Higher-risk MDS and newly diagnosed AML: What are the latest developments from EHA 2022?

Dr Esther Oliva

Haematologist
Grande Ospedale Metropolitano
Reggio Calabria, Italy

Recorded following the EHA2022 Hybrid Congress, 9–12 June

touch™ ONCOLOGY

Overview

Higher-risk MDS and newly diagnosed AML: What are the latest developments from EHA 2022?

- **Part 1:** Emerging therapeutic strategies for patients with HR-MDS
- **Part 2:** Emerging treatments for patients with newly diagnosed AML who are unfit for intensive chemotherapy
- **Part 3:** Advances in risk assessment and treatment personalization for patients with HR-MDS or AML

AML, acute myeloid leukaemia; EHA, European Hematology Association; HR-MDS, higher-risk myelodysplastic syndrome.

touch™ ONCOLOGY

EHA2022 Hybrid Congress

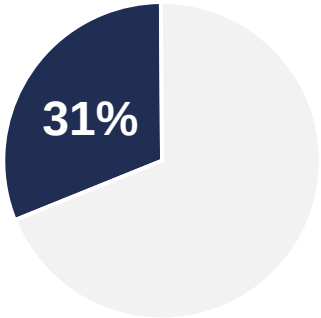
Emerging therapeutic strategies for patients with HR-MDS

touch™ ONCOLOGY

Treatment aims for HR-MDS

Despite therapeutic advances, HR-MDS continues to have a poor prognosis:[1]

5-year survival rate[1]



Current treatment aims for HR-MDS:[2,3]

- **Delay disease progression**
- **Prolong survival**
- **Improve quality of life**

HR-MDS, higher-risk myelodysplastic syndrome.

1. Zeidan AM, et al. Blood Rev. 2019;34:1-15; 2. Saygin C, Carraway HE. *Blood Rev.* 2021;48:100791; 3. Palacios-Berraquero ML, et al. *J Clin Med*. 2021;10:2107.

touch™ ONCOLOGY

Emerging therapeutic strategies for HR-MDS

Progress has been made in identifying genomic features for MDS and AML, in addition to understanding the immune and inflammatory mechanisms involved[1]

Emerging treatments for MDS and AML[1,2]	
Immune checkpoint inhibitors	CAR-T and NK cell therapy
Antibody drug conjugates	Bispecific T-cell-engaging antibodies
Vaccine therapies	Targeted IDH1/2 inhibitors

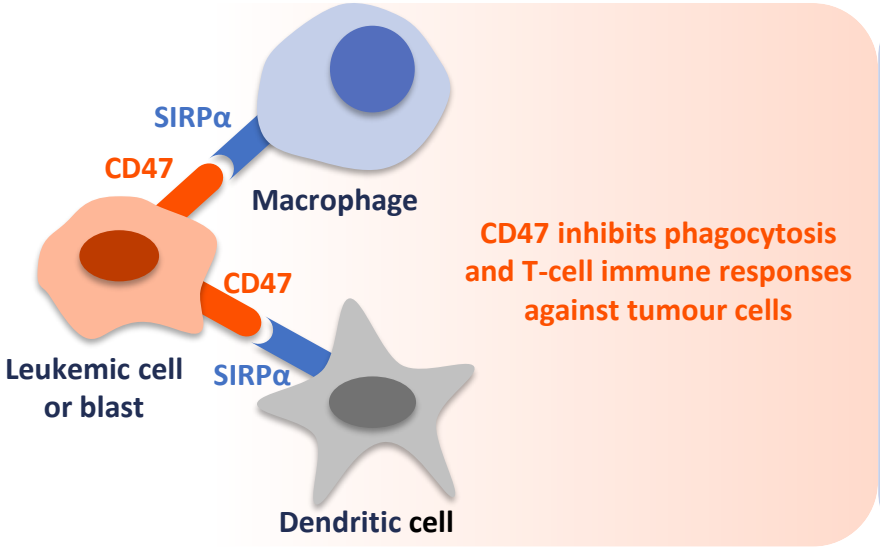
Venetoclax, a Bcl-2 inhibitor, plus HMA is one of the most promising combination for HR-MDS, however, phase 3 data is needed[3]

AML, acute myeloid leukaemia; BCL-2, B-cell lymphoma 2; CAR, chimeric antigen receptor; HMA, hypomethylating agent; HR-MDS, higher-risk MDS; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; NK, natural killer.

1. Kapoor S, et al. *Cancers (Basel)*. 2021;13:5026; 2. Saygin C, Carraway HE. *Blood Rev*. 2021;48:100791; 3. Greenberg PL, et al. *JNCCN*. 2022;20:106–17.

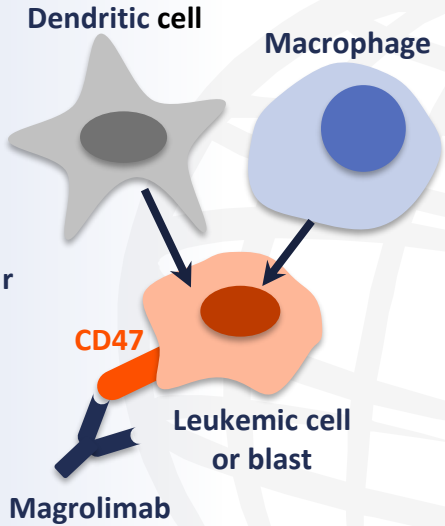
touch™ ONCOLOGY

Magrolimab: Anti-CD47



CD47 inhibits phagocytosis and T-cell immune responses against tumour cells

Magrolimab blocks CD47 and promotes phagocytosis of malignant cells and anti-tumour T-cell immunity



Magrolimab has demonstrated clinical activity in MDS and AML and is being evaluated in the ENHANCE programme[1]

AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome, SIRPα, signal regulatory protein alpha.

Haddad F, Daver N. *J Immunother Precis Oncol*. 2021;4:67–71.

touch™ ONCOLOGY

Magrolimab + AZA in previously untreated HR-MDS

Sallman DA, et al.

Phase Ib study (5F9005) of patients with previously untreated HR-MDS receiving magrolimab + AZA

N=95
Intermediate-, high- or very high-risk MDS

Magrolimab IV priming dose 1 mg/kg on D1 and D4 followed by 30 mg/kg QW or Q2W (maintenance);
AZA 75 mg/m^2 IV or SC on days 1–7 of each 28-day cycle

Primary endpoints

- Safety and tolerability
- Efficacy (CR rate)

Baseline characteristics:

- Median age: 69 years
- IPSS-R: intermediate 27%; high 52%; very high 21%
- *TP53* mutation: 26%
- Poor-risk cytogenetics: 62%
- Median number of cycles: 6

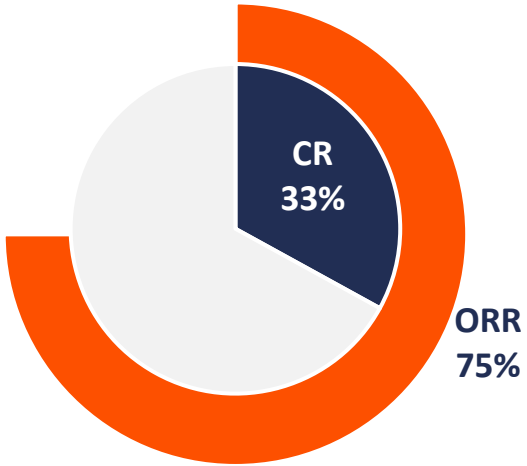
AZA, azacitidine; CR, complete remission; HR-MDS, higher-risk MDS; IPSS-R, International Prognostic Scoring System-Revised; IV, intravenous; MDS, myelodysplastic syndrome; QW, once weekly, Q2W, every 2 weeks; SC, subcutaneous.

Sallman DA, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S166.

Magrolimab + AZA in previously untreated HR-MDS

Sallman DA, et al.

Treatment response (N=95)



2-year OS:
77% for SCT group (n=35; median follow-up 19.6 months)
34% for non-SCT group (n=60; median follow-up 12.9 months)

Safety outcomes

- Common TEAEs ≥40%: constipation, thrombocytopenia, anaemia, neutropenia, nausea and diarrhoea
- IRR occurred in 25% of patients, including grade 3 IRR in 6%
- Expected on-target anaemia was manageable with priming-dose mitigation and transfusion support
- 60-day mortality: 2%

AZA, azacitidine; CR, complete remission, HR-MDS, higher-risk myelodysplastic syndrome; IRR, infusion-related reaction; ORR, objective response rate; OS, overall survival; SCT, stem cell transplant; TEAE, treatment-emergent adverse event.

Sallman DA, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S166.

touch™ ONCOLOGY

Magrolimab + AZA in previously untreated HR-MDS

Sallman DA, et al.

OS: Sub-analysis by *TP53* mutation (median follow-up of 17.1 months)

Patient group	Median OS
***TP53* mutation (n=25)**	**16.3 months 95% CI 10.8–NR**
***TP53* wild-type (n=61)**	**NR 95% CI 21.3–NR**
All patients (N=95)	**NR 95% CI 16.3–NR**

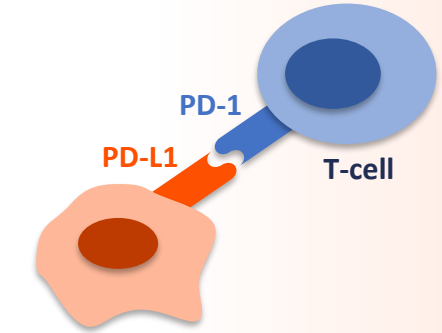
Phase III ENHANCE trial is ongoing

Magrolimab + AZA was well tolerated, with promising efficacy in patients with untreated HR-MDS including those with *TP53*-mutated or *TP53* wild-type disease

AZA, azacitidine; CI, confidence interval; HR-MDS, higher-risk myelodysplastic syndrome; NR, not reached; OS, overall survival.
Sallman DA, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S166.

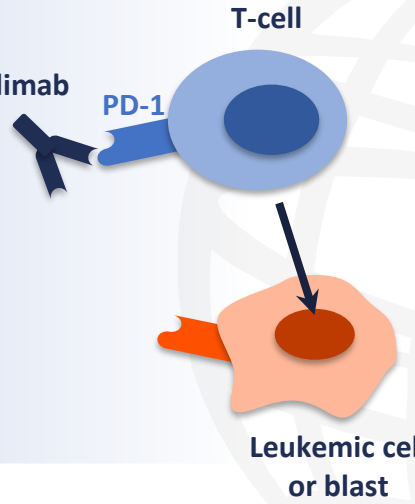
touch™ ONCOLOGY

Sintilimab: Anti-PD-1



PD-1 inhibits T-cell immune responses against tumour cells

Sintilimab blocks PD-1 and reinvigorates anti-tumour T-cell immunity



PD-1, programmed cell-death protein 1; PD-L1, programmed cell-death ligand-1.

.Kaplon H, et al. *MAbs*. 2022;14:2014296.

touch™ ONCOLOGY

Sintilimab + decitabine as first-line in HR-MDS

Wang J, et al.

Phase II, single-arm, open-label study investigating the efficacy and safety of sintilimab plus decitabine for newly diagnosed HR-MDS in patients who are unfit for intensive chemotherapy

N=52

Decitabine 20 mg/m^2 IV on days 1–5
+ sintilimab 200 mg IV on day 1 and day 22
1 cycle = 42 days

Maximum 8 cycles or until unacceptable toxicity, progression, death or withdrawal of consent

Primary endpoint

- ORR (CR + PR + mCR)

Secondary endpoints

- Safety
- Survival
  (overall improvement rate, CR, DFS, EFS and OS)

Endpoint assessment and genomic profiling

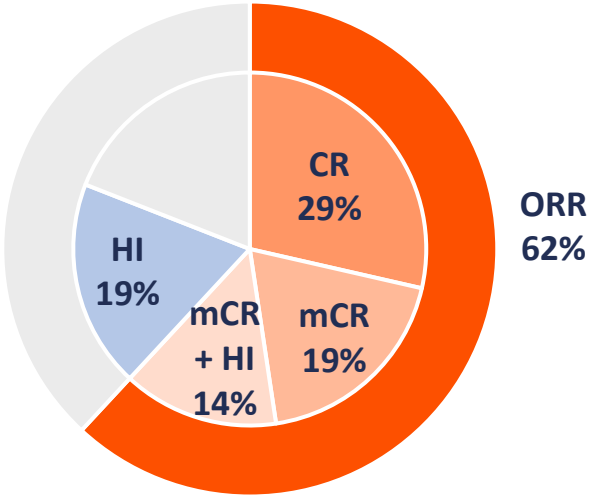
CR, complete response; DFS, disease-free survival; EFS, event-free survival; HR-MDS, higher-risk myelodysplastic syndrome; IV, intravenous; mCR, marrow CR; ORR, overall response rate; OS, overall survival; PR, partial response.

Wang J, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P786.

Sintilimab + decitabine as first-line in HR-MDS

Wang J, et al.

Key response outcomes (n=21*)



Median follow-up: 7.1 months

Safety outcomes (n=26†)

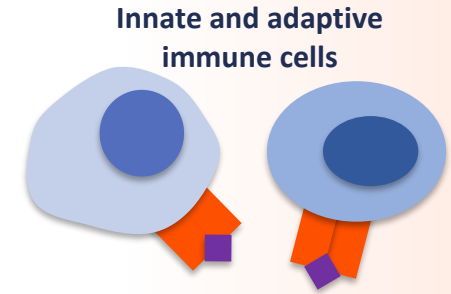
- Common grade 3 TEAEs (≥10%) were febrile neutropenia (35%) and pulmonary infection (27%)
- No grade 4 TEAEs or treatment-related deaths were reported
- 13 patients (50%) experienced immune-related AEs, which were all resolved with glucocorticoid treatment

Preliminary results demonstrated that sintilimab plus decitabine in patients with untreated HR-MDS had manageable safety and clinical activity

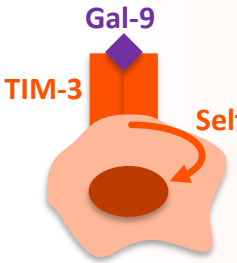
*Patients eligible for response evaluation at data cut-off (16 April 2022); †Patients enrolled in the study at data cut-off (16 April 2022).
AE, adverse event; CR, complete response; HI, haematological improvement; HR-MDS, higher-risk myelodysplastic syndrome; mCR, marrow CR; ORR, overall response rate; TEAE, treatment-emergent AE.
Wang J, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P786.

touch™ ONCOLOGY

Sabatolimab: Anti-TIM-3

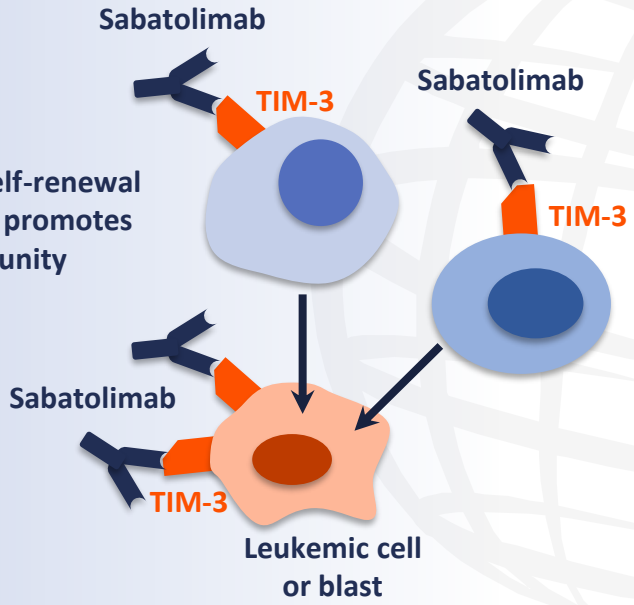


TIM-3 engagement on immune cells suppresses anti-tumour immunity



TIM-3-Gal-9 interactions promote self-renewal of leukemic cells

Sabatolimab inhibits self-renewal of leaukemic cells and promotes anti-tumour immunity



Gal-9, galectin 9; TIM-3, T-cell immunoglobulin and mucin domain 3.

Acharya N, et al. *J Immunother Cancer*. 2020;8:e000911

touch™ ONCOLOGY

STIMULUS-MDS trials

Zeidan AM, et al.

Previously untreated HR-MDS
Ineligible for intensive chemotherapy or HSCT

		Primary endpoint(s)	Enrolment	Actual or estimated primary completion
STIMULUS-MDS1 NCT03946670	**Randomized, double-blind, placebo-controlled, phase II trial Sabatolimab + HMA for intermediate–very high risk MDS**	CR, PFS	N=127	April 2022
STIMULUS-MDS2 NCT04266301	**Randomized, double-blind, placebo-controlled, phase III trial Sabatolimab + AZA for intermediate–very high risk MDS/CMML-2**	OS	N=530	January 2027
STIMULUS-MDS3 NCT04812548	**Open-label, single-arm, phase II trial Sabatolimab + AZA + VEN for intermediate–very high risk MDS**	Part 1: Safety Part 2: CR	Target N~76	December 2025
STIMULUS-MDS-US NCT04878432	**US-based, open-label, single-arm, phase II trial Sabatolimab + HMA* for intermediate–very high risk MDS**	Safety (AE, SAE)	Target N~90	January 2024

*Investigator's choice.
AE, adverse event; AZA, azacitidine, CMML-2, chronic myelomonocytic leukaemia-2; CR, complete response; HMA, hypomethylating agent; HR-MDS, higher-risk MDS; HSCT, haematopoietic stem cell transplant; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression-free survival; SAE, serious AE; VEN, venetoclax.
Zeidan AM, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P787.

touch™ ONCOLOGY

Summary

- Magrolimab + AZA was well tolerated, with promising efficacy in patients with untreated HR-MDS including those with *TP53*-mutated or wild-type disease (phase III ENHANCE study is ongoing)
- Preliminary results demonstrated that sintilimab plus decitabine in patients with untreated HR-MDS had manageable safety and clinical activity
- Four ongoing STIMULUS-MDS trials are investigating the efficacy and safety of sabatolimab combination therapies for HR-MDS in previously untreated patients who are ineligible for intensive chemotherapy or HSCT

AZA, azacitidine; HR-MDS, higher-risk myelodysplastic syndrome; HSCT, haematopoietic stem cell transplant.

EHA2022 Hybrid Congress

Emerging treatments for patients with newly diagnosed AML who are unfit for intensive chemotherapy

AML, acute myeloid leukaemia; EHA, European Hematology Association.

touch™ ONCOLOGY

Patients with ND-AML who are unfit for intensive chemotherapy

Patients with AML who are ineligible for standard induction chemotherapy can be challenging to treat:[1,2]

Older patients may have high-risk cytogenetic and molecular features that lead to chemoresistance[2]

Despite the availability of emerging therapies, many elderly patients still receive palliative care[2]

Poor performance status often means treatment cannot be tolerated[2]

Patients may be ineligible for intensive treatment if considered unfit and/or elderly[1]

AML, acute myeloid leukaemia; ND-AML, newly diagnosed AML.

1. Othman TA, et al. *Future Oncol*. 2021;17:2989–3005; 2. Lazarevic VL. *J Intern Med*. 2021;290:279–93.

touch™ ONCOLOGY

Emerging treatments for ND-AML in patients who are unfit for intensive chemotherapy

Venetoclax + HMA or low-dose cytarabine has improved outcomes for patients who are unfit for intensive CT, with manageable toxicity[1,2]

- Lower-intensity therapies, such as HMA, are now widely used: they are usually more tolerable, but with reduced efficacy[3]
- Emerging therapies for older patients with ND-AML include oral AZA (CC-486), venetoclax, FLT3 inhibitors and IDH1/2 inhibitors[3]
- Venetoclax + AZA is considered the new SoC for patients who are unfit for intensive chemotherapy[2]
- Evaluation of triple therapies in patients who are unfit for intensive chemotherapy are also ongoing (ENHANCE-3)[4]

Novel therapies are needed to improve clinical outcomes in patients with ND-AML who are unfit for intensive therapy

AZA, azacitidine; CT, chemotherapy; FLT3, fms-like tyrosine kinase 3; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; ND-AML, newly diagnosed acute myeloid leukaemia; SoC, standard of care.

1. Othman TA, et al. *Future Oncol*. 2021;17:2989–3005; 2. Lazarevic VL. *J Intern Med*. 2021;290:279–93; 3. Kadia TM, Wei AH. *Cancer J.* 2022;28:67–72;
4. ClinicalTrials.gov. 2022. Available at: www.clinicaltrials.gov/ct2/show/NCT05079230 (accessed 21 June 2022).

First-line magrolimab + AZA in *TP53*-mutated ND-AML

Daver NG, et al.

Phase Ib study (5F9005) of first-line magrolimab + AZA in patients with AML who are unfit for intensive chemotherapy

N=72
TP53-mutated AML

Magrolimab IV priming dose 1 mg/kg on days 1 and 4 followed by 30 mg/kg once or twice weekly (maintenance); AZA 75 mg/m^2 IV or SC at days 1–7 of each 28-day cycle

Primary endpoints

- Safety and tolerability
- Efficacy

Baseline characteristics:

- Median age: 73 years
- Poor-risk cytogenetics: 79%

AML, acute myeloid leukaemia; AZA, azacytidine; IV, intravenous; QW, once weekly, Q2W, every 2 weeks; SC, subcutaneous.

Daver NG, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S132.

First-line magrolimab + AZA in *TP53*-mutated ND-AML

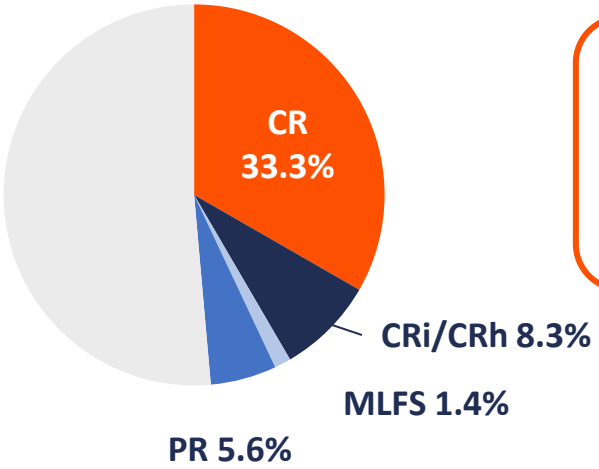
Daver NG, et al.

Safety outcomes

Common TEAEs ≥40%:

- Constipation, diarrhoea, febrile neutropenia and nausea
- Infusion-related reactions: 22%
- 60-day mortality: 18%

Key response outcomes (N=72)



Survival outcomes

- Median follow-up: 8.3 months
- Median OS: 10.8 months [95% CI: 6.8–12.8]
- 1-year OS: 83% for SCT group; 36% for non-SCT group

Phase III ENHANCE-2 trial is ongoing

Magrolimab + AZA had an acceptable safety/tolerability profile in untreated patients with *TP53*-mutated AML who are unfit for standard induction chemotherapy

AML, acute myeloid leukaemia; AZA, azacitidine; CI, confidence interval; CR, complete remission; CRh, CR with partial haematological recovery; CRi, CR with incomplete blood count recovery; MLFS, morphological leukaemia-free state; OS, overall survival; PR, partial response; SCT, stem cell transplant; TEAE, treatment-emergent adverse event.

Daver NG, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S132.

touch ONCOLOGY

ENHANCE-3: Magrolimab + VEN + AZA in ND-AML

Daver NG, et al.

Phase III, randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of a triple therapy for AML in untreated patients who are unfit for IC

N=432*
ND-AML
Unfit for IC

1:1

Experimental arm (n~216)
Magrolimab IV + VEN + AZA IV or SC

Control arm (n~216)
Placebo IV + VEN + AZA IV or SC

Treatment until PD, relapse, loss of clinical benefit, unacceptable toxicities or until other discontinuation criteria are met

Primary endpoints
- CR rate within 6 cycles
- OS

Secondary endpoints
- Duration of CR
- Transfusion independence
- EFS

Patient enrolment ongoing
NCT05079230

*Anticipated recruitment.
AML, acute myeloid leukaemia; AZA, azacitidine; CR, complete remission; EFS, event-free survival; IC, intensive chemotherapy; IV, intravenous; ND-AML, newly diagnosed AML; OS, overall survival; PD, progressive disease; SC, subcutaneous; VEN, venetoclax.
Daver NG, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P550.

touch ONCOLOGY

Lower-intensity frontline therapy for ND-AML

Venugopal S, et al.

Specific patients with AML may benefit from a lower-intensity treatment regimen, including those with abnormal organ function, poor performance status, other active malignancies and active infections

Study to evaluate lower-intensity regimen of cladribine plus low-dose cytarabine alternating with decitabine for ND-AML in patients who are ineligible to participate in other clinical trials

N=31

Induction:
cladribine 5 mg/m^2 IV on days 1–5
+ cytarabine 20 mg SC twice daily on days 1–10

Cladribine 5 mg/m^2 IV on days 1–3
+ cytarabine 20 mg SC twice daily on days 1–10
alternating with
decitabine 20 mg/m^2 IV QD on days 1–5

Primary endpoint

- 60-day OS rate

Endpoint assessment

AML, acute myeloid leukaemia; IV, intravenous; ND-AML, newly diagnosed AML; OS, overall survival; SC, subcutaneous; QD, once daily.

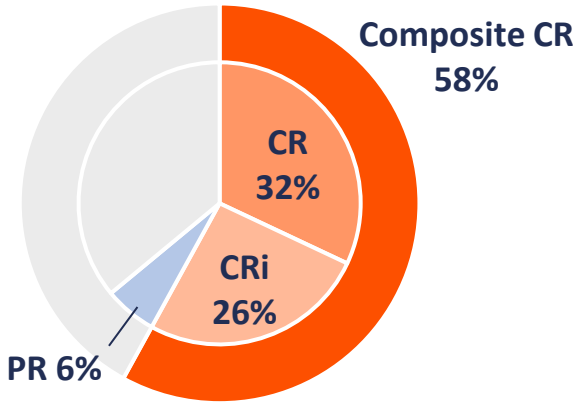
Venugopal S, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P581.

touch™ ONCOLOGY

Lower-intensity frontline therapy for ND-AML

Venugopal S, et al.

Key response outcomes (N=31)



Endpoint	% (n)
ORR	65% (n=20)
MRD-negative	19% (n=6)

Survival outcomes at median follow-up of 12.6 months

Outcome	Result
Median OS	8.3 months 95% CI [3.71, NR]
60-day survival probability	81% 95% CI [0.679, 0.958]
1-year survival probability	38% 95% CI [0.226, 0.653]

Induction therapy with cladribine + LDAC was effective and well tolerated in patients with ND-AML who were unfit for other clinical trials

CI, confidence interval; CR, complete response; CRi, CR with incomplete count recovery; LDAC, low-dose cytarabine; MRD, measurable residual disease; ND-AML, newly diagnosed acute myeloid leukaemia; NR, not reached; ORR, overall response rate; OS, overall survival; PR, partial response.

Venugopal S, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P581.

touch™ ONCOLOGY

ASCERTAIN: Phase III oral vs IV decitabine in ND-AML

Geissler K, et al.

Phase III, randomized, cross-over study to demonstrate DEC exposure bioequivalence of oral DEC-C (35 mg DEC/100 mg cedazuridine) and IV-DEC (20 mg/m^2) and to generate clinical data for DEC-C in patients with AML

N=89

1:1

Sequence A:
Oral DEC-C in cycle 1; IV-DEC in cycle 2

Sequence B:
IV-DEC in cycle 1; oral DEC-C in cycle 2

Cycle 3 onwards:
Oral DEC-C until treatment discontinuation

Primary endpoint

- AUC equivalence over 5 days of dosing

Endpoint assessment

AML, acute myeloid leukaemia; AUC, area under curve; DEC, decitabine; DEC-C, fixed dose combination of DEC and cedazuridine; IV, intravenous; PK, pharmacokinetic.

Geissler K, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P573.

ASCERTAIN: Phase III oral vs IV decitabine in ND-AML

Geissler K, et al.

PK (primary endpoint)

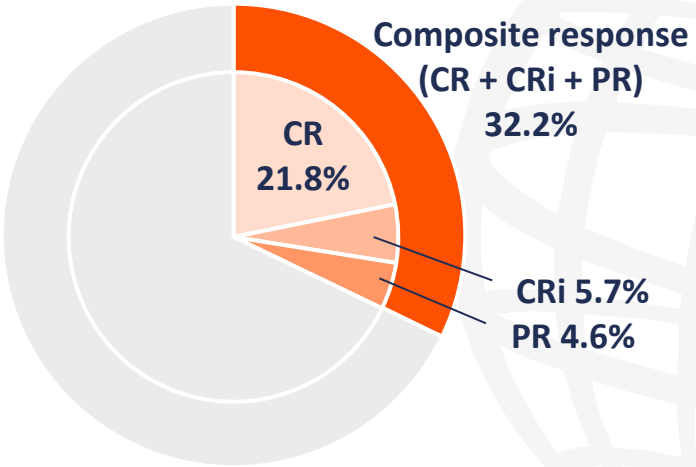
- PK equivalence was demonstrated for oral vs IV DEC (oral/IV LSM AUC ratio was ~100%)

Safety

- Safety data for DEC-C were consistent with those expected for DEC

- Median follow-up: 7.95 months
- **mOS: 7.9 months** (95% CI 5.9–13.0)

Key response outcomes (n=87*)



Based on preliminary safety data and clinical activity, oral DEC-C has the potential to be an alternative to the standard IV-DEC regimen

*patients who received treatment out of N=89 randomized

AML, acute myeloid leukaemia; AUC, area under curve; CI, confidence interval; CR, complete response; CRi, CR with incomplete blood cell count recovery; DEC, decitabine; DEC-C, fixed-dose combination oral DEC; IV, intravenous; LSM, limited sampling model; mOS, median overall survival; PK, pharmacokinetic; PR, partial response.

Geissler K, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P573.

touch™ ONCOLOGY

Summary

- Magrolimab + AZA was well tolerated, with durable responses in patients with high-risk *TP53*-mutated ND-AML who were unfit for intensive chemotherapy (phase III ENHANCE-2 study is ongoing)
- ENHANCE-3 aims to evaluate the efficacy and safety of a triple therapy (magrolimab + VEN + AZA) for ND-AML in untreated patients who are ineligible for intensive chemotherapy
- Induction therapy with cladribine + LDAC was effective and well tolerated in patients with ND-AML who were unfit for other frontline clinical trials
- Based on preliminary safety data and clinical activity, oral DEC-C has the potential to be an alternative to the standard IV DEC regimen in ND-AML

AML, acute myeloid leukaemia; AZA, azacitidine; DEC, decitabine; DEC-C, fixed-dose combination of DEC and cedazuridine; IV, intravenous; LDAC, low-dose cytarabine; ND-AML, newly diagnosed AML; VEN, venetoclax.

touch™ ONCOLOGY

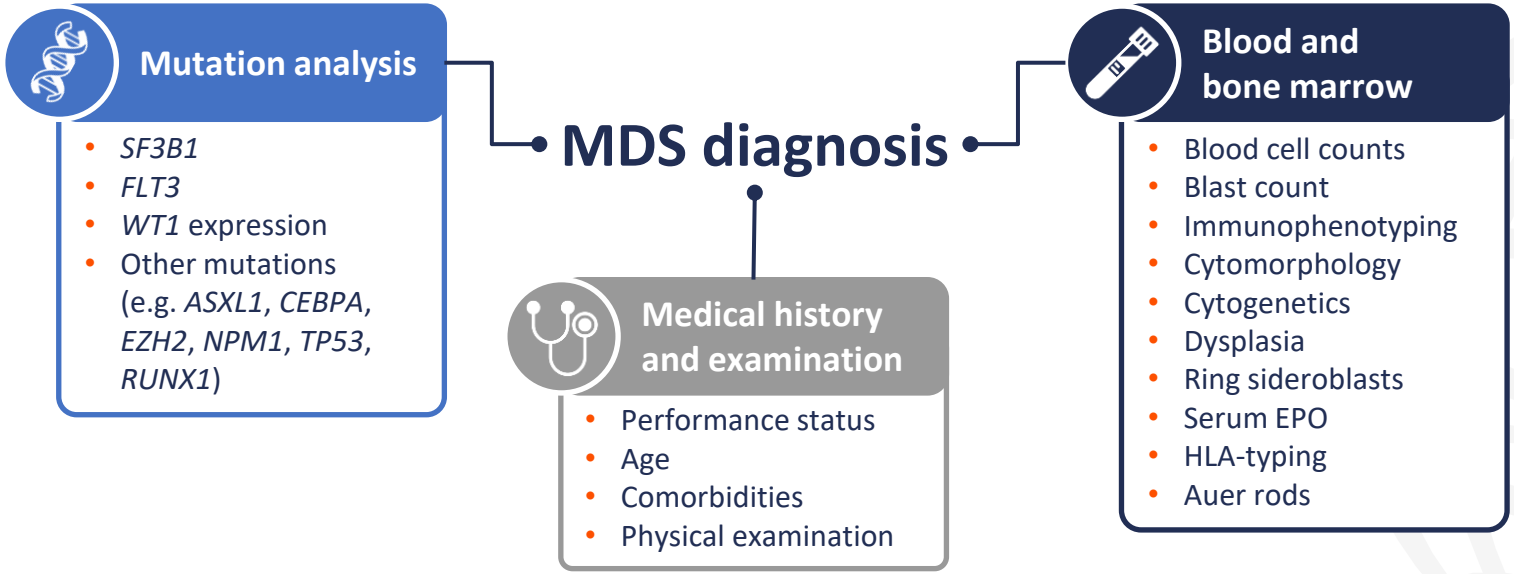
EHA2022 Hybrid Congress

Advances in risk assessment and treatment personalization for patients with HR-MDS or AML

AML, acute myeloid leukaemia; EHA, European Hematology Association.

touch™ ONCOLOGY

Current approach for diagnosing MDS[1,2]



The use of ctDNA to determine MRD status for patients with MDS and AML is of increasing importance as a non-invasive prognostic biomarker[3]

ctDNA, circulating tumour DNA; EPO, erythropoietin; HLA, human leukocyte antigen; MDS, myelodysplastic syndrome; WT, Wilms tumour protein.

1. Kasprzak A, et al. *Int J Environ Res Public Health*. 2021;18:7629; 2. Heuser M, et al. *Ann Oncol*. 2020;1:697–712; 3. Ogawa M, e tal. *Cancers (Basel)*. 2021;13:2078.

touch™ ONCOLOGY

Intra-patient functional heterogeneity of AML to determine clinical outcomes

Severin Y, et al.

A non-interventional study to analyse the intra-patient functional heterogeneity of AML blasts and to improve clinical response predictions from drug response profiling

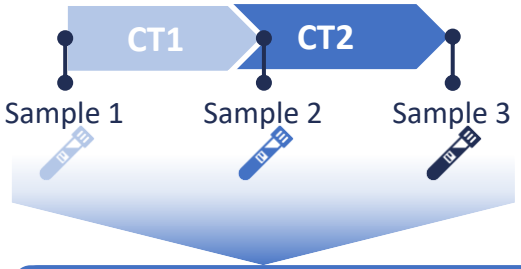
180 AML patient biopsies* → Patient-matched bone marrow and blood samples obtained at three timepoints during treatment → Ex vivo drug response profiling of 100 distinct drugs/drug combinations → Patient-matched serum cytokine profiling, RNA-sequencing and clinical data

Analyses aim to identify cellular subpopulations whose functional response is predictive of treatment response

*From 44 patients with ND-AML undergoing intensive induction chemotherapy.
AML, acute myeloid leukaemia; ND-AML, newly diagnosed AML.
Severin Y, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S134.

Intra-patient functional heterogeneity of AML to determine clinical outcomes

Severin Y, et al.



Patient characteristics

- Serum cytokine profiling
- RNA sequencing
- Clinical data

Ex vivo drug response screening

- Immunofluorescence
- Automated microscopy
- Morphological profiling

Drug library

- 100 drugs/drug combinations

Drug response data

- Highly heterogeneous blast composition across samples
- AML blast composition and maturity predicted first-line treatment success
- Ex vivo drug screening predicted clinical response
- Results led to the development of a pan-clonal drug score

Functional precision medicine can help guide treatment choice at relapse in patients with AML

AML, acute myeloid leukaemia; CT, chemotherapy.

Severin Y, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr S134.

touch™ ONCOLOGY

Unfavourable biomarkers in MDS

Trubkina H, et al.

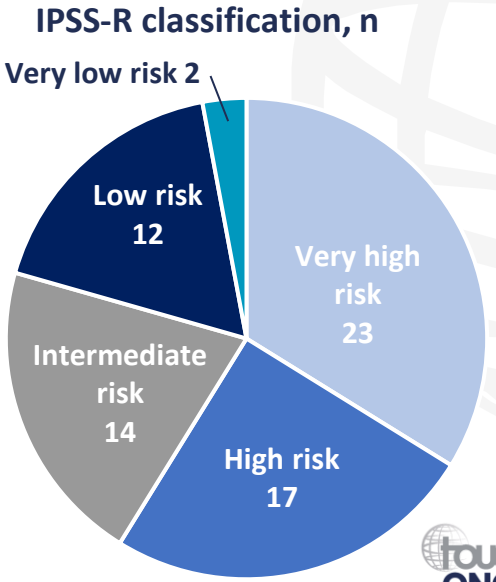
Study to identify unfavourable prognostic immunophenotypic and molecular genetic markers in patients with MDS

N=68
ND-MDS

Primary diagnostic complex of MDS performed from bone marrow

Genetic markers identified:

- Complex aberrations >3
- Trisomy 8 chromosome
- Isolated 5q chromosome
- TP53
- Changes to chromosome 7
- Deletion of chromosome 20
- Deletion of chromosome 11



HR-MDS, higher-risk MDS; IPSS-R, International Prognostic Scoring System-Revised; MDS, myelodysplastic syndrome; ND-MDS, newly diagnosed MDS.

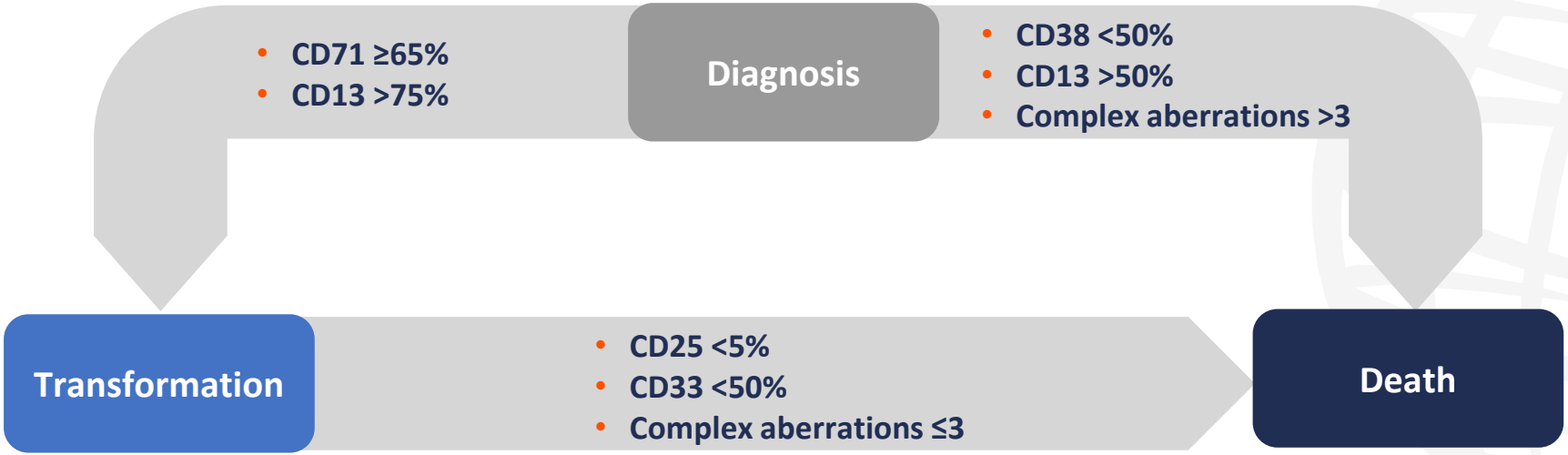
Trubkina H, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P782.

touch™ ONCOLOGY

Unfavourable biomarkers in HR-MDS

Trubkina H, et al.

Three-state ‘illness-death’ model



Grouping patients with HR-MDS by identified immunophenotypic and molecular genetic markers for risk of transformation or death warrants consideration as a new approach to guiding treatment choices

HR-MDS, higher-risk myelodysplastic syndrome.

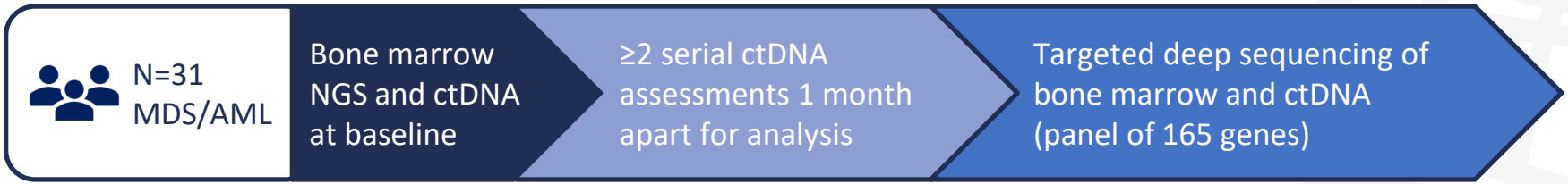
Trubkina H, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P782.

touch™ ONCOLOGY

Prognostic value of ctDNA in MDS and AML

Tong H, et al.

Study to assess role of ctDNA as a biomarker for monitoring therapeutic response and clonal evolution in patients with MDS and AML



These methods assessed the clinical relevance of dynamic ctDNA monitoring during active treatment

AML, acute myeloid leukaemia; ctDNA, circulating tumour DNA; MDS, myelodysplastic syndrome; NGS, next-generation sequencing.

Tong H, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P749.

Prognostic value of ctDNA in MDS and AML

Tong H, et al.

Prognostic impact of serial NGS results on OS and PFS

ctDNA status after treatment	Median PFS	Median OS
Positive	5.6 months 95% CI 4.08–7.13	12.0 months 95% CI 9.08–15.0
Negative	NR	NR
	p=0.009	p=0.023

- ctDNA-negative status post-treatment was associated with longer PFS and OS
- New subclones were identified in 4/7 patients with MDS prior to transformation to AML

AML, acute myeloid leukaemia; CI, confidence interval; ctDNA, circulating tumour DNA; MDS, myelodysplastic syndrome; NGS, next-generation sequencing; NR, not reached; OS, overall survival; PFS, progression-free survival.

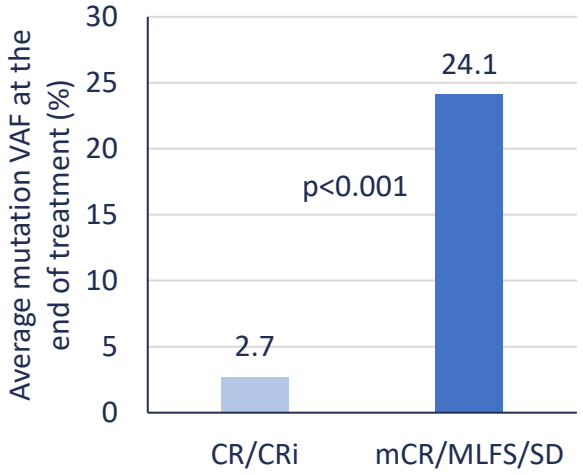
Tong H, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P749.

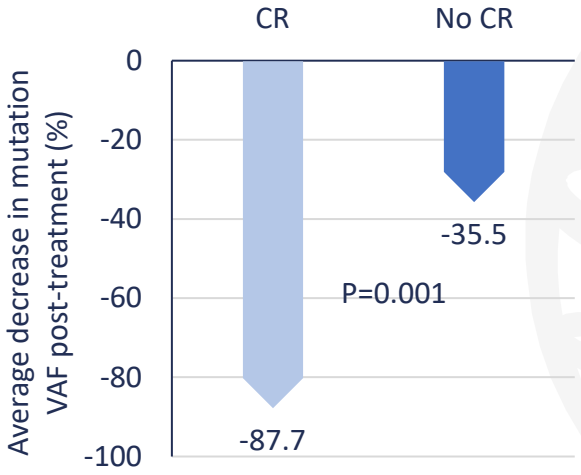
touch™ ONCOLOGY

Prognostic value of ctDNA in MDS and AML

Tong H, et al.

Dynamics of VAF changes pre- and post-treatment





ctDNA status was demonstrated to be a prognostic indicator for disease progress, relapse and clinical response

AML, acute myeloid leukaemia; CR, complete response; CRi, complete response with incomplete blood cell count recovery; ctDNA, circulating tumour DNA; mCR, marrow CR; MDS, myelodysplastic syndrome; MLFS, morphological leukaemia-free state; SD, stable disease; VAF, variant allele frequency.

Tong H, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P749.

UNIFY: Prognostic value of MRD in AML

Thiede C, et al.

Phase III, prospective, placebo-controlled study (UNIFY) to explore the prognostic implications of MRD as detected by NGS at CR/CRi

UNIFY study* assessed midostaurin plus chemotherapy in patients with *FLT3* mutation-negative ND-AML

N=501 (UNIFY)
Bone marrow and peripheral blood samples

Analysis focused on samples reaching CR/CRi at end of induction therapy

NGS-MRD (74 gene panel)

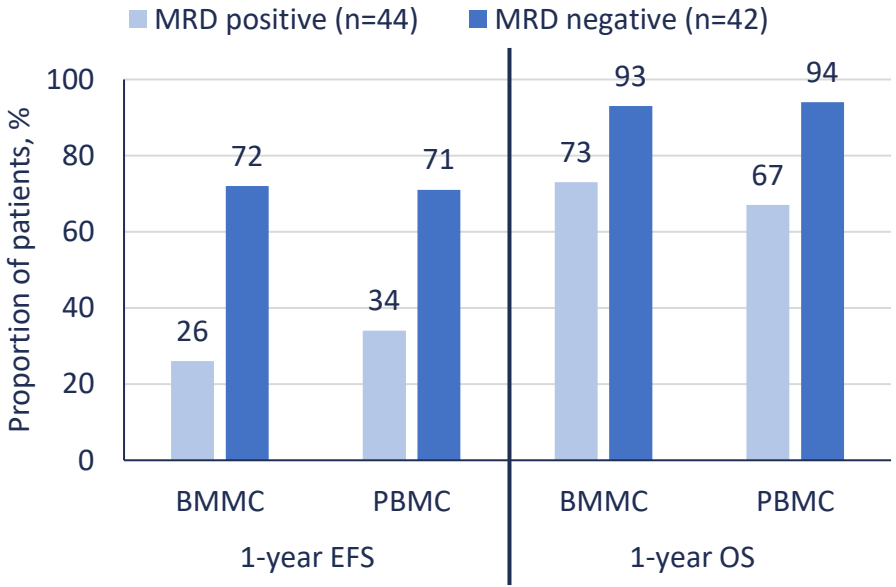
The 10 most frequently used genes for MRD monitoring were *NRAS, IDH2, RUNX1, SRSF2, TP53, PTPN11, IDH1, BCOR, CEBPA* and *GATA2*

*UNIFY study stopped due to futility.
AML, acute myeloid leukaemia; CR, complete response; CRi, CR with incomplete blood count recovery; FLT3, fms-like tyrosine kinase 3; MRD, measurable residual disease; ND-AML, newly diagnosed AML; NGS, next-generation sequencing.
Thiede C, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P470.

UNIFY: Prognostic value of MRD in AML

Thiede C, et al.

OS and EFS in patients with CR/CRi based on MRD status



Significantly lower EFS and OS were observed for MRD-positive patients compared with MRD-negative patients among those completing induction treatment and achieving CR/CRi*

Results from this analysis further support the use of molecular MRD assessment to predict outcomes in patients with AML

*Interpret with caution due to premature termination of study and limited follow-up.
AML, acute myeloid leukaemia; BMMC, bone marrow mononuclear cell; CR, complete response; CRi, CR with incomplete blood count recovery; EFS, event-free survival; MRD, measurable residual disease; OS, overall survival; PBMC, peripheral blood mononuclear cell.
Thiede C, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P470.

touch™ ONCOLOGY

Prognostic value of MRD clearance in ND-AML

Bazinet A, et al.

Retrospective, chart review study to assess treatment intensity and MRD status as prognostic indicators of OS and RFS in patients with ND-AML who have achieved a first response

Intensive therapy (n=385)
Low-intensity therapy (n=250)

→ Treatment intensity and MRD status in patients with CR/CRi/MLFS

→ Analysis of OS and RFS

- **Intensive regimen**
  Intermediate/high-dose cytarabine + anthracycline-based treatment, without venetoclax
- **Low-intensity regimen**
  LDAC/HMA-based treatment, with venetoclax

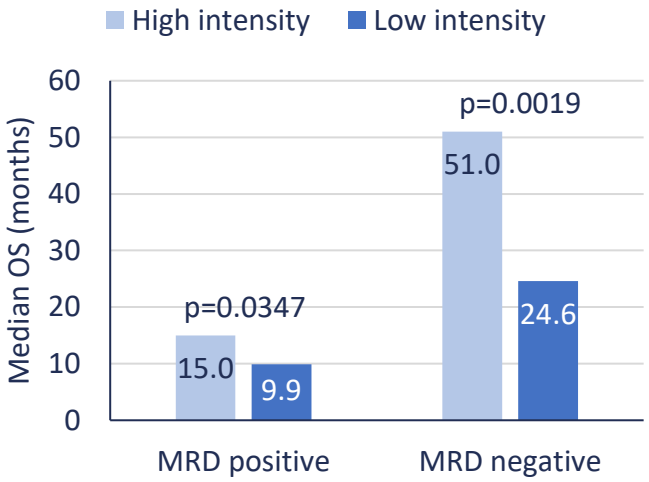
AML, acute myeloid leukaemia; CR, complete response; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; LDAC, Low-dose cytarabine; MLFS, morphological leukaemia-free state; MRD, measurable residual disease; ND-AML, newly diagnosed AML; OS, overall survival; RFS, relapse-free survival.

Bazinet A, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P506.

Prognostic value of MRD clearance in ND-AML

Bazinet A, et al.

OS stratified by treatment and MRD status



	OS	RFS
MRD positive	**HR: 1.68 p=0.0005**	**HR: 1.98 $p=9.8\times10^{-7}$**
ELN adverse	**HR: 2.09 p=0.0002**	**HR: 2.31 $p=5.7\times10^{-6}$**

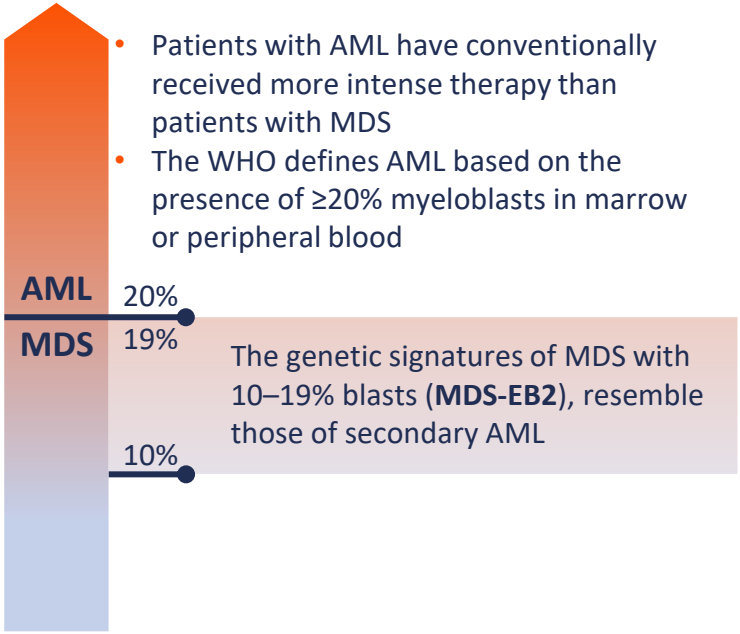
- ELN 2017 risk category and MRD-positive status were prognostic indicators for OS and RFS ($p<0.001$)
- MRD-negative patients had similar OS and RFS as patients in the ELN intermediate or adverse categories

In patients with ND-AML, MRD status at the time of first response and ELN 2017 category were strong predictors of patient outcomes

ELN, European LeukemiaNet; HR, hazard ratio; MRD, measurable residual disease; ND-AML, newly diagnosed acute myeloid leukaemia; OS, overall survival; RFS, relapse-free survival.

Bazinet A, et al. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Abstr P506.

Distinguishing AML from MDS



- Patients with AML have conventionally received more intense therapy than patients with MDS
- The WHO defines AML based on the presence of ≥20% myeloblasts in marrow or peripheral blood

The genetic signatures of MDS with 10–19% blasts (**MDS-EB2**), resemble those of secondary AML

Retrospective outcomes analysis

WHO-defined AML (n=769)
MDS-EB2 (n=202)

- Patients with WHO–defined AML and patients with MDS had similar:*
  - OS: HR 0.89 (95% CI 0.74–1.09; p=0.21)
  - EFS: HR 0.89 (95% CI 0.75–1.06; p=0.20)
  - CR/CRi: HR 1.06 (95% CI 0.99–1.13; p=0.11)

*After accounting for ELN 2017 risk, age, performance status, clinically secondary AML, and treatment including allogeneic transplantation.
AML, acute myeloid leukaemia; CI, confidence interval; CR, complete remission; CRi, complete response with incomplete hematologic recovery; ELN, European LeukemiaNet; HR, hazard ratio; MDS, myelodysplastic syndrome; MDS-EB2, MDS with excess blasts type 2; OS, overall survival; RFS, relapse-free survival; WHO, World Health Organization.

Estey E, et al. *Blood*. 2022 Jan 20;139:323–32.

International Consensus Classification: Major changes

Döhner H

- **Changes to the AML-defining blast threshold**
  - AML with recurrent genetic abnormalities require ≥10% blasts
  - Other categories:
    - 10–19% blasts = MDS/AML (formerly MDS-EB2)
    - ≥20% blasts = AML
- **New genetically-identified entities**
  - AML with *TP53* mutation
  - AML with myelodysplasia-related mutations
    - High association with secondary AML/AML (formerly MDS-EB2)
  - AML with myelodysplasia-related cytogenetic abnormalities
- **Previous history of AML**
  - Prior MDS or MDS/MPN and prior therapy are now ‘qualifiers’ to the diagnosis
    - The category AML/MRC was eliminated

AML, acute myeloid leukaemia; AML/MRC, AML with myelodysplasia-related changes; MDS, myelodysplastic syndrome; MDS-EB2, MDS with excess blasts type 2; MDS/MPM, myelodysplastic/myeloproliferative neoplasms.

Döhner H. Presented at: EHA2022 Congress, Vienna, Austria. 9–12 June 2022. Pres p117–1.

Summary

- Intra-patient functional heterogeneity of AML blasts was a strong predictor of clinical response to first-line intensive induction chemotherapy in AML
- ctDNA status was a prognostic indicator for disease progression, relapse and clinical response in patients with MDS or AML
- Grouping patients with HR-MDS by immunophenotypic and genetic markers for risk of transformation or death may be a useful approach to guide therapy selection
- The use of molecular MRD assessment may be useful for predicting outcomes in patients with AML
- In patients with ND-AML, ELN 2017 risk category and MRD status at the time of first response were strong predictors of patient outcomes
- The change in ICC nomenclature from MDS-EB2 (10–19% blasts) to MDS/AML may impact treatment approaches in MDS and AML in the nearest future

AML, acute myeloid leukaemia; ctDNA, circulating tumour DNA; ELN, European LeukemiaNet; HR-MDS; higher-risk MDS; MDS, myelodysplastic syndrome; MDS-EB2, MDS with excess blasts type 2; MRD, measurable residual disease; ND-AML, newly diagnosed AML.

EHA2022 Hybrid Congress

Thank you for watching!

touch ONCOLOGY