immunomodulatory (IMiD), 45.9% had a proteasome inhibitor (PI), 17.7% had both, and 9.0% had no novel agent. The drug classes by line of therapy are shown in **Table 1**. An early stem cell transplant (defined as within 12 months of start of first line treatment) was used in 49.4% of patients. The median time to next treatment (TTNT) after starting initial treatment was 26.6 (95% CI: 23.9 to 29.2) months. The median overall survival (OS) from diagnosis for the entire cohort was 95.1 (95% CI: 85.9 to 105.9) months; 4-year estimates for those diagnosed from January 2005 to December 2009, and from January 2010 to December 2014 were 77.5% and 78.6%, respectively. The median OS for those with any one high risk FISH lesion (del 17p/ 1q amp) was 67.5 (55.2, 97.1) versus 101.7 (89.7, 107.3) months. Patients with early SCT (within 12 months of diagnosis) had better OS: 108.3 (103.8, 133.0) vs. 69.8 (61.5, 80.3) months.

Conclusion: Patients with t(11;14) without high risk FISH abnormalities have an excellent survival. Patients receiving a PI + IMiD combination and those receiving autologous SCT as part of initial therapy had best

survival. Though numbers are limited, patients in the later lines receiving newer drugs such as venetoclax and daratumumab had high response rates and durable responses.

Table 2: Number (%) of patients in regimen category by line of therapy.

Regimen type	First line of therapy			Second line of therapy			Third line of therapy		
	n (%)	ORR (%)	TTNT (median, months)	n (%)	ORR (%)	TTNT (median, months)	n (%)	ORR (%)	TTNT (median, months)
IMiD	281 (27.2)	73	26.3	254 (37.2)	64	25.3	193 (41.4)	51	13.2
PI	474 (45.9)	74	24.3	224 (32.8)	65	15.6	121 (26.0)	47	10.0
PI + IMiD	183 (17.7)	90	37.0	117 (17.1)	64	11.8	61 (13.1)	52	9.0
Dara	2 (0.2)	100	22.8	14 (2.0)	86	17.3	20 (4.3)	45	9.46
Venetoclax	0 (0.0)	NA	-	3 (0.4)	100	-	7 (1.5)	86	25.3
Other	93 (9.0)	66	19.0	71 (10.4)	54	4.2	64 (13.7)	44	8.4
Total	1033	76	26.6	683	64	17.9	466	49	11.2

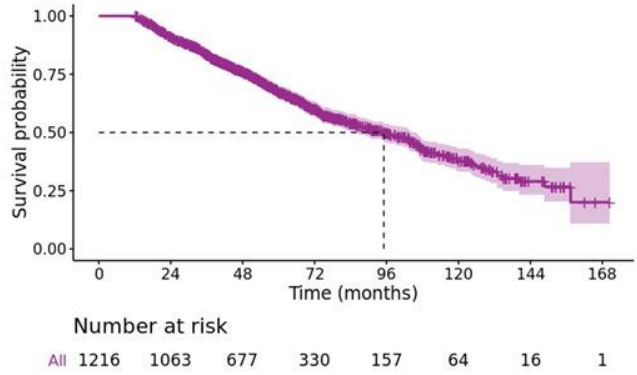
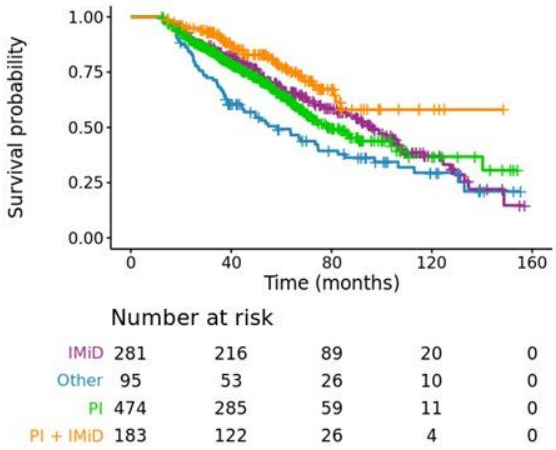


Figure 1: Overall survival of all t(11;14) patients from date of diagnosis

Figure 2: Survival of patients by regimen type received in the first line of therapy, from date of diagnosis



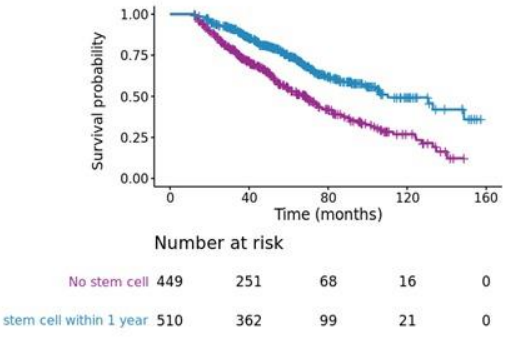


Figure 3: Survival of patients by stem cell transplant received within 12 months of the first line of therapy, from date of diagnosis

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Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria. **Kastritis:** *Amgen:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding; *Takeda:* Honoraria; *Pfizer:* Honoraria; *Prothena:* Honoraria; *Genesis:* Honoraria. **Yee:** *Amgen:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Karyopharm:* Consultancy; *Adaptive:* Consultancy. **Raje:** *Amgen Inc.:* Consultancy; *Bristol-Myers Squibb:* Consultancy; *Celgene Corporation:* Consultancy; *Takeda:* Consultancy; *Janssen:* Consultancy; *Merck:* Consultancy. **Rosta:** *Cornerstone Research Group:* Employment. **Haltner:** *Cornerstone Research Group:* Employment. **Cameron:** *Cornerstone Research Group:* Employment, Equity Ownership. **Durie:** *Amgen, Celgene, Johnson & Johnson, and Takeda:* Consultancy.

3012 Persistent Red Blood Cell (RBC) Transfusion Is Associated with Increased Mortality Risk in Transfusion-Dependent (TD) Patients with Myelodysplastic Syndromes (MDS) with Ring Sideroblasts (RS+)

Program: Oral and Poster Abstracts

Session: 637. Myelodysplastic Syndromes—Clinical Studies: Poster II

Hematology Disease Topics & Pathways:

survivorship, Biological, Diseases, Therapies, MDS, Quality Improvement , Myeloid Malignancies, transfusion

Sunday, December 8, 2019, 6:00 PM-8:00 PM

Hall B, Level 2 (Orange County Convention Center)

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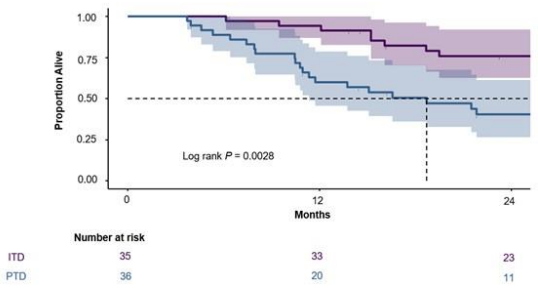
Introduction: Patients with lower-risk (LR) MDS, defined as very low-, low-, and intermediate-risk by the Revised International Prognostic Scoring System (IPSS-R), have a reduced risk of progressing to acute myeloid leukemia compared with higher-risk patients, but a shortened overall survival (OS) compared with age-matched controls. MDS patients with RS have a better prognosis than those without RS, but may experience extended periods of RBC transfusion dependence. RBC transfusion dependence is associated with reduced OS in patients with LR-MDS, but studies focusing on RBC transfusion dependence and OS in RS+ MDS patients are lacking. To address this gap, data from the Canadian MDS Registry were used to assess the relationship between RBC transfusion dependence patterns and OS in this patient population.
Methods: Patients with a diagnosis of RS+ MDS who were identified as transfusion dependent (TD) in the Canadian MDS Registry from 2008 to 2019 were included. Patients were considered TD if they received ≥ 1 RBC transfusion in at least one 8-week cycle. A sensitivity analysis was conducted wherein patients were considered TD if they received ≥ 1 RBC transfusion for 2 consecutive 8-week cycles. Patients were considered persistently TD (PTD) if they were TD throughout follow-up, or intermittently TD (ITD) if they were transfusion independent for periods of ≥ 8 weeks after an initial onset of TD. Covariates that were assessed included age, sex, IPSS-R risk score at enrollment, Eastern Cooperative Oncology Group performance status score at enrollment, ferritin level at first TD onset, Charlson Comorbidity Index at first TD onset, and receipt of iron chelation and anemia-treating therapies at first TD onset. Cox proportional hazards regression was used to test the association between PTD and mortality risk. Treatment patterns during follow-up were also examined.
Results: Between 2008 and 2019, 191 patients had a diagnosis of RS+ MDS, of which 107 required ≥ 1 RBC transfusion over at least one 8-week cycle during follow-up. Of the 107 patients who received ≥ 1 RBC transfusion, 71 had ≥ 2 assessments for transfusion dependence and complete data on all outcomes and covariates, 36 (50.7%) of whom were classified as PTD (Table 1). Compared with ITD patients, PTD patients were older (mean age ± standard deviation [SD]: 75.11 ± 8.34 vs 69.59 ± 13.33 years) and had higher IPSS-R risk (17% of PTD patients were intermediate- or higher-risk compared with 3% of ITD patients). Median OS from first TD onset was 18.7 months (95% confidence interval [CI] 11.3–46.9) for PTD patients, compared with 48.7 months (95% CI 39.0–not evaluable) for ITD patients (Figure). After adjusting for baseline covariates, being PTD was associated with significantly greater mortality risk than being ITD (hazard ratio [HR] 2.24, 95% CI 1.18–4.25). Similar results were observed for the sensitivity analysis requiring ≥ 1 RBC transfusion for 2 consecutive 8-week cycles prior to the onset of TD (HR 2.18, 95% CI 1.13–4.21). Compared with ITD patients,

PTD patients were less likely to receive iron chelation therapies (42% vs 54%), erythropoiesis-stimulating agents (25% vs 40%), and lenalidomide (14% vs 20%) during follow-up (Table 2).

Conclusions: In this study, we extracted Canadian MDS Registry data on RBC transfusions and OS for MDS patients with RS+ MDS. More than half (50.7%) of the identified cohort became TD during follow-up. Among those who received RBC transfusions, PTD patients had significantly shorter OS and increased mortality risk compared with ITD patients, and RBC transfusion dependence independently predicted inferior outcomes. These conclusions are consistent with previous findings on the relationship between RBC transfusions and OS in all patients with LR-MDS.

Figure 1. Kaplan–Meier Curve for OS by ITD Versus PTD



ITD, intermittently transfusion dependent; OS, overall survival; PTD, persistently transfusion dependent; TD, transfusion dependent.

Table 1. Summary Statistics by ITD Versus PTD

Patient characteristic	ITD (n = 35)	PTD (n = 36)
Follow-up, median (IQR), months	45.57 (25.32–89.75)	27.16 (12.43–59.38)
Age, mean (SD), years	69.59 (13.33)	75.11 (8.34)
CCI score, mean (SD)	0.77 (1.09)	0.86 (1.46)
Serum ferritin level, mean (SD), ng/mL	886.98 (764.75)	1,053.72 (968.27)
Female, n (%)	13 (37.1)	17 (47.2)
IPSS-R risk category, n (%)		
Very low	27 (77.1)	16 (44.4)
Low	7 (20.0)	14 (38.9)
Intermediate	1 (2.9)	4 (11.1)
High	0	2 (5.6)
ECOG PS score, n (%)		
1	14 (40.0)	7 (19.4)
2	18 (51.4)	26 (72.2)
3	3 (8.6)	3 (8.3)
Anemia therapies[a], n (%)	11 (31.4)	14 (38.9)
Iron chelation therapies[b], n (%)	5 (14.3)	4 (11.1)

[a] Receiving treatment with ≥ 1 of the following at first onset of transfusion dependence: ESA (e.g. erythropoietin [Eprex®], darbepoetin [Aranesp®]), HMA (azacitidine [Vidaza®], decitabine), immunosupressants (cyclosporine, antithymocyte globulin), lenalidomide (Revlimid®), or allogenic stem cell transplantation.
[b] Receiving treatment with ≥ 1 of the following at first onset of transfusion dependence: deferoxamine (Desferal®) or deferasirox (Exjade® or Jadenu®).
CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; IPSS-R, Revised International Prognostic Scoring System; IQR, interquartile range; ITD, intermittently transfusion dependent; n, observations; PTD, persistently transfusion dependent; SD, standard deviation; TD, transfusion dependent.

Table 2. Therapies Received During Follow-Up by ITD Versus PTD

Treatments, n (%)	ITD (n = 35)	PTD (n = 36)
Iron chelation therapy	19 (54)	15 (42)
G-CSF	3 (9)	2 (6)
ESA	14 (40)	9 (25)
HMA	10 (29)	10 (28)
Chemotherapy	3 (9)	2 (6)
Immunosuppressant	1 (3)	1 (3)
Lenalidomide	7 (20)	5 (14)
Allogenic stem cell transplantation	1 (3)	1 (3)
Other (e.g. valproic acid, tranexamic acid)	4 (11)	8 (22)
Percentage AML-free after 12-months (95% CI)	91.1 (82.0–100.0)	81.1 (68.4–96.2)

AML, acute myeloid leukemia; CI, confidence interval; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; ITD, intermittently transfusion dependent; PTD, persistently transfusion dependent.

Disclosures: Buckstein: *Takeda:* Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding. **Keating:** *Celgene:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria; *Seattle Genetics:* Consultancy; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *Shire:* Membership on an entity's Board of Directors or advisory committees; *Hoffman La Roche:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees. **Leber:** *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Celgene Corporation:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AbbVie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Astellas:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Jazz:* Honoraria, Membership on an entity's Board of

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4737 A Discrete Event Simulation Model to Evaluate the Impact of Treatment Sequences on Long-Term Patient Outcomes in Multiple Myeloma (MM)

Program: Oral and Poster Abstracts

Session: 902. Health Services Research—Malignant Conditions (Lymphoid Disease): Poster III

Hematology Disease Topics & Pathways:

Diseases, multiple myeloma, therapy sequence, survivorship, Therapies, Combinations, Plasma Cell Disorders, Lymphoid Malignancies, Quality Improvement

Monday, December 9, 2019, 6:00 PM-8:00 PM

Hall B, Level 2 (Orange County Convention Center)

Jinan Liu, PhD[1*], *Daniel Moldaver, PhD*[2*], *Xinmei Zhu, PhD*[3*], *Allen Zhou, BASc*[2*], *Eric M Maiese, PhD*[1*] *and Sarah Hollmann, M.Biotech*[2*]

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Purpose: Many new therapies have been approved for the treatment of multiple myeloma (MM) in recent years. In June 2019, daratumumab (Darzalex®), a CD38-directed monoclonal antibody, in combination with lenalidomide and dexamethasone (DRd), received FDA approval for the treatment of newly diagnosed MM (NDMM) patients ineligible for stem cell transplantation. This approval provides NDMM patients with a new option as first-line therapy, however, with many options for MM treatment available, identification of the optimal sequence of treatments becomes of critical importance to healthcare providers and payers.

Objective: To develop a treatment sequencing discrete event simulation (DES) model that compares unique treatment sequences and estimates the impact of first-line DRd on longer-term outcomes (i.e. survival through multiple lines of therapy) in a general population of MM patients.

Methods: A DES model of MM treatment sequences was developed. FDA approved and NCCN recommended non-transplant therapies were included. Treatment efficacy was estimated by digitizing and extrapolating progression-free and overall survival (OS) Kaplan-Meier (KM) data, using established methods (Guyot *et al.,* 2012). Five common parametric functions were fit, and the curve-of-best-fit was determined by standard statistics (i.e., Akaike & Bayesian information criterion) and visual inspection. The model was developed to allow patients to go through up to 6 lines of treatment. The time of progression and death events were randomly assigned based on the estimated parametric functions. All-cause mortality data (US Census 2016)

were considered in the simulation of survival. Where data were not available, previous therapies were assumed not to impact the efficacy of subsequent therapies.

Model survival predictions were validated against published real-world estimates of survival from: 1) a retrospective analysis of a large American electronic medical record database, Humedica (Hari *et al.,* 2018) and 2) a retrospective analysis of the Dutch PHAROS registry (Verelst *et al.,* 2017). The Humedica and PHAROS datasets reported on the effects of three and four lines of treatment, respectively, starting with newly diagnosed patients. From the Humedica dataset, first-line therapy consisted of proteasome inhibitor- (PI), immunomodulatory- (IMiD), and PI + IMiD-based regimens in 42%, 34% and 18% of patients, respectively, with other regimens used in 7% of cases. Treatment was primarily doublets (63%) rather than triplets (37%). From the PHAROS registry, first-line therapy was primarily thalidomide-based (66%), bortezomib-based (15%), or lenalidomide-based (7%). Statistically, validation was quantified through the calculation of the mean absolute percent error (MAPE), a commonly used statistic to assess the accuracy of forecasts.

To estimate the impact of first-line DRd, a hypothetical analysis was simulated wherein all first-line treatments described within both the Humedica and PHAROS datasets were replaced with DRd. Following DRd, patients received subsequent treatment as described within those datasets.

Results: Restriction of the modeled treatment algorithm to treatment patterns described within the Humedica database and PHAROS registry led to valid simulated OS estimates that were in line with the published data (MAPE values of 9% and 19% for Humedica and PHAROS, respectively).

Utilization of DRd as first-line treatment was estimated to increase OS in scenario analyses (**Table 1**). The DES model estimated 5-year survival rates for frontline DRd with subsequent therapy based upon the Humedica and PHAROS datasets were 62% and 57%, respectively. In contrast, the estimated 5-year survival for the Humedica and PHAROS datasets without DRd frontline was 40% and 26% respectively, highlighting a 22-31% incremental survival benefit due to DRd at 5-years.

Conclusions: The MM DES model validated well to the published estimates of real-world OS. Preliminary results indicate that first-line treatment with DRd may improve OS in MM compared with historical treatment sequences, that include PI+IMiD based triplets as first-line treatment. The model is being further developed to

describe the impact of sequencing other MM treatment regimens to estimate the optimal treatment pathways.

Table 1. Overall Survival without DRd as First-Line Therapy and with DRd as First-Line Therapy

	Overall Survival (months)				
	12	**24**	**36**	**48**	**60**
Scenario without DRd as First-Line Therapy					
Up to 3 lines of therapy[a]	95%	83%	68%	53%	40%
Up to 4 lines of therapy[b]	86%	66%	48%	35%	26%
Scenario with DRd as First-Line Therapy					
First-line DRd followed by up to two lines of subsequent treatment, based upon Hari (2018)[c]	96%	89%	80%	71%	62%
First-line DRd followed by up to three lines of subsequent treatment, based upon Vereslt (2017)[c]	93%	83%	73%	64%	57%

Notes:
DRd = daratumumab+lenalidomide+dex

[a] Treatments were doublets or triplets classified as PI-based, IMID-based, PI+IMID-based, or other.
[b] Treatments were classified based on their backbone, including melphalan/prednisone, thalidomide, bortezomib, lenalidomide, pomalidomide/dexamethasone, or other.
[c] DRd data were derived from the MAIA trial; subsequent treatment was assumed equivalent to later lines therapy in Hari (2018) and Verelst (2017). After those described in the publications, patients were assumed to move on to best supportive care alone.
Sources: 1) Hari et al., (2018) J Geriatr Oncol 9: 138-144. 2) Verelst et al., (2017) HemaSphere 2(4): e45.

Disclosures: Liu: *Janssen Scientific Affairs, LLC:* Employment, Equity Ownership. **Moldaver:** *Janssen Scientific Affairs, LLC:* Consultancy. **Zhu:** *Janssen Scientific Affairs, LLC:* Other: contractor for Janssen. **Zhou:** *Janssen Scientific Affairs, LLC:* Consultancy. **Maiese:** *Janssen:* Employment, Equity Ownership. **Hollmann:** *Janssen Scientific Affairs, LLC:* Consultancy.

2167 Relationship between Vaso-Occlusive Crises and Important Complications in Sickle Cell Disease Patients

Program: Oral and Poster Abstracts

Session: 904. Outcomes Research—Non-Malignant Conditions: Poster I

Hematology Disease Topics & Pathways:

Diseases, sickle cell disease, Hemoglobinopathies

Saturday, December 7, 2019, 5:30 PM-7:30 PM

Hall B, Level 2 (Orange County Convention Center)

Miranda Bailey[1*], *Ajibola Abioye*[1*], *George Morgan*[2*], *Tom Burke, MSc*[2*], *Tim Disher*[3*], *Stephen Brown*[3*], *Ashley Bonner*[3*], *Eleonore Herquelot*[4*], *Ludovic Lamarsalle*[4*] *and Fanny Raguideau*[4*]

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Background: Sickle Cell Disease (SCD) describes a group of inherited hemolytic disorders caused by structurally abnormal variants of hemoglobin, which result in the sickle-shaped red blood cells (RBCs) that are characteristic of the disease. In patients with SCD, overexpression of adhesion molecules such as P-selectin bind sickled RBCs to endothelial cells; this contributes to hemolytic anemia and vaso-occlusive crises (VOCs), which are associated with severe acute and chronic pain.

Patients with sickle cell disease often experience disease-related complications, affecting a diverse range of organs, thought to be due to the systemic impact of chronically inflamed vasculature, ongoing hemolysis and ischemic damage as a result of vaso-occlusive events. Many of these SCD-related complications are associated with significant morbidity and poor quality of life. The relationship between VOC frequency and the incidence of these complications is still being assessed. This study aimed to assess the relationship between the number of VOC experienced in the previous year and the occurrence of complications using real world evidence from the UK, specifically the Hospital Episode Statistics (HES) database.

OBJECTIVE: To examine the relationship between the number of VOCs reported in the previous 12 months and the presence of SCD-related complications using a mixed modelling approach.

METHODS: All patients reported with a diagnosis of SCD between 2008 and 2017 in the NHS England's HES database were identified. Detailed follow-up data on the number of vaso-occlusive crisis events and occurrence of complications was evaluated using ICD-10 diagnosis codes. Assuming no unmeasured confounding, the causal effect of VOCs, categorized into 3 groups (0, 1-2, 3+), was estimated using marginal structural models (MSM) for the complications reported in the dataset. To obtain inverse probability of treatment and censoring weights (IPTW and IPCW), the probability of being in each VOC category was estimated with a multinomial logistic model, and subsequently, the probability of being censored was estimated with a binary logistic model. The two models were adjusted for age, gender, ethnicity, and the occurrence in the previous 12 months of the 20 most common SCD complications and comorbidities in the dataset. Pooled logistic regressions were used to approximate the IPW-MSM Cox model. E-values were used to assess the minimum strength of association that an unmeasured confounder would have to have with both exposure (VOC) and outcome in order to fully explain away the observed relationship. Uncertainty in the magnitude of the E-value required to explain observed associations was explored by calculating values for both the point estimate and the lower bound of the confidence interval.

RESULTS: A total of 15,076 patients were identified with a diagnosis of SCD in the HES database for this analysis. Patients had a median age of 30 and a female-male ratio of 1.7:1. A broad range of SCD related-complications were experienced by patients in the UK as shown in Table 1. Rates of some complications were

observed less frequently than expected, in particular, leg ulcers, pulmonary hypertension, osteomyelitis, priapism and acute kidney injury, reported at <5% (Table 1). The hazard ratio associated with experiencing 3+VOCs versus 0 VOC in the previous year was calculated for all identified complications, resulting in a HR ≥5, for: priapism, osteomyelitis and acute chest syndrome; HR ≥2 to <5 for: gall stones, avascular necrosis, sepsis, cardiomegaly, pulmonary hypertension, CNS complications, leg ulcers, cellulitis, hyposplenism, liver complications and acute kidney injury.

E-values (Table 1) suggest that most outcomes are robust to considerable unmeasured confounding, although large confidence intervals resulted in small lower-bound E-values for some outcomes (e.g. leg ulcers: 3.62 lower-bound: 1.00). Large E-values (>= 3 based on similar research in SCD) suggest results are robust to considerable unmeasured confounding, while small values imply greater fragility.

CONCLUSIONS: This analysis shows that vaso-occlusive crises are related to the occurrence of important complications of sickle cell disease. Reducing the annual incidence of VOC may significantly lessen the ongoing organ damage and morbidity but may also improve the patient's quality of life with respect to these

conditions.

Table 1. Relationship of the number of vaso-occlusive crisis in the previous year and SCD-related complications; and sensitivity analysis for unmeasured confounding of the relationship using E-values

Complication	% of patients in the dataset at the index year (n=15,076)	0 VOCs , HR (95% CI)[a]	3+ VOCs, HR (95% CI)[a]	3+ VOCs, E-value for HR (CL)
Acute chest syndrome	27	Ref	5.33 (4.29, 6.62)	10.13 (8.05)
Gall stones	10		2.70 (1.83, 3.99)	4.84 (3.06)
Avascular Necrosis	9		2.48 (1.62, 3.80)	4.40 (2.62)
Sepsis	7		2.76 (1.67, 4.57)	4.96 (2.73)
Cardiomegaly	7		3.07 (2.0, 4.72)	5.59 (3.41)
Chronic kidney disease	6		0.14 (0.05, 0.31)	13.77 (5.91)
Orthopedic joint implant	5		1.16 (0.45, 3.01)	1.59 (1.00)
Pulmonary hypertension	4		2.60 (1.42, 4.75)	4.64 (2.19)
Cardiac complications (e.g. arrest and arrhythmia)	4		1.29 (0.58, 2.89)	1.90 (1.00)
CNS complications (e.g. hemorrhage, infarct and infection)	4		2.63 (1.23, 5.64)	4.7 (1.76)
Leg ulcers	4		2.10 (0.94, 4.68)	3.62 (1.00)
Pulmonary embolism	4		1.11 (0.57, 2.16)	1.46 (1.00)
Cellulitis	4		2.35 (1.05, 5.23)	4.13 (1.28)
Hyposplenism	3		3.55 (1.86, 6.77)	6.56 (3.12)
Retinal vascular occlusion	3		0.87 (0.32, 2.34)	1.56 (1.00)
Osteomyelitis	2		6.59 (3.42, 12.71)	12.66 (6.3)
Cardiomyopathy	2		0.57 (0.21, 1.55)	2.9 (1.00)
Priapism	1		7.58 (4.07, 14.1)	14.64 (7.6)
Liver – chronic passive congestion and other specified diseases	1		3.11 (0.73, 13.25)	5.67 (1.00)
Acute kidney injury	<1		3.81 (1.11, 13.0)	7.08 (1.46)

Abbreviations: HR - Hazard ratio; CI - confidence interval; CL – confidence limit

Note - a: Of the 15,076 patients identified in the index year, the proportion of patients reported with 0 VOCs and 3+ VOCs was 85% and 4% respectively. As the HR were calculated across all patient years, variations in the proportion of patients reported for each VOC category are expected, due movement of patients between VOC categories.

Disclosures: Bailey: *Novartis:* Employment. **Abioye:** *Novartis:* Employment. **Morgan:** *HCD Economics:* Employment. **Burke:** *HCD Economics:* Employment. **Disher:** *Cornerstone Research Group:* Employment. **Brown:** *Cornerstone Research Group:* Employment. **Bonner:** *Cornerstone Research Group:* Employment. **Herquelot:** *HEVA:* Employment. **Lamarsalle:** *HEVA:* Employment. **Raguideau:** *HEVA:* E mployment.