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Recovering from a therapeutic stall in higher-risk myelodysplastic syndromes: re-examining biology, backbones and study designs

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Abstract

Therapeutic progress in higher-risk myelodysplastic syndromes (HR-MDS) has stalled. Despite repeated attempts to improve outcomes through incremental refinements to classification systems and hypomethylating agent (HMA)-based backbones, no phase 3 study since AZA-001 has replicated even the modest survival benefit observed with azacitidine. We propose that this stagnation results from a fundamental mismatch between the biological realities of HR-MDS and the assumptions underpinning contemporary drug development. HR-MDS encompasses biologically diverse ecosystems characterised by distinct clonal architectures, evolutionary trajectories and marrow microenvironmental dysfunction, despite overlapping phenotypic and genotypic features. Treating this heterogeneity as a single entity anchored to a hypomethylating agent backbone, risks obscuring therapeutic signals and misinterpreting responses. Here, we examine the potential biological, microenvironmental, and methodological drivers of therapeutic insufficiency in HR-MDS, to advocate for biologically coherent adaptive platform trials using biomarker-enriched patient selection, and propose shifting away from default HMA backbones. Only by redesigning strategy around biology, rather than prioritising ease of recruitment, or historical precedent, can we restore momentum and lift in HR-MDS drug development.

In higher-risk myelodysplastic syndromes (HR-MDS), promising agents from early-phase clinical studies have repeatedly failed to improve survival in phase 3 trials of previously untreated patients.[1-4] Much like an aircraft entering a slow-speed stall, continued progression along the same trajectory, through minor adjustments to existing frameworks or trial designs, risks deepening descent. Recovery will require abandoning ingrained reflexes and embracing counterintuitive inputs, including a biological and phenotypic re-examination of disease boundaries, rethinking trial design, and aligning trial endpoints with outcomes meaningful to patients. Recent reviews have elegantly summarised lessons from contemporary trials in treatment-naïve HR-MDS, highlighting opportunities to refine study design and endpoints.[1-4]

Here, we extend this discussion by focusing on relatively under-explored biological constraints related to disease dynamics, microenvironmental dysfunction, and treatment backbones, beginning with the challenge of defining what constitutes 'HR-MDS'. In practice, this umbrella term is pragmatic but imprecise, encompassing patients defined by increased blast burden, adverse genetic features, or combinations of these factors, in whom variable degrees of marrow failure represent a shared phenotypic feature.[5,6] Reliance on prognostic frameworks, such as IPSS-R[7] or IPSS-M,[8] designed to estimate risk rather than to inform therapeutic strategy, has shaped clinical trial enrolment in HR-MDS and contributed to the uniform therapy of biologically heterogeneous diseases. Identifying and sub-categorising biologically distinct diseases within the umbrella of HR-MDS may therefore be a pre-requisite for meaningful therapeutic progress.

Recent updates to the WHO, and International Consensus Classification (ICC) of myeloid neoplasms represent important attempts to align disease classification more closely with underlying biology, particularly at the blurred boundary between MDS and acute myeloid leukaemia (AML). The existence of differences between these classification systems despite shared biological intent, highlights the inherent difficulty of imposing static categorical definitions on dynamically evolving diseases, and reinforces the distinction between disease classification, prognostic stratification, and therapy.[5,6] Our biology-focused approach, adopted here for newly diagnosed HR-MDS, centres on patients with IPSS-R scores >3.5 and moderately high- or higher-risk disease by IPSS-M.[7,8] However, it is also applicable to genetically defined high-risk subgroups, including biallelic *TP53*-mutated MDS, cases with complex or monosomal karyotypes or multiple adverse mutations, MDS with excess blasts (MDS-EB), MDS/AML (synonymous with MDS-IB2), and select patients with lower-risk disease with a higher risk of AML transformation.

Phenotypic and genotypic convergence of HR-MDS on AML: utility and limitations

Although the risk of transformation to AML is increased in HR-MDS, a substantial proportion of patients die from complications of bone marrow failure without ever developing AML.[7,8] Distinguishing patients whose disease biology more closely resembles AML is therefore clinically important, as this subgroup may be more likely to benefit from AML-directed therapies. A practical approach to this heterogeneity has been to use differentiation arrest, morphologically reflected by blast excess, as a

phenotypic surrogate for AML-like biology, with a bone marrow blast threshold of 10%-19% to define MDS/AML.[5,9] Shared genotypic features between MDS/AML, AML arising from prior MDS and de novo AML, with so called 'secondary-type' gene signatures that associate with poorer outcomes following intensive therapy,[5,9,10] further support the inclusion of patients with MDS/AML for treatment in clinical trials of AML.

However, the simple transference of AML-directed therapy to all patients with HR-MDS with ≥10% blasts may not be uniformly effective. This limitation is exemplified in the VERONA study, in which azacitidine and venetoclax, considered standard AML treatment for patients unsuitable for intensive therapy, failed to improve survival, including among HR-MDS patients with ≥10% blasts.[11] By contrast, signals of benefit restricted to response rates in VERONA,[11] or survival in the sub-group of patients with ≥10% blasts in the phase 3 STIMULUS-MDS2 trial of sabatolimab[12] - together with comparable responses in newly diagnosed AML patients in early phase studies of sabatolimab,[13] support maintaining a distinction between MDS/AML and MDS with a lower (<10%) blast burden. One explanation for these divergent outcomes could be disease dynamics, reflecting changes in proliferative capacity and apoptosis-resistance within blasts, that is not routinely quantified in clinical practice.[14,15] *De novo* AML is typically characterised by rapidly progressive cytopenias and higher blast burden, mandating urgent therapy, whereas MDS is relatively clinically and haematologically stable in the peri-diagnostic period. Due to the perceived invasive nature of bone marrow sampling, risk-stratification in MDS usually relies on a single baseline marrow assessment, and without elective interval surveillance biopsies.[16] While longitudinal changes in cytopenias, reflected

in serial blood counts,[16] or captured by machine-learning models using longitudinal patient data[17] may help predict broader disease outcomes in MDS, there remain no reliable indicators of blast tempo at the individual patient level.[18,19] Consequently, it remains uncertain whether patients with HR-MDS who demonstrate a slow, incremental rise in blasts derive the same benefit from AML-directed therapy as those with more abrupt disease acceleration.

Reliance on the blast burden alone for trial enrolment is further complicated by time-dependent hazard patterns: in lower-risk MDS, the risks of death and AML transformation remain relatively stable,[19] whereas in HR-MDS these hazards diminish with increasing time from diagnosis, suggesting fundamental biological differences between *de novo* higher-risk disease and cases re-classified following progression. Trial eligibility based solely on a ≥10% blast threshold, thereby combining patients with progressive lower-risk disease and those with *de novo* HR-MDS/AML, may therefore confound interpretation of therapeutic outcomes. Moreover, given the imprecision of morphological blast enumeration at lower levels,[20] advanced disease may be under-recognised in some patients with blast percentages below 10%.

Recent refinements in genetic classification further challenge reliance on blast thresholds alone. Certain genetic abnormalities, including *NPM1* mutations, the *RUNX1::RUNX1T1* or *PML::RARA* re-arrangements, define AML irrespective of blast count and are directly therapeutically informative.[5,6] Extension of this biology-driven classification to define unique MDS sub-types, for example, in patients with isolated

SF3B1 mutations, del(5q) and 'multi-hit' *TP53*-mutated disease has therefore been advocated,[5,6] even if the blast burden remains integral to most genetic classifiers. An exclusively genetic categorization of MDS has also been proposed;[21] however, as blast burden remains independently associated with outcomes even within genetically defined groups,[22,23] blast percentages may be better viewed as a marker of disease stage within specific genetic contexts rather than as an exclusive binary classifier. In this framework, phenotypic and genotypic convergence of HR-MDS on AML should be considered context-dependent, shaped by genotype, blast burden and potentially, the tempo of change, rather than captured by static thresholds alone. If so, traditional therapeutic algorithms that allocate intensive 'AML-type' therapy preferentially to younger or fitter patients may warrant reconsideration, with greater emphasis on genotype- and blast-informed treatment stratification. The promise of this strategy is supported by early results from the phase 2 randomized PARADIGM study in AML, in which outcomes with lower-intensity therapy in predominantly adverse-risk patients eligible for intensive treatment were superior to those with intensive chemotherapy.[24]

The limitations of blast-centred classification are most evident in patients with HR-MDS with lower blast percentages, in whom disease phenotype is defined less by tumour mass than by ineffective hematopoiesis and marrow failure. In this setting, and even in patients with higher blast burden, where cytoreduction does not reliably translate into durable hematopoietic recovery or improved survival,[25] conventional blast-directed therapy alone may be insufficient, supporting consideration of the marrow and immune microenvironment as a key, yet clinically under-addressed, determinant of therapeutic response in HR-MDS.

The Marrow Microenvironment: the Unaccounted Dimension

Across AML trials, some of which include MDS patients with ≥10% blasts, lower-intensity therapies[26-29] are frequently associated with less frequent count recovery than intensive induction,[30,31] despite effective blast clearance. This contrast extends to intensively treated older patients with secondary AML including adverse karyotype, in whom complete remission with incomplete count recovery (CRi) contributes less to the overall response than complete remission (CR).[32] The biological basis for the dissociation between blast clearance and hematopoietic recovery with lower-intensity therapy, often attributed simplistically to 'poor hematopoietic reserve', is likely to be more complex and not restricted to intrinsic defects in normal hematopoietic stem cells. Consistent with this view, studies demonstrating higher rates of flow cytometry-based measurable residual disease (MRD) in AML patients achieving CRi compared with CR following intensive chemotherapy, suggest an inhibitory effect of residual disease on normal hematopoiesis.[33,34] However, incomplete hematopoietic recovery can be independently prognostic of outcome beyond residual disease,[33,35] although not consistently observed across studies.[34] This may reflect disease persistence below the limits of MRD detection,[33,35] or sustained dysfunction within the marrow microenvironment. The latter hypothesis is supported by the observation that reduced survival in intensively treated younger patients achieving CRi is not explained by increased relapse.[36]

Could intensive chemotherapy induce a broader "reset" of marrow cellular and microenvironmental interactions that is not consistently replicated by lower-intensity

therapies across disease genotypes? Indirect support for a microenvironmental contribution to count recovery comes from the AML LI-1 study, which evaluated combinations of novel agents with a low-dose cytarabine backbone and included MDS patients with ≥10% blasts. In these studies, a relative reduction in CRi and corresponding increase in CR were observed with arginase (BCT-100)[37] and lenalidomide,[38] agents with recognised immunomodulatory properties.[39,40] Modulating marrow environmental function may therefore be synergistic with low-dose cytarabine to influence hematopoietic recovery. This hypothesis is supported further by the identification of a gene expression profile indicative of changes in angiogenesis, cell cycle and immune function in an Italian study of lenalidomide with low-dose cytarabine, with 33% of patients achieving CR.[41,42] In contrast, adding lenalidomide to intensive chemotherapy is of limited benefit,[43,44] suggesting that the effect on the microenvironment might be restricted to the context of less intensive therapies, lenalidomide dose, or disease sub-type.[38,41-44] The therapeutic targeting of the microenvironment to convert blast clearance with limited haemopoietic recovery into CR, would be worthy of further investigation as a potential determinant of longer-term outcomes in both MDS and AML.

Microenvironmental dysfunction is well described in MDS, with lower-risk disease frequently characterised by immune activation, including inflammasome signalling,[45] pro-inflammatory cytokine production,[46] adaptive monocyte responses[47] and immune-mediated suppression of hematopoiesis.[48-50] In contrast, HR-MDS is associated with a more immune-evasive marrow environment, marked by functional immune exhaustion, regulatory T cell expansion[46,48,49-51] and reduced frequency of dendritic cells with functional alterations,[51,52] features that in combination with

mesenchymal stroma cells could remodel the hematopoietic niche to favour clonal stem cell persistence. In particular, dysfunction within monocytoid and immunosuppressive myeloid compartments[51] which are less dependent on BCL-2 signalling,[53-54] could, in part, account for the failure of venetoclax-based lower-intensity therapy to improve survival of HR-MDS patients in the phase 3 VERONA clinical trial.[11] These patterns of microenvironmental dysfunction represent overlapping and not absolute states, therefore requiring characterisation in individual patients.[51] Therapies aiming to modulate the marrow microenvironment may be particularly relevant in HR-MDS with low, stable blast numbers, where disease phenotype appears to be driven less by tumour burden than by ineffective hematopoiesis. In patients with a higher blast burden, cytotoxic approaches similar to AML-therapy may require combining with treatments that modulate immune and inflammatory pathways, to support hematopoietic recovery alongside clonal eradication.

With advances in multiparameter flow-cytometry–based immunophenotyping, a single marrow specimen can now be analysed in specialist laboratories for simultaneous assessment aberrant differentiation patterns[55] or MDS-initiating stem cell populations[56,] and immune cell compartments,[51] prognostication[56,57] and identifying measurable residual disease (MRD) targets.[58,59] Integrating such assessments at diagnosis, and longitudinally alongside evolving genomic dynamics, could provide critical insights into disease biology and responses under therapeutic selection pressure. Given the heterogeneity of microenvironmental interactions across HR-MDS, failure to incorporate this dimension into patient stratification may explain why outcomes with hypomethylating agent (HMA) monotherapy (despite

acceptance as ‘standard-of-care’), or combinations built upon it, remain disappointing for many patients.

‘Hypomethylating agents’ – an appropriate backbone or a bottleneck for some?

The survival advantage of the HMA azacitidine over conventional care in AZA-001 was widely regarded as a major advance in HR-MDS almost two decades ago.[60] Since then, azacitidine has become the *de facto* therapeutic backbone for HR-MDS, with novel agents tested almost exclusively in combination with azacitidine and benchmarked against azacitidine monotherapy.[1-4] However, important limitations of AZA-001, including heterogeneous control-arm therapies and a modest absolute survival benefit, [60] coupled with difficulty in reproducing these outcomes in real-world populations,[61,62] highlight the risks of anchoring drug development to a single standard within a biologically heterogeneous disease. Decitabine, the alternative HMA, has demonstrated broadly comparable activity in HR-MDS,[63] with pharmacokinetic and pharmacodynamic equivalence between oral and intravenous formulations,[64] and has therefore served as the alternative HMA in clinical trials.

Uncertainty regarding the precise mechanisms underlying HMA activity complicates their role as universal backbones for combination therapy. Disease genotype is not reliably predictive of response,[65] and the association with hypomethylation in responding patients is inconsistent.[66] In addition, alternative mechanisms, including RNA disruption and immune activation, may contribute to

both efficacy and toxicity.[67-69] In clinical practice, HMA therapy is administered for 4-6 cycles before assessment of efficacy, effectively selecting for fitter patients, able to tolerate prolonged cytopenias. A combination of inter-patient and disease-specific variables, difficult to measure prospectively, is therefore a likely explanation for the failure of real-world studies to replicate the survival benefit observe with azacitidine monotherapy in AZA-001. [61,62] The absence of reliable predictive bio-markers to inform patient selection for HMA monotherapy extends to combination strategies, where putative synergy between HMAs and novel agents is largely inferred from *in vitro* studies. As a result, it is challenging to delineate true mechanistic interactions, attribute toxicity, or identify optimal dosing and scheduling in patients.

Taken together with the heterogeneity of clonal genotype and microenvironmental interactions in MDS described earlier, it is quite possible that hypomethylating agents, while effective for many patients, may also act as a bottleneck to therapeutic progress in biological subgroups, particularly where resistance, incomplete hematopoietic recovery, or microenvironmental dysfunction limit durable benefit. Experimental studies performed over 4 decades ago demonstrated that although azacitidine induces rapid DNA hypomethylation, this effect is neither sufficient nor efficient to drive terminal differentiation, with most clonogenic cells persisting in an epigenetically altered, yet functionally plastic state.[70] More recent studies indicate the potential for senescence and escape following azacitidine therapy,[71] along with marked heterogeneity in cellular responses to azacitidine across model systems,[72] mirroring clinical observations in which clonal progenitor cells in responders undergo differentiation following therapy.[73,74] While this variability appears to reflect differences in methylation patterns within stem cell

and progenitor compartments between patients,[75] longitudinal interactions with other epigenetically modified cellular elements of the marrow microenvironment[76] may ultimately determine the quality and durability of response.

Importantly, even in clinical responders, including those achieving CR/CRi, the malignant clone is not eradicated,[73] highlighting the inability of HMA-mediated effects to eliminate disease-sustaining cells. In both responders and non-responders, the induction of cellular senescence[77] could further preserve malignant compartments capable of subsequent escape and aggressive relapse, consistent with clonal shifts observed at disease progression.[78] Confirmation of these mechanistic limitations will be relevant when considering HMA therapy as a bridge to allogeneic stem cell transplantation (alloSCT), as the failure to restore microenvironmental fitness, or induction of clonal instability prior to transplant, may influence post-transplant outcomes.

Allogeneic stem cell transplantation – maximising the benefit

Although alloSCT remains the only potentially curative strategy for patients with HR-MDS, substantial uncertainty persists regarding pre-transplant disease optimisation and the acceptable blast burden for improving outcomes.[79] Retrospective analyses have demonstrated inferior survival in patients transplanted with 5–20% blasts compared with those with <5% blasts, as well as poorer outcomes in patients with platelet counts <100 × 10^9/L, to suggest that both disease burden and marrow function at the time of transplantation are important determinants of outcomes.[80]

Prospective observational studies in HR-MDS patients, whilst confirming the survival advantage associated with alloSCT, indicate the detrimental impact of blast percentage on both survival, and the likelihood of proceeding to transplantation.[81] However, closer examination of multivariable modelling[81] suggests that clinical discretion, more than biological rationale, is likely to influence decisions regarding transplantation across different levels of disease burden. Whether a reduction of disease burden with HMA or intensive chemotherapy prior to alloSCT[82] is necessary in all patients with HR-MDS to improve post-allograft outcomes, remains unclear. Indeed, retrospective analyses suggest that although achieving CR following intensive chemotherapy is associated with improved survival compared with non-responders, post-transplant survival does not appear superior to that observed in patients proceeding directly to transplantation without pre-transplant therapy.[83]

Additional stratified analyses incorporating disease dynamics, using the sequential change in IPSS-R scores at diagnosis and at transplantation, further suggest that the apparent benefit of pre-transplant therapy is confined to patients with favourable disease biology rather than conferring uniform improvements in outcomes.[84] For example, the reduced survival observed with blast progression following chemotherapy, but not HMA in patients with blasts <5% at diagnosis, and improved survival in untreated patients who proceeded to transplant with higher blast burdens, appear most consistent with selection effects driven by underlying disease biology. Taken together, these observations suggest that pre-transplant interventions with chemotherapy or HMA primarily act as biological filters, rather than reliably altering the natural history of HR-MDS.[84]

Accordingly, transplant strategies focused solely on blast reduction and MRD eradication, without biology-driven patient selection may be insufficient to improve outcomes in HR-MDS. Achieving durable remission could also require restoration of a permissive marrow microenvironment capable of sustaining effective donor hematopoiesis and immune surveillance. A logical starting point towards this objective would be the comprehensive immunophenotypic characterisation of marrow cellular compartments,[56,57] integrated with genomic profiling at diagnosis.[85] Longitudinal monitoring of these parameters before and around transplantation[86,87] could define evolving disease genotype and microenvironmental biology[51,57] and begin to elucidate the relationship between them, informing the need for, and type of, pre- and post-transplant intervention. This relationship may be particularly relevant in the post-alloSCT setting, as donor hematopoiesis develops within a predominantly host-derived stromal niche[88] that might have been previously 'conditioned' to influence engraftment dynamics and lineage-specific immune reconstitution. A combined immunophenotypic and genomic approach could thus complement MRD- and post-transplant immune chimerism-based strategies that are currently being used to address key questions around risk-adapted conditioning intensity, T-cell chimerism, and maintenance therapies, aiming to balance relapse risk against non-relapse mortality.[89-94] Importantly, as patients with HR-MDS are currently included within AML cohorts, it will be important to confirm the applicability of monitoring and intervention strategies through dedicated analyses of MDS and MDS/AML subgroups.

Rethinking Trial Design: Towards Adaptive and Biologically Informed Strategies

Ultimately, patient selection for intensive chemotherapy, HMA monotherapy, novel agents, or combination therapy will be central to the success of future trials in HR-MDS. Closely linked to this strategy is the recognition that sustained therapeutic pressure may differentially shape clonal evolution or shifts in distinct disease genotypes.[95,96] In order to subvert clonal escape, sequential or alternating therapeutic strategies, once a feature of AML therapy,[97] may warrant reconsideration in a modern biological context, rather than reliance on metronomic exposure to the same treatment across all patients. While activity observed in early-phase studies often justifies progression to later-phase trials, this signal may be diluted when agents are evaluated in larger, biologically heterogeneous populations, selected primarily to satisfy statistical, rather than biological criteria.

It will therefore be important to revisit biological samples and data from early-phase trials of now 'abandoned' agents, to identify biological predictors of response through integrated analysis of genotypic, transcriptomic, methylation, and proteomic profiles,[98] with validation in archived specimens from responding patients enrolled in corresponding phase 3 studies that failed to meet their primary endpoints. These approaches could offer new insights to develop functional classification of HR-MDS, re-define risk groups and identify cell targets amenable to therapeutic intervention. Validation of biologically meaningful disease subgroups could then inform future trial

design. The characterisation of cellular immunophenotypes and the immune microenvironment will further help evaluate potential biomarkers of response.

Investment in the re-evaluation of ‘failed’ agents using this framework would allow clearer assessment of target engagement and drug activity, thereby setting the stage for prospective testing of therapies, both established and novel, as monotherapy or within biomarker-enriched cohorts, before commitment to large-scale combination studies. For MDS patients under consideration for recruitment in AML trials, it should be feasible to await genotyping results prior to trial entry, given the relatively less urgent need for immediate disease-modifying therapy in MDS compared with AML. Eligibility criteria, power calculations, and outcome analyses for such patients should explicitly account for time from diagnosis. In trials exclusively focused on HR-MDS, adaptive, signal-seeking platform designs offer an efficient means to support rapid ‘go/no-go’ decisions, minimise patient exposure to inactive regimens, and reduce the inefficiency inherent in fixed, large phase 3 trials of unselected patients. Experience with ‘pick-a-winner’ approaches in AML illustrates that, even when definitive therapeutic advances are not identified, such designs efficiently de-prioritise unpromising strategies.[99] A comparable paradigm in HR-MDS, focused on phenotypically and biologically defined disease subsets, incorporating longitudinal tracking of disease and microenvironmental evolution, and using alternative endpoints such as duration of remission to progress agents from early phase studies,[100] could streamline drug development and help address the persistently high attrition rate of therapies in this disease.

Conclusions (Figure 1)

The results of recent trials suggest that overcoming the therapeutic stall in HR-MDS will require a deliberate re-alignment of therapeutic strategy with clonal biology, characterised more comprehensively at diagnosis and longitudinally, and within its microenvironmental context. Restoring momentum in drug development will depend on re-thinking trial design and treatment backbones to prioritise biological uniformity within disease-subsets, over rapid recruitment. Do sponsors and trial investigators have the willingness, patience, and collaborative instinct to do so?

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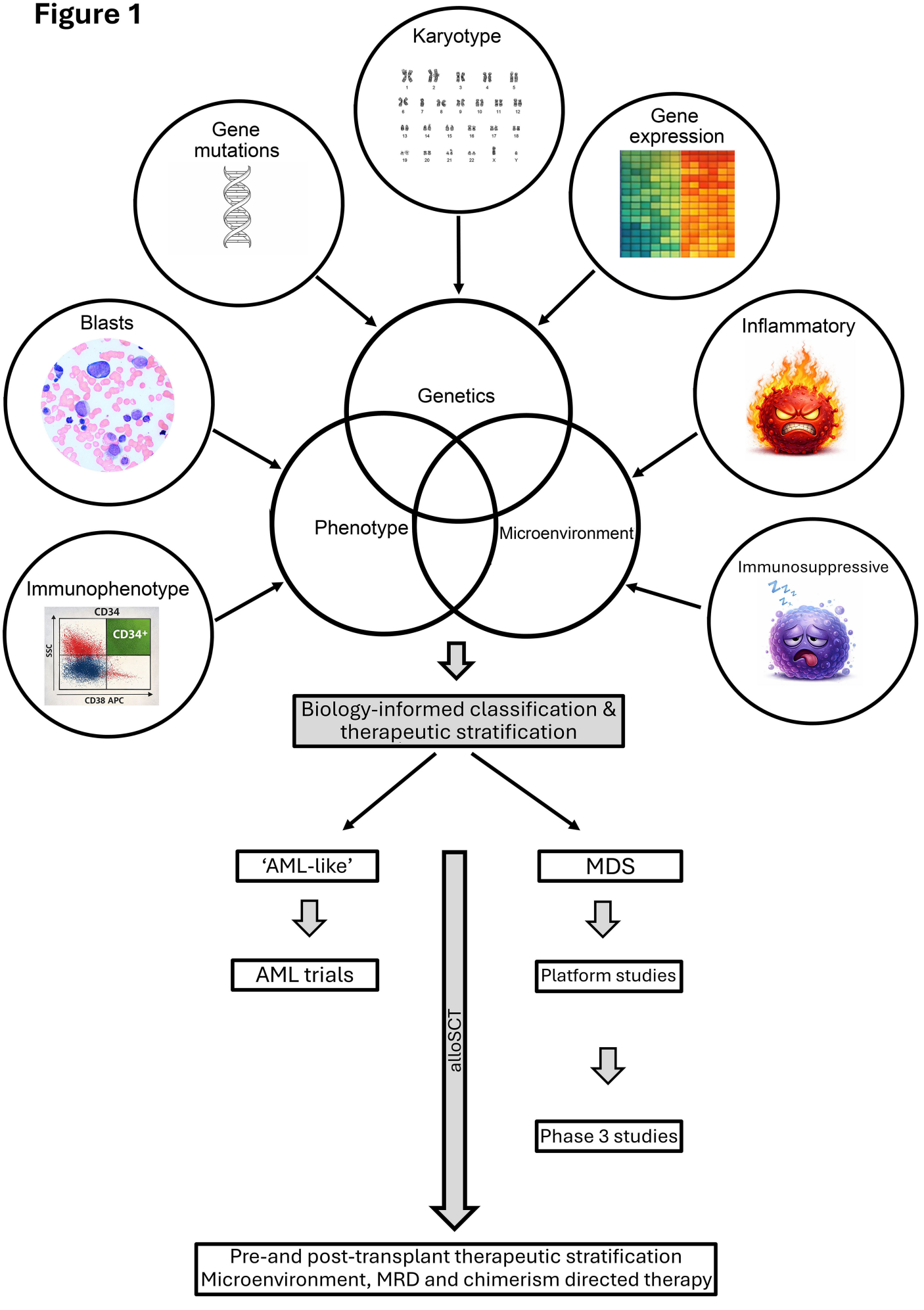
Figure 1. Biology-aligned framework for therapeutic decision-making in higher-risk myelodysplastic syndromes (HR-MDS). Schematic representation of overlapping domains HR-MDS reflect a biologically heterogeneous disease continuum, in which blast burden, genotype, immunophenotype, and microenvironmental state can be used to define therapeutic vulnerability. The region of overlap highlights functional subsets of HR-MDS that may benefit from a unified therapeutic approach including AML-directed strategies ('AML-like'). These variables are potential dynamic modifiers of disease phenotype and treatment response across the spectrum. This framework advocates for biology-informed trial design and therapeutic sequencing, and in suitable patients, optimisation of allogeneic stem cell transplantation (allo-SCT) through tailored pre- and post-transplant strategies, including measurable residual disease (MRD)-directed interventions.

Figure 1


Karyotype
Gene mutations
Gene expression
Blasts
Inflammatory
Genetics
Phenotype
Microenvironment
Immunophenotype
CD34
CD34+
SSC
CD38 APC
Immunosuppressive
Biology-informed classification & therapeutic stratification
'AML-like'
MDS
AML trials
Platform studies
Phase 3 studies
alloSCT
Pre-and post-transplant therapeutic stratification
Microenvironment, MRD and chimerism directed therapy