Highlights in myelodysplastic syndromes

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In this article, a selection of interesting abstracts related to myelodysplastic syndromes (MDS) will be discussed. In lower-risk MDS, most attention goes to therapies that address anaemia. In this respect updated results of a phase III trial evaluating luspatercept were presented, while also the hydroxylase inhibitor roxadustat showed promising results. In addition to this, interesting data were presented on the restoration of erythropoietin sensitivity by lenalidomide. In higher-risk MDS, an abstract will be discussed looking at the optimal schedule for the administration of hypomethylating agents (HMA) next to a study evaluating the safety and efficacy of an oral HMA formulation. In addition to this, several new therapeutic options are being explored in higher-risk MDS. This includes combinations of novel agents (*e.g.* venetoclax, rigosertib, telaglenastat) with azacitidine and the use of targeted agents, specifically directed against mutations in MDS (*e.g.* olutasidenib, APR-246 and enasidenib).

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LOWER-RISK MDS

LUSPATERCEPT FOR LOW-RISK MDS PATIENTS WITH RING SIDEROBLASTS, REQUIRING RED BLOOD CELL TRANSFUSIONS: UPDATED ANALYSIS OF MEDALIST

Anaemia is the most common cytopenia in patients with low-risk (LR) MDS and is associated with a number of complications, such as fatigue, falls and a decreased quality of life. The standard of care to treat this anaemia consists of erythropoiesis-stimulating agents (ESAs) and red-blood cell transfusions (RBC). However, RBC dependence is associated with a reduced survival and responses to ESAs are limited.[1] For patients with transfusion-dependent LR-MDS for whom ESAs have become ineffective (or who are not candidates for ESA therapy), the treatment options are limited. Luspatercept is a first-in-class erythroid maturation agent that binds select TGF-β superfamily ligands to reduce aberrant Smad2/3 signalling and enhance late-stage erythropoiesis.[2] This agent is already FDA approved for the treatment of anaemia in adult patients with β-thalassemia. In the randomised phase III MEDALIST trial, luspatercept significantly reduced the transfusion burden compared to placebo.[3] During ASH 2019, updated results of this study were presented. Eligible patients were ≥18 years of age with IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS with ring sideroblasts (RS). In total, 229 patients (refractory, intolerant, or unlikely to respond to and requiring regular RBC transfusions) were randomised (2:1) to luspatercept (1.0 mg/kg titrated up to 1.75 mg/kg, if needed) or placebo, subcutaneously every 3 weeks. The updated results indicate that 47.7% of patients treated with luspatercept achieved RBC transfusion independence (RBC-TI) ≥8 weeks at any time during the treatment period as compared to only 15.8% in the placebo arm (OR[95%CI]: 5.978[2.840-12.581]; p< 0.0001) (*Figure 1*).[4] This higher RBC-TI ≥8 weeks with luspatercept *vs.* placebo was seen regardless of baseline transfusion burden. Interestingly, approximately 70% of responders in the luspatercept arm had multiple response periods during the treatment. The median cumulative duration of RBC-TI ≥8 weeks in all responders was substantially longer with luspatercept than with placebo (79.9 *vs.* 21.0 weeks; HR[95%-CI]: 0.485[0.205-1.149]). The median treatment duration

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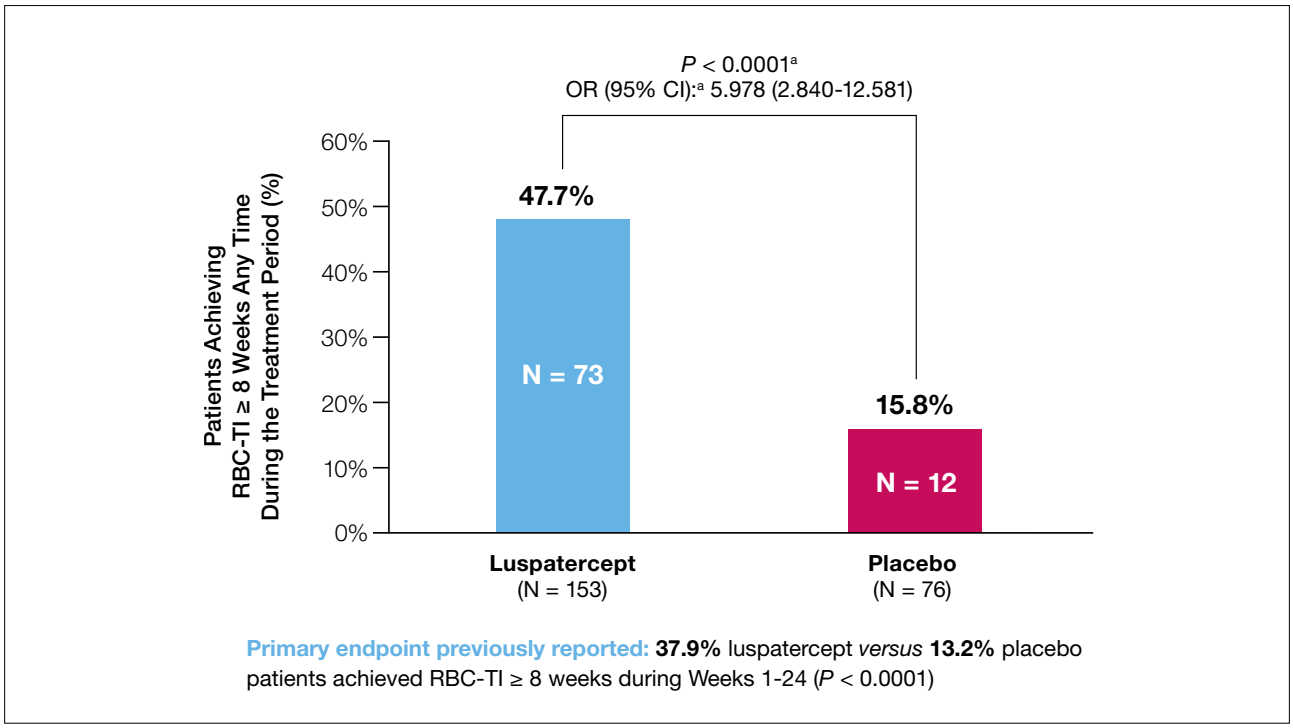

FIGURE 1. RBC-TI ≥8 weeks at any time during the treatment with luspatercept *vs*. placebo in the phase III MEDALIST trial.[4]

with luspatercept was 50.9 weeks as compared to 24 weeks with placebo (109 *vs*. 53.9 weeks in patients with RBC-TI ≥ 8 weeks). Of the 153 luspatercept-treated patients, 7.8% remained transfusion-free after the first dose of luspatercept throughout week 48. The percentage of patients experiencing at least 1 treatment-related adverse event (TRAE) during the study was comparable for both arms at 87.6% with luspatercept and 82.9% with placebo. However, the incidence of TRAEs leading to treatment discontinuation was higher with luspatercept (13.7% *vs*. 7.9%). AEs occurring more frequently with luspatercept *vs*. placebo (fatigue, diarrhoea, asthenia, dizziness) occurred early (cycles 1–4), were mainly grade 1 or 2, decreased over time, and were not associated with a higher dose level. Progression to high-risk (HR) MDS or acute myeloid leukaemia (AML) was similar in patients receiving luspatercept or placebo (3.3% *vs*. 2.6% and 2.0% *vs*. 2.6% for HR-MDS and AML, respectively).[4]

As such, luspatercept is a potential new therapy to treat anaemia in patients with LR-MDS and RS. The COMMANDS trial is currently comparing luspatercept to epoetin alfa (EA) in transfusion-dependent (TD) patients with LR-MDS.

LENALIDOMIDE RESTORES SENSITIVITY TO ERYTHROPOIETIN IN LR-MDS PATIENTS WITHOUT A DEL(5Q)

Only a small subset of LR- MDS patients benefit from treatment with Erythropoietin (Epo). In the MDS-002 and -005 trials, treatment with lenalidomide (LEN) monotherapy gave rise to RBC-TI in 26% of TD LR, non-del(5q) MDS patients for a median of 10.2 and 7.75 months, respectively.[5,6] In a pilot study of Epo-refractory LR-MDS patients, the addition of epoetin alfa (EA) to LEN treatment yielded erythroid responses in 28% of patients who were unresponsive to LEN alone. This indicates that LEN may overcome clinical resistance and augment the response to Epo.[7] To further test this hypothesis, a randomised phase III trial was performed comparing LEN to LEN + EA in LR non-del(5q) MDS patients who were refractory to, or ineligible for treatment with Epo.[8] In the study at hand, 215 patients with low- or intermediate-1 IPSS MDS with ESA failure, or a low response profile were randomly assigned to LEN (10mg/d x21d q28d) or LEN + EA (60.000 SC/week). The primary endpoint was major erythroid response (MER) at week 16, which was defined according to the transfusion status at baseline: (I) achievement of RBC-TI for ≥8 consecutive weeks AND a sustained ≥1 g/dL haemoglobin rise compared to mean pre-transfusion baseline value in TD patients; and (II) a >2 g/dL rise in haemoglobin without transfusion for ≥ 8 consecutive weeks in non-TD patients (<4U RBC/8 weeks). In case of a non-response to LEN alone, patients were allowed to cross-over to the combination treatment. The median age of patients in the study was 74 years, 93% received prior Epo and at baseline patients received a median of 4 RBC transfusions over an 8-week period. In an intent to treat analysis, 28/99

patients (28.3%) in the combination arm achieved MER compared to 11/96 (11.5%) in the LEN monotherapy arm (p= 0.004). Of the 44 patients who crossed over from LEN to the combination, 11 (25%) obtained a MER. Of note, the MER rate was independent of the RBC transfusion burden at baseline. Interestingly, the modulation of the Epo responsiveness by LEN also led to a longer, clinically meaningful response duration with a median MER duration of approximately 2 years compared to 13 months with LEN monotherapy (p= 0.24). There was no significant difference in the frequency or distribution of grade ≥3, non-haematologic AEs between treatment arms.[8]

As such, these findings support the combined use of LEN and EA in patients with low- or intermediate-1, non-del(5q) MDS who are unresponsive/refractory to ESAs.

ROXADUSTAT FOR THE TREATMENT OF ANAEMIA IN LR-MDS PATIENTS WITH A LOW RBC TRANSFUSION BURDEN

Roxadustat (FG-4592) is an oral hypoxia–inducible factor (HIF) hydroxylase inhibitor that promotes coordinated erythropoiesis through HIF-mediated transcription. Transient, intermittent HIF activation by roxadustat mimics a physiological response that increases endogenous Epo production to near physiologic range and stimulates Epo receptor synthesis. In addition, roxadustat promotes the iron metabolism by reducing serum hepcidin to allow absorption of iron from the gut and mobilize iron from cellular storage, making more iron available for erythropoiesis. As indicated before, responses to ESAs vary across LR-MDS patients with limited response durability. To address this medical need, roxadustat was evaluated in the treatment of anaemia in primary MDS patients. The study at hand consists of two parts: an open-label (OL), dose-finding segment (N= 24) followed by a randomised double-blind (DB) placebo-controlled segment (N= 156) comparing roxadustat to placebo. During ASH 2019, results of the OL part were presented.[9] In total, 24 patients were included with a median age of 73 years, a median RBC transfusion burden of 4 units/8 weeks and a median pre-transfusion haemoglobin (Hb) level of 8.4g/dL. During weeks 1-28, 38% of patients achieved RBC-TI ≥8 weeks (42% during weeks 1-52), with 58% of patients obtaining a ≥50% reduction in RBC units in any 8 weeks during week 1-52. In total, 79% of patients experienced any AE (most frequent AEs: diarrhoea, dyspnoea, bronchitis and nausea), including 20.8% of serious AEs and 4.2% of AEs leading to treatment discontinuation. There were no conversions to AML.[9] For the DB part of the trial, a dose of 2.5 mg/kg was selected as 78% of patients were on this dose at the time of TI in the OL phase, without dose-limiting toxicity.

HIGHER-RISK MDS

WHAT IS THE OPTIMAL AZACITIDINE SCHEDULE FOR PATIENTS WITH HR-MDS: 7-DAY SCHEDULE SEEMS BETTER THAN 5 DAYS

Azacitidine (AZA) is a HMA that significantly prolongs the overall survival (OS) of patients with HR-MDS. However, the optimal treatment schedule of AZA for HR-MDS has not yet been prospectively determined. As a 7-day treatment schedule includes weekends, a 5-day administration is often applied, although solid evidence for this has not been established. To address this issue, a prospective clinical trial was set up. The trial included 201 patients with *de novo* or treatment-related MDS, aged 16 years or older with an adequate performance status (ECOG PS 0-2) and no history of HMA treatment or chemotherapy. Patients were randomly assigned to AZA-7 (N= 99) or AZA-5 (N= 102). Of note, in order to test the non-inferiority of AZA-5 to AZA-7, the 2-year OS of AZA-7 was estimated at 30%, and the delta was defined as 11%, for which 410 patients were needed to complete the trial. However, because of the poor recruitment, the study closed prematurely, and the protocol-planned interim analysis (when 200 patients were registered) was performed.[10] At the time of last follow-up, 59 and 67 patients died in AZA-7 and AZA-5, respectively. The Kaplan-Meier estimates of the 2-year OS were 35.1% for AZA-7 and 22.4% for AZA-5 (median OS: 16.22 *vs.* 15.67 months). The 2-year leukaemia-free survival (LFS) was reported at 27.3% for AZA-7 and 20.5% for AZA-5. There was no significant difference in the frequency of erythroid, platelet or neutrophil improvement, or haematological response (complete or partial response, or any haematological improvement) between the two groups.[10]

Because of the premature termination of this trial, statistical analysis for the primary endpoint of 2-year OS could not provide any solid evidence. However, the authors concluded that the 10% difference in 2-year OS without any difference in safety profile supports the use of AZA-7 over AZA-5 in patients with HR-MDS.

EQUIVALENT DECITABINE EXPOSURE WITH AN ORAL FORMULATION OF THE DRUG COMPARED TO INTRAVENOUS DECITABINE

HMAs such as decitabine (DEC) or AZA require intravenous (IV) infusion for 1 hour or subcutaneous (SC) injections daily for 5-7 days of every 28-day treatment cycle. As such, these treatments come with a significant therapeutic burden. In addition, they both have limited oral bioavailability due to rapid degradation by cytidine deaminase (CDA) in the gut and liver. An orally bioavailable HMA option could reduce the clinic visit frequency and reduce the incidence of infu-

sions/injections related AEs and burden. ASTX727 is an oral tablet comprised of a fixed-dose combination of CDA inhibitor cedazuridine (C) at 100 mg with DEC at 35 mg. In a phase II study, C-DEC (ASTX727) demonstrated pharmacokinetic (PK) AUC exposure similar to IV-DEC at 20 mg/m^2 with comparable clinical activity and safety. During ASH 2019, results of a phase III study were presented that was designed to demonstrate exposure bioequivalence of oral C-DEC and IV-DEC.[11]

The study used a randomised cross-over design in which patients were randomised (1:1) to either Sequence A: C-DEC (100 mg/35 mg respectively) in Cycle 1 followed by IV-DEC at 20 mg/m^2 in Cycle 2, or Sequence B receiving IV-DEC in Cycle 1 followed by C-DEC on Cycle 2. All patients received C-DEC from Cycle 3 onwards. In total, 133 patients with a median age of 71 years were enrolled in the study. The IPSS status of patients was Intermediate-1 in 44%, Intermediate-2 in 20%, and HR in 16% (12% of patients had CMML). The study convincingly met its primary endpoint with a DEC AUC0-24 (h*ng/mL) 5-Day geometric mean estimate of 856 for C-DEC and 865 with IV-DEC resulting in an oral/IV AUC ratio of 98.9% (90%CI of 92.7-105.6%).[11] A comparison of hypomethylating activity as measured by LINE-1 demethylation showed a difference between oral C-DEC and IV-DEC demethylation of <1%, with the 95% confidence interval of this difference including zero. Preliminary efficacy data in all evaluable patients (N= 101) indicate a CR in 11.9% of patients with a marrow CR (mCR) in an additional 45.5%. A haematologic improvement (HI) was seen in 6.9%, translating to an overall response rate (ORR= CR+ mCR + HI) of 64%.[11] With respect to safety, no difference was seen between both treatment arms.

NOVEL THERAPEUTIC COMBINATIONS FOR HR-MDS

VENETOCLAX PLUS AZA

Two abstracts addressed the use of venetoclax (Ven) in patients with MDS. A first abstract discussed an ongoing phase Ib study in patients with relapsed/refractory (R/R) MDS. Key eligibility criteria for this trial include age ≥18 years, failure of HMA after receiving at least 4 cycles of AZA or 4 cycles of decitabine within the previous 5 years, marrow blasts <20%, and ECOG PS of ≤2. In cohort 1 patients received Ven monotherapy, either 400 mg (Arm A) or 800 mg (Arm B) per cycle (28 days), while in cohort 2 patients received AZA combined with escalating doses of Ven (100, 200 and 400 mg daily for 14 of 28-day cycles).[12] In total, 64 patients were included: 26 in cohort 1 and 38 in cohort 2. The median time on study was 8 months for Ven monotherapy and 7 months for the Ven-AZA combination. At the time of the analysis, none of the Ven monotherapy patients was still on therapy as compared to 14 with Ven + AZA. Twenty-one deaths were reported (14 with Ven, 7 with Ven + AZA). Overall, 88% of patients experienced a grade ≥3 AE (81% with Ven and 97% with Ven + AZA). The most frequently observed grade ≥3 AE were neutropenia (35% and 50%), leukopenia (35% and 39%), thrombocytopenia (12% and 42%) and febrile neutropenia (23% and 29%). Serious AEs were reported in 85% of the Ven-treated patients and in 97% of patients who received the combination. With respect to efficacy, an ORR of 8% was reported with Ven monotherapy, mounting to 40% with the combination (including a CR in 8%). The median PFS was 3.3 months when Ven was used alone and 9.1 months when combined with AZA. For Ven treated patients, the median OS was 5.5 months, while the median was not yet reached with the Ven + AZA combination (12-month OS rate: 65%).[12]

A second abstract looked at the efficacy and safety of Ven + AZA in the first-line treatment of higher risk MDS patients.[13] In the presented dose escalation study, cohorts were enrolled with escalating doses of Ven administered orally for the first 14 days of each 28-day cycle with cohorts from 100 mg daily up to 400 mg daily. Patients started at 100% of the prescribed Ven dose without intra-individual ramp up. AZA was administered at the standard dose (75 mg/m^2, subcutaneously or IV) from Day 1-7 per 28-day cycle.[13] In total, 57 patients were enrolled in the study with a median age of 71 years. Three quarters of patients had IPSS Intermediate-2 disease with 26% having HR disease. At the time of the analysis, 32% of patients was still on treatment and 79% of patients were still alive. In line with the results in the R/R setting, neutropenia (67%), febrile neutropenia (44%) and thrombocytopenia (37%) were the most common grade ≥3 AEs. Overall, 67% obtained a TI (RBC and platelet) of 8 weeks or more. A CR was reported in 38.6%, with a mCR in additional 38.7% (ORR: 77.2%). Importantly, the CR also proved to be durable with a 12-month estimate of response duration of 83.3%. Overall, a HI was seen in 61%. At a median follow-up of 8.9 months, the median OS was not yet reached, with a 12-month OS rate of 76.9%. Specifically looking at the subgroup of patients with CR, or mCR, the 12-month OS rate was 93.8% and 85.9%, respectively.[13]

RIGOSERTIB PLUS AZA

RAS and other signalling molecules in the Ras pathway are frequently mutated in HR MDS and are believed to drive leukemic transformation. Given the fact that rigosertib interferes with the RAS-binding domain of RAF kinases and inhibits the RAS-RAF-MEK and the PI3Ks pathways, it is an attractive candidate for combination with AZA. ASH

2019 featured the presentation of a phase II study in which 39 treatment-naïve HR MDS/RAEB-t patients were treated with a combination of rigosertib and AZA.[14] The median age of the patients in the trial was 64 years and the majority of patients had high (21%) or very-high risk MDS (44%) (IPSS-R).[14] Among the 29 patients who were evaluable for response, an ORR of 90% was reported (34% CR). The median duration of the responses was 12.2 months. Responses were seen in all cytogenetic risk subgroups, including an ORR in 8/9 patients with poor or very poor cytogenetics. Overall, 90% of patients experienced a grade ≥3 AE with neutropenia (33%), thrombocytopenia (31%), anaemia (28%) and febrile neutropenia (23%) being most common. Based on these efficacy results and the generally favourable safety profile, a pivotal phase III trial in higher-risk HMA naïve MDS patients is planned.

TELAGLENASTAT PLUS AZA

Glutaminase (GLS) is an enzyme catalysing the conversion of glutamine to glutamate, providing key metabolic fuel utilized by tumour cells. GLS is highly expressed in AML and HR-MDS. In a phase Ib/II trial, the safety and efficacy of the oral GLS inhibitor CB-839 (Telaglenastat) in combination with AZA was evaluated in intermediate and HR MDS.[15] In order to be eligible for the trial, patients had to be 18 years or more and have HR MDS (IPSS intermediate-2 or high risk) or intermediate-1 risk with high-risk genomic features including *TP53, ASXL1, EZH2*, or *RUNX1* mutations. The presented study included 19 patients of whom 26% received prior HMA therapy. In all patients, an ORR of 63% was reported (57% frontline, 80% in patients with prior HMA use) with a CR rate of 11% (2 patients who received it in frontline) and a mCR in 47%. In 5 patients (all HMA naïve), a cytogenetic response was observed. At 1-year, 50% of patients were still alive, with a 1-year event-free survival (EFS) rate of 33% (59% and 47% in frontline). Overall, the treatment was well tolerated, with the most common non-haematological AEs being gastrointestinal in nature (72% with nausea in 62% and constipation in 42%). The most common grade ≥3 AEs were infections (48%), thrombocytopenia (41%) and neutropenia (38%).[15]

TARGETING GENE MUTATIONS IN MDS

OLUTASIDENIB FOR IDH1 MUTANT MDS

Isocitrate dehydrogenase 1 mutations *(IDH1)* occur in approximately 3-4% of MDS patients. Olutasidenib is a highly potent, selective small molecule inhibitor of mutant *IDH1* with clinical activity in AML. The presented phase I/II study is evaluating the safety, PK/PD, and clinical activity of olutasidenib alone or in combination with AZA in *IDH1*-mutant MDS patients. In total, 23 patients with *IDH1*-mutant MDS had received olutasidenib continuously either as a single agent (SA; N=6) or in combination (COMBO; N=17) with AZA (75 mg/m^2 × 7 days q 4 weeks).[16] Approximately 70% of patients in the study had R/R MDS and the majority of patients had high or very high risk MDS (100% in SA cohort, 76% in COMBO cohort). Two thirds of patients in the study received prior HMA therapy. At the time of the analysis, treatment was ongoing in 33% of SA patients and in 59% of patients treated with the COMBO. The median time on treatment was 6.3 months and 15 months for SA and COMBO, respectively. The ORR with SA was reported at 50%, with 2 of the 3 responding patients obtaining a CR. The median duration of these responses was not reached. In the COMBO cohort, an ORR of 56% was reported with a CR rate of 25%. The median duration of response with COMBO was 12.9 months. An important difference was seen between SA and COMBO in terms of the time to response with a median of 8.3 and 2.8 months, respectively. Interestingly, *IDH1* mutation clearance was observed in 44% of the evaluable patients. Olutasidenib has been well tolerated both as SA and in combination with AZA. Overall in SA and COMBO, regardless of causality, most treatment-emergent AEs (TEAEs) were grade 1/2, with most common (≥20%) TEAEs being nausea (57%), fatigue (43%), arthralgia and constipation (39% each). The most common (≥15%) grade 3/4 TEAEs for the overall population were neutropenia (30%), thrombocytopenia (25%), febrile neutropenia, fatigue and leukocytosis (15% each).[16]

In summary, olutasidenib has shown a favourable safety profile and clinical activity in *IDH1*-mutant MDS. A phase II trial is ongoing at 150 mg BID single agent and in combination with AZA.

APR-246 FOR TP53 MUTANT MDS

TP53 gene mutations are found in up to 20% of MDS or AML patients and 30-40% of therapy-related (TR) MDS/AML cases. They represent a distinct molecular cohort with poor outcomes.[17] The current standard of care for *TP53* mutated MDS consists of HMA, which yield a CR rate of 15-20% and an ORR of 40-45% (similar to *TP53* wildtype patients). However, despite these comparable response rates to HMA between *TP53* mutant and wild-type patients, the median OS seen in mutant patients is significantly inferior (6-8 months). APR-246 is a novel, first-in-class small molecule that selectively induces apoptosis in mutant *TP53* cancer cells via thermodynamic stabilisation of the p53 protein and a shift in the equilibrium towards the wild-type conformation.[18] At ASH 2018, *Sallman et al*. presented phase Ib results of APR-246 + AZA indicating no dose limiting toxicities, tran-

TABLE 1. Response to APR-246 + AZA in *TP53* mutant patients with HMA-naïve MDS, or AML.[19]

	All patients (N=55)	Evaluable patients (N=45)
ORR, N (%) [95% CI]	39 (71) [57 - 82]	39 (87) [73 - 95]
Time to first response in months, median (range)		2.1 (0.1 - 5.4)
Duration of response in months, median [95% CI]		8.0 [6.5 - 11.2]
Best response by IWG, N (%)		
CR	24 (44	24 (53)
PR	0 (0)	0 (0)
mCR + HI	8 (15)	8 (18)
mCR / MLFS	4 (7)	4 (9)
HI	3 (5)	3 (7)
SD	4 (7)	4 (7)
NR	11 (20)	1 (2)
PD	1 (2)	1 (2)
CR, N (%) [95% CI]	24 (44) [33 - 58]	24 (53) [38 - 68]
Time to CR in months, median (range)		3.1 (2.5 - 6.1)
Duration of CR in months, median [95% CI]		7.3 [5.8 - N.E.]
Cytogenetic response, N (%) [95% CI]		26/44 (59) [43 - 74]
Partial		8/44 (18) [8 - 33]
Complete		18/44 (41) [26 - 57]
TP53		
NGS negative, N (%)		20 (44)
Serial IHC ≤ 5%		22 (49)

scriptional activation of p53 targets and high response rates, identifying a phase II dose of 4500mg on days 1-4. At ASH 2019, results of the phase II part of this trial were presented.[19] In total, 55 HMA-naïve MDS or AML patients with a median age of 66 years were enrolled in the study (40 had MDS, 11 AML-MRC and 4 CMML/MDS-MPN). All patients had higher risk disease by IPSS-R (7% Intermediate, 24% High, 69% Very High). All patients in the trial had a *TP53* mutation with a median variant allele frequency (VAF) of 21%. In 34 patients (62%), TP53 was the sole mutation. The most common AEs to APR-246 were gastrointestinal (64% nausea, 45% vomiting, 42% constipation), or neurological (31% peripheral neuropathy, 36% dizziness, 24% ataxia, 20% tremor) in nature, but these AEs rarely reached grade 3/4 in severity. The most common grade ≥3 AE was febrile neutropenia (33%). Among the 45 evaluable patients, an ORR of 87% was reported with a CR in 53% of patients (61% in MDS patients). The responses occurred soon (median 2.1 months) and also proved to be durable (median 8.0 months) (*Table 1*). Interestingly, an isolated *TP53* mutation was predictive for a higher CR rate (69% *vs.* 25%; p= 0.006) with a trend for higher ORR (93% *vs.* 75%; p= 0.17). Additionally, also >10% p53 IHC+ BM-MNC was a covariate associated with higher CR rate (66% *vs.* 13%; p= 0.01).[19] In an intent-

to-treat analysis, the median OS was 10.8 months, with a significantly longer OS in responding patients (13.7 *vs.* 3.9 months; p< 0.0001).[19]

In addition to the study discussed above, also the Groupe Francophone Des Myélodysplasies (GFM) presented results of a phase II trial evaluating the AZA+APR-246 combination in *TP53* mutated MDS and AML patients.[20] The study included 53 HMA-naïve and not previously allografted patients with intermediate, high or very high IPSS-R *TP53* mutated MDS (N= 34) or AML (N= 19). Patients received APR-246 4500 mg IV/day (6-hour infusions) (days 1-4) followed by AZA 75 mg/m²/day (days 4-10) in 28-day cycles. As in the other phase II trial evaluating this combination, febrile neutropenia was the most common grade ≥3 AE (36%) and also the neurological toxicity signal was picked up in this trial (40% neurological AEs, 6% grade ≥3). In total, 35 patients were evaluable for response, revealing an ORR of 66% (74% in MDS cohort) with a CR in 49% (66% in MDS cohort). Among patients with a CR, a complete cytogenetic response was seen in 78%. After a median follow-up of 6.4 months, the median OS was not yet reached (not reached in responders *vs.* 3 months in non-responders, p< 0.0001).[20] Based on the positive findings in these two studies, an international, randomised phase III trial was set up to evaluate AZA +/- APR-246 in *TP53* mutant HR-MDS patients (NCT03745716).

ENASIDENIB FOR IDH2-MUTANT MDS

Isocitrate dehydrogenase 2 (*IDH2*) mutations occur in 5-10% of MDS patients and are frequently associated with intermediate-risk cytogenetics, excess bone marrow blasts, neutropenia and sustained platelets. Enasidenib (ENA) is a selective oral inhibitor of the mutant IDH2 enzyme with single-agent activity in R/R AML. During ASH 2019, results were presented of a multicentre phase II trial evaluating ENA in patients with *IDH2*-mutated MDS. In cohort A of the study, HMA-naïve patients with HR-MDS (IPSS int-2 or high-risk; IPSS-R high-risk or very high risk; or high-risk molecular features including *TP53, ASXL1, EZH2* and/or *RUNX1* mutations) received AZA + ENA, while in cohort B R/R patients with prior HMA therapy received ENA alone. All patients received ENA at a dose of 100 mg orally daily, on days 1-28 of each 28-day cycle. In arm A, ENA is given in combination with AZA 75 mg/m² IV or SC on days 1-7 of each cycle.[21] In total, 31 patients were enrolled: 13 in cohort A (treatment ongoing in 6) and 18 in cohort B (8 ongoing). In the entire study population, an ORR of 68% was reported with a CR in 26% (85% and 23% with AZA+ENA in cohort A, 56% and 28% with ENA alone in cohort B). After a median follow-up of 4 months, the median OS in cohort A was not yet reached (6-month OS rate: 70%), with a corresponding median EFS of 3.8 months (6-month EFS rate: 50%). In cohort B, the median follow-up was 6.6 months but also there the median OS was not yet reached (6-months OS rate: 92%). The median EFS in cohort B was 8.4 months with 62% of patients being event free at 6 months.[21] A HI was seen in 41% of patients overall (45% in cohort A, 38% in cohort B), with a quarter of patients becoming RBC TI. Infections were the most common AE (32%), with 29% of patients suffering a grade 3-5 infection. Other common grade ≥3 AEs included pneumonia (23%), differentiation syndrome (16%) and neutropenic fever (10%).[21]

As such, ENA shows promising activity in *IDH2*-mutant MDS patients, both in combination with AZA in HMA-naïve patients (ORR 85%) and as a single agent in R/R patients after HMA failure (ORR: 55%). The drug is generally well tolerated, but care is warranted with respect to differentiation syndrome and infections.

CONCLUSIONS

The treatment landscape for patients with MDS is rapidly evolving. In LR-MDS, the main research focus concerns the development of new therapeutic options to address the anaemia of these patients. In HR-MDS, several new agents are being tested, both as monotherapy, or in combination with HMAs. In addition to this, increasing insights into the molecular basis of MDS opens the door for targeted therapies in this disease type. The results obtained with targeted agents directed against *IDH* or *TP53* mutations are prime examples of this.

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