Advancing the management of MDS and AML: Novel immune-based approaches
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The role of immune dysregulation in the pathophysiology and progression of MDS and AML

Prof. Dr. med. Uwe Platzbecker
Head of the Department of Hematology and Cell Therapy, University Hospital Leipzig, Leipzig, Germany
How does the hallmark of immune dysregulation in cancer play a role in the development of MDS and AML?
Immune dysfunction in MDS and AML$^{1,2}$

As age increases,$^{1,3}$

- Systemic inflammation
- Reactive oxygen species
- GM-CSF, IFN-γ, IL-6, IL-8, IL-1β, TGF-β, TNF-α

AML, acute myeloid leukaemia; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; IRAK, interleukin-1 receptor-associated kinase; MDS, myelodysplastic syndromes; MyD88, myeloid differentiation primary response 88; TGF, transforming growth factor; TIRAP, toll-interleukin-1 receptor domain-containing adaptor protein; TNF, tumour necrosis factor; TRAF6, tumour necrosis factor receptor-associated factor 6.

Immune dysfunction in MDS and AML\textsuperscript{1,2}

**Anti-cancer immune response**
Under physiological conditions, immune cells within the microenvironment eliminate HSC/leukaemic cells

**Immune evasion**
During cancer progression, changes in the local milieu affect the phenotype of surrounding cells, which inhibit effective immune responses against HSC/leukaemic cells

**Components of the TME**
- Osteoclast
- Cytotoxic T lymphocyte
- Macrophage
- Leukaemic cell
- Natural killer cell
- Myeloid-derived suppressor cell
- Blood vessels
- Treg
- Dendritic cell
- B cell

AML, acute myeloid leukaemia; HSC, haematopoietic stem cell; MDS, myelodysplastic syndromes; TME, tumour microenvironment; Treg, regulatory T cell.

What cells play a role in the development of an immunosuppressive microenvironment in MDS and AML?
The immunosuppressive microenvironment\(^1\text{−}^5\)

- High levels of MDSCs and Tregs
- Dysfunction of cytotoxic T cells with reduced proliferation
- Expression of immunosuppressive cytokines
- Production of proinflammatory cytokines to support LSC proliferation
- Increased expression of immune checkpoint receptors

Disease progression and development of relapsed/refractory disease

LSC, leukaemic stem cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell.
What are some overexpressed targets for therapies on these immune cells that could reactivate the immune system against MDS and AML?
Overexpressed targets for therapy in MDS and AML

**TIM-3**

- Marks the most dysfunctional or terminally exhausted T cells
- Inhibits macrophages, natural killer cells and dendritic cells
- A potential therapeutic marker of LSCs in AML

**LAG-3**

- Used as a T-cell activation marker for both CD4+ and CD8+ cells
- Blocking LAG-3 can mitigate Treg function

AML, acute myeloid leukaemia; LAG-3, lymphocyte-activation gene 3; LSC, leukaemic stem cell; MDS, myelodysplastic syndromes; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3.

Overexpressed targets for therapy in MDS and AML

<table>
<thead>
<tr>
<th><strong>TIGIT</strong>&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th><strong>CD47</strong>&lt;sup&gt;3,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Expressed on activated T cells, Tregs and natural killer cells</td>
<td>• Expressed on cell surface to prevent phagocytosis by macrophages via binding to SIRPα</td>
</tr>
<tr>
<td>• High expression is associated with poor clinical outcome in AML</td>
<td>• Expressed on AML blasts and leukaemic cells; high expression seen in primary AML patients</td>
</tr>
<tr>
<td>• Combination of PD-1 and TIGIT blockade may prove useful in treating AML</td>
<td>• High levels of CD47 mRNA are a poor prognostic factor</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukaemia; MDS, myelodysplastic syndromes; mRNA, messenger ribonucleic acid; PD-1, programmed cell death protein 1; SIRPα, signal regulatory protein alpha; TIGIT, T-cell with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain; Treg, regulatory T cell.

What is the evidence for immune checkpoint inhibitors in high-risk MDS and AML?

Prof. Agnieszka Wierzbowska
Head of the Department of Hematology
Medical University of Łódź
Copernicus Memorial Hospital
Łódź, Poland
What is the rationale for investigating immune checkpoint inhibition in MDS and AML?
Why target PD-1/PD-L1 in MDS and AML?

Mechanisms underpinning PD-1/PD-L1 signalling implicated in the pathogenesis of MDS/AML

- Conferring PD-L1+ CD34+ blasts a proliferative advantage
- Haematopoietic stem cell apoptosis (ineffective haematopoiesis)
- Immunosuppression

Factors implicated in the mechanisms of PD-1/PD-L1 signalling regulation

- Abnormal inflammatory signalling
- Genetic mutations or epigenetic alterations
- Cell–cell interactions

A correlation between HMA resistance and dysregulated PD-1/PD-L1 signalling has been identified

What data are available for immune checkpoint inhibitor monotherapy for treating MDS and AML?
Immune checkpoint inhibitors as monotherapy

<table>
<thead>
<tr>
<th>Anti-PD-1</th>
<th>Anti-PD-L1</th>
<th>Anti-CTLA-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembrolizumab</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Nivolumab</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td><strong>Atezolizumab</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| - Phase I<sub>b</sub> trial (N=28)  
  - HR-MDS, HMA fail  
  - mFU: 5.6 mo | - Phase II trial (N=76)  
  - HR-MDS, HMA fail (n=15)  
  - mFU: 20 mo | - Phase I<sub>b</sub> trial (N=42)  
  - HR-MDS, HMA fail (n=10)  
  - mFU: not specified |
| **ORR: 4%** (no CRs) | **ORR: 13%** (no CRs) | Early termination |
| OS (24 weeks): 49% | mOS: 8 mo | mOS: 5.9 mo |

**Toxicity:** Most frequent TRAEs were hyperthyroidism and fatigue

<table>
<thead>
<tr>
<th><strong>Anti-PD-L1</strong></th>
<th><strong>Anti-CTLA-4</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atezolizumab</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td><strong>Ipilimumab</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| - Phase I<sub>b</sub> trial (N=29)  
  - HR-MDS, HMA fail  
  - mFU: not specified | |
| **ORR: 3%** (no CRs) | |
| mOS: 9.5 mo<sup>*</sup> | |

**Toxicity:** Most frequent TRAEs were skin rash and fatigue

Seven patients (70%) died, mainly due to disease progression

**Toxicity:** Most frequent TRAEs were febrile neutropenia and anaemia

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*294 days.  
CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated antigen; HMA, hypomethylating agent; HR-MDS, higher-risk myelodysplastic syndromes; mCR, marrow CR; mFU, median follow-up; mo, months; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; TRAE, treatment-related adverse event.

What are the data for combination therapy with immune checkpoint inhibitor plus hypomethylating agent/chemotherapy for MDS and AML?
Efficacy and safety of AZA + anti-PD-1/CTLA-4 ICI

**Phase II trial in MDS (N=76)**
- Two cohorts:
  - HMA naive (n=41)
  - HMA fail (n=35)
- mFU: 20 mo

**Phase II trial in MDS* (N=37)**
- Two cohorts:
  - HMA naive (n=17)
  - HMA fail (n=20)
- mFU: 12.8 mo (naive)/6.0 mo (fail)

**Phase II trial in R/R AML (N=70)**
- Single arm
  - HMA naive (n=25)
  - HMA pre-treated (n=45)
- mFU: 21.4 mo

**Toxicity:**
- Acceptable; comparable safety profiles observed across treatment arms
- Manageable; the most common AEs were pneumonia, arthralgias and constipation
- Non-immune toxicities similar for other HMA-based therapies; irAEs grade ≥3 observed in 11% of patients

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
<th>CR/CRp (%)</th>
<th>mOS (mo)</th>
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<tbody>
<tr>
<td>NIV + AZA</td>
<td>75</td>
<td>50%</td>
<td>12</td>
</tr>
<tr>
<td>IPI + AZA</td>
<td>71</td>
<td>38%</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Graphs:**

- Phase II trial in MDS
- Phase II trial in MDS*
- Phase II trial in R/R AML

*Intermediate and high risk.

AE, adverse event; AML, acute myeloid leukaemia; AZA, azacytidine; CR, complete response; CRI, CR with incomplete recovery of peripheral counts; CRp, CR with platelet recovery; CTLA-4, cytotoxic T lymphocyte-associated antigen; HMA, hypomethylating agent; ICI, immune checkpoint inhibitor; IPI, ipilimumab; irAE, immune-related AE; MDS, myelodysplastic syndromes; mFU, median follow-up; mo, months; mOS, median overall survival; NIV, nivolumab; NR, not reached; ORR, overall response rate; PD-1, programmed cell death protein 1; R/R, relapsed or refractory.

Efficacy and safety of DEC + anti-PD-1 ICI

Phase II trial in HR-MDS (N=52)
- Single arm
  - HMA naive (n=21*)
  - mFU: 7.1 mo

Toxicity: Grade 3 AEs (≥10%): febrile neutropenia and pulmonary infection; no grade 4 AEs; 50% of patients experienced an irAE, all were resolved with corticosteroids

ORR 62%
CR: 29%
mCR: 19%
mCR–HI: 14%

*Patients eligible for response evaluation at data cut-off (16 April 2022).
AE, adverse event; CR, complete response; DEC, decitabine; HI, haematological improvement; HMA, hypomethylating agent; HR-MDS, higher risk myelodysplastic syndromes; ICI, immune checkpoint inhibitor; irAE, immune-related AE; mCR, marrow CR; mFU, median follow-up; mo, months; ORR, overall response rate; PD-1, programmed cell death protein 1.
Efficacy and safety of AZA + anti-PD-L1 ICI

**Atezolizumab**

Phase Ib trial in HR-MDS (n=32)
- Two cohorts:
  - HMA naive (n=21)
  - HMA fail (n=11)
- mFU: not specified

**Durvalumab**

Randomized phase II trial in HR-MDS (N=84)
- Two cohorts:
  - AZA + DUR (n=42)
  - AZA mono (n=42)
- mFU: 15.3 mo

**Durvalumab**

Randomized phase II trial in older patients with AML (N=129)
- Two cohorts:
  - AZA + DUR (n=64)
  - AZA mono (n=65)
- mFU: 15.7 mo

**Toxicity**
- High mortality; study terminated early
- Grade 3/4 haematologic AEs were reported in 89.5% (AZA + DUR) vs 68.3% (AZA mono) of patients
- No new safety signals with combination therapy; most frequently reported TRAEs were constipation and thrombocytopenia

**Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>AZA + DUR</th>
<th>AZA mono</th>
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<tbody>
<tr>
<td>ORR (%)</td>
<td>62</td>
<td>48</td>
</tr>
<tr>
<td>mOS (mo)</td>
<td>11.6</td>
<td>16.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>AZA + DUR</th>
<th>AZA mono</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>mOS (mo)</td>
<td>13.0</td>
<td>14.4</td>
</tr>
</tbody>
</table>

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AE, adverse event; AML, acute myeloid leukaemia; AZA, azacytidine; CR, complete remission; DUR, durvalumab; HI, haematological improvement; HMA, hypomethylating agent; HR-MDS, higher-risk myelodysplastic syndromes; ICI, immune checkpoint inhibitor; mCR, marrow CR; mFU, median follow-up; mono, monotherapy; mo, months; mOS, median overall survival; ND, newly diagnosed; ORR, overall response rate; PD-L1, programmed death-ligand 1; TRAE, treatment-related adverse event.

Efficacy and safety of CT + anti-PD-1

**Pembrolizumab + high-dose cytarabine CT¹**
- Phase II trial in R/R AML (N=37)
  - mFU: 15.1 mo

**Nivolumab + 7+3 induction CT²**
- Phase II trial in ND-AML or HR-MDS (N=44)
  - Single arm
    - AML (n=42)
    - HR-MDS (n=2)
  - mFU: 17.3 mo

**Efficacy**
- ORR: 46% in R/R AML
- ORR: 80%† in ND-AML or HR-MDS
- CRc*: 38%
- CR: 64%
- CRp: 12%
- CRi: 2%
- PR: 2%
- mOS: 11.1 mo
- mOS: 18.5 mo

**Toxicity**
- Manageable; most common AEs were febrile neutropenia and liver toxicity; grade ≥3 irAEs were rare (14%) and self-limiting.

References:

*CR+CRi; †78% achieved a response (CR+CRi+CRp) together with 1 (2%) partial response resulting in an ORR of 80%. AE, adverse event; AML, acute myeloid leukaemia; CR, complete response; CRc, composite complete remission; CRi, CR with incomplete count recovery; CRp, CR with platelets recovery; CT, chemotherapy; GI, gastrointestinal; HR-MDS, higher-risk myelodysplastic syndromes; irAE, immune-related adverse event; mFU, median follow-up; mOS, median overall survival; mo, months; ND, newly diagnosed; ORR, overall response rate; PD-1, programmed cell death protein 1; PR, partial remission; R/R relapsed or refractory.
What factors could be driving the mixed response to immune checkpoint inhibitors in patients with MDS and AML?
Factors driving mixed response to ICI in MDS and AML

What is the mechanistic rationale and clinical trial data for emerging agents targeting immune dysregulation in high-risk MDS and AML?

Prof. Valeria Santini
Associate Professor of Hematology
University of Florence
Florence, Italy
What is the rationale for using anti-TIM-3 agents in treating MDS and AML?
Mechanism of action of anti-TIM-3 agents

Sabatolimab

Role of TIM-3 in MDS and AML\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Innate and adaptive immune cells</th>
<th>TIM-3 is expressed on leukaemic and immune cells (NK cells and T lymphocytes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemic cell or blast</td>
<td>TIM-3 engagement on immune cells suppresses anti-tumour immunity</td>
</tr>
<tr>
<td>TIM-3–Gal-9 interactions</td>
<td>TIM-3–Gal-9 interactions promote self-renewal of leukaemic cells</td>
</tr>
</tbody>
</table>

Activity of sabatolimab\textsuperscript{2}

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

AML, acute myeloid leukaemia; Gal-9, galectin-9; MDS, myelodysplastic syndromes; NK, natural killer; TIM-3, T-cell immunoglobulin and mucin domain 3.

What clinical trial data are currently available for the investigational anti-TIM-3 agent sabatolimab?
Most common AEs (≥15%, grade ≥3) in each group:
Thrombocytopenia, neutropenia, anaemia and febrile neutropenia

AE, adverse event; AML, acute myeloid leukaemia; CR, complete response; CRi, CR with incomplete haematologic recovery; HI, haematologic improvement; HMA, hypomethylating agent; HR, high risk; mCR, marrow CR; mDoR, median duration of response; MDS, myelodysplastic syndromes; ND, newly diagnosed; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD–HI, stable disease with HI; vHR, very high risk.

What is the rationale for using anti-CD47 agents in treating MDS and AML?
Mechanism of action for anti-CD47 agents

Magrolimab

Role of CD47 in MDS and AML

CD47, a ‘don’t eat me’ signal, inhibits phagocytosis and T-cell immune responses against tumour cells

Activity of magrolimab

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

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

What clinical trial data are currently available for the investigational anti-CD47 agent magrolimab?
Magrolimab in patients with HR-MDS
Phase Ib study of the safety and tolerability of magrolimab + azacitidine

Previously untreated HR-MDS
(N=95)

- ORR: 74.7%
- CR: 32.6%
- mCR: 31.6%
- SD–HI: 10.5%
- mDoR: 9.8 months
- mOS: Not reached

Most common AEs (grade ≥3):
Anaemia, neutropenia, thrombocytopenia and decrease in white blood cell count

AE, adverse event; CR, complete response; HR-MDS, high risk-myelodysplastic syndromes; mCR, marrow complete response; mDoR, median duration of response; mOS, median overall survival; ORR, overall response rate; PFS, progression-free survival; SD–HI, stable disease with haematologic improvement.

Magrolimab in patients with ND-AML
Phase Ib studies of the safety and tolerability of magrolimab + azacitidine

Untreated ND-AML\(^1\) (Evaluable n=34)

- ORR: 65%
- CR: 44%
- MLFS: 6%
- PR: 3%
- CRi: 12%

Most common AEs:
Anaemia, fatigue, blood bilirubin increase, neutropenia, thrombocytopenia and nausea

Expansion cohort: untreated \(TP53m\) AML\(^2\) (N=72)

- ORR: 48.6%
- CR: 33.3%
- CRi/CRh: 8.3%
- MLFS: 1.4%
- PR: 5.6%
- mDoR: 8.7 mo
- mPFS: 7.3 mo

Most common AEs (grade ≥3):
Febrile neutropenia, anaemia, thrombocytopenia, pneumonia and neutropenia

AE, adverse event; AML, acute myeloid leukaemia; CR, complete response; CRi, CR with incomplete haematologic recovery; CRh, CR with partial haematologic recovery; mDoR, median duration of response; MLFS, morphological leukaemia-free survival; mPFS, median progression-free survival; ND, newly diagnosed; ORR, overall response rate; PR, partial response; SD–HI, stable disease with haematologic improvement; TP53m, TP53-mutant.

What other novel immunotherapy strategies are currently in development for the management of high-risk MDS and AML?
Therapeutic strategies targeting the immune system

Novel therapeutic agents under investigation targeting tumour escape and disease resistance

- **Immunotherapy**
- **Adoptive T-cell transfer**
- **Tumour-specific T-cell stimulation**

- Inflammasome complex
- Toll-like receptors
- NK cells
- CAR T cells
- Vaccination