

Toward eRASing the challenge of CMML heterogeneity

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Comment on Montalban-Bravo et al, page 5105

Chronic myelomonocytic leukemia (CMML) is a clonal hematologic malignancy at the interface between myelodysplastic syndromes (MDS) and myeloproliferative neoplasms, defined by sustained monocytosis, bone marrow dysplasia, and variable myeloproliferation. Treatment options remain limited, mostly consisting of cytoreduction (typically hydroxyurea) or hypomethylating agents (HMAs).¹ Targeted therapies remain elusive, with CMML still representing a major unmet clinical need.

Despite a limited repertoire of recurrently mutated genes, CMML displays marked clinical heterogeneity.² Disease courses range from indolent to aggressive, with up to one-third transforming to acute myeloid leukemia (AML). Clinically dichotomous subtypes, predominantly myelodysplastic (MD-CMML) and myeloproliferative (MP-CMML) in nature, are distinguished by an arbitrary white blood cell (WBC) cutoff ($13 \times 10^9/L$) and characterized by distinct clinicopathological features and therapeutic goals. Heterogeneity derives partly from variable patterns and distribution of mutations, driving different aspects of disease biology. A prevailing model posits early acquisition of epigenetic and/or splicing mutations in a primitive stem cell, driving expansion of a myelomonocytic-skewed progenitor compartment, with downstream secondary mutations refining and shaping the expressed disease phenotype.¹

Among the latter, mutations activating RAS pathway signaling are especially pertinent. Present in 30% to 40% of CMMLs, they have long been linked to proliferative disease. Despite their prominence, RAS mutations remain incompletely integrated into risk stratification and treatment selection. Four major prognostic systems recognize the adverse impact of *ASXL1* mutations, but only the CMML Prognostic Scoring System (CPSS)-Molecular³ also incorporates *SETBP1*, *RUNX1*, and *NRAS*, the most frequent RAS mutation in CMML. *NRAS* also features in a model predicting stem cell transplant outcomes,⁴ but otherwise the diverse landscape of RAS mutations remains absent from clinical decision-making tools.

In this issue of *Blood Advances*, Montalban-Bravo et al⁵ report the most comprehensive study of RAS pathway mutations in CMML to date, describing their mutational landscape, clonal architecture, phenotypic associations, and clinical correlates in unprecedented detail. Applying broad sequencing panels to one of the largest described CMML cohorts, they extend scrutiny beyond *NRAS*, *KRAS*, and *CBL* to the less common mutations in *NF1*, *PTPN11*, *BRAF*, and *CBL*, providing a richly detailed atlas of the RAS-mutated CMML genomic and prognostic landscape.

Reaffirming associations between RAS mutations and MP-CMML, they go further: mapping comutation patterns to reveal enrichment of distinct mutation partners alongside *NRAS* and *CBL* (but notably none with *KRAS*) and differences in clonal placement between mutations in *CBL*, *KRAS*, and *NRAS* (usually dominant) and those involving *BRAF*, *NF1*, and *PTPN11* (more often subclonal). These and other findings highlight quite variable genomic landscapes, arguing against a simplistic view of interchangeable routes to pathway activation to equivalent biological and phenotypic effect.

The cohort size and depth enable robust survival analysis, stratified by mutation type, burden, and comutation context, offering a refined view of how RAS pathway lesions influence prognosis. Consistent with previous reports,⁶ RAS mutations overall conferred poorer outcomes. Intriguingly, MD-CMML with RAS mutations displayed comparable survival to MP-CMML, suggesting that genomics might supersede snapshot WBC counts as more important in prognostication. It remains unclear whether such MD-CMML cases are destined to develop proliferative disease, as intuitively might be predicted.

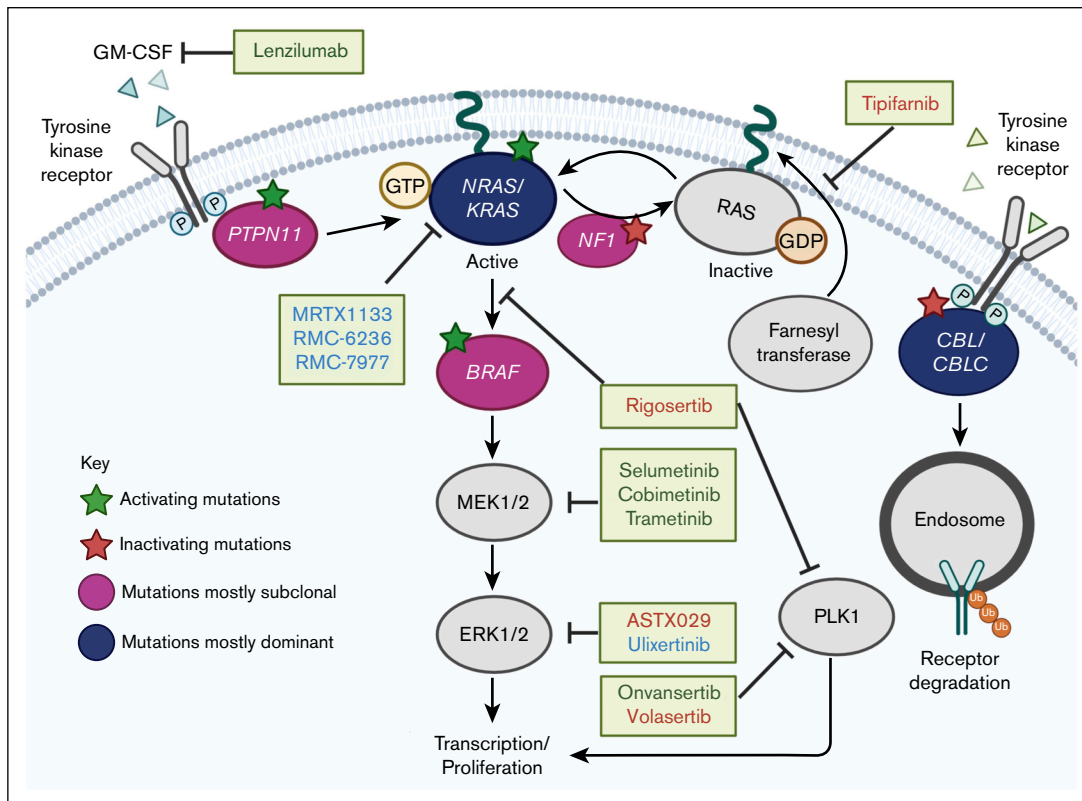


Figure 1. The RAS pathway in CMML: recurrent mutations and therapeutic approaches. Activating and inactivating mutations are indicated by green and red stars, respectively. Mutations most commonly dominant are indicated in navy bubbles; those mostly subclonal are in pink bubbles. Selected therapeutic agents and their targets are showcased: those considered to have failed clinical development are in red text; those currently in clinical trials that include patients with CMML are in green text; agents with potential promise for repurposing to RAS-mutated CMML are in blue text. GDP, guanosine diphosphate; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Although pooled RAS pathway mutations were (as a group) strongly prognostic, no individual RAS gene was independently prognostic for overall survival (OS) in multivariate analysis. Still larger data sets may be required to fully resolve their differential impacts. Nevertheless, findings such as *CBL* and *KRAS* mutations associating with shorter leukemia-free survival in certain karyotypic contexts, and prognostic modulation by specific mutation partners (eg, *RUNX1* with *NRAS*; *IDH2* with *KRAS/CBL*) add novel and important nuance to our understanding.

Notable among their findings are apparently divergent implications for *KRAS* and *NRAS* mutations: despite sharing high homology and similar frequencies, variant allele frequency distributions, hot spot profiles, and clonal architecture, as well as distinct comutation patterns, *KRAS* (but not *NRAS*) mutations predicted shorter LFS in select contexts, challenging its omission from contemporary prognostic tools. This aligns with reports of inferior outcomes in *KRAS*-mutant (vs *NRAS*-mutant and RAS wild-type) AML.^{7,8} Granularity may run deeper still, with recent reports suggesting different clinical implications for *KRAS* G12/13 vs Q61 hot spots.⁸

An unanswered question remains how to exploit RAS pathway mutations for therapeutic benefit. Decades of effort to directly inhibit RAS have been marked by frustration (Figure 1). Farnesyltransferase inhibitors failed to deliver on early promise, undermined by alternative prenylation pathways and off-target toxicity. Rigosertib, a purported RAS mimetic, ultimately failed late-phase trials in MDS/

CMML and AML, reflecting its unclear mechanism of action and nonspecific toxicity. MEK inhibitors targeting downstream signaling showed preclinical efficacy in *NRAS*-mutant CMML mouse models⁹ but have thus far displayed disappointing activity and tolerability in early-phase trials, with bypass resistance remaining a challenge for these agents. Notable success stories from elsewhere in oncology (eg, BRAF inhibitors) target pathway components less relevant to CMML, although they might have a role for rare *BRAF*-mutated cases (as highlighted in Montalban-Bravo's study).

There is now renewed hope, with more selective and potent agents under investigation (Figure 1). ERK inhibitors, acting downstream of MEK, are in clinical development and may circumvent resistance associated with upstream blockade. Mutation-specific *KRAS* inhibitors, such as those targeting G12C/D, show activity in solid tumors and are now being explored in hematologic malignancies. These (and others) could potentially be repurposed for CMML.¹⁰

PLK1 inhibitors show synthetic lethality in RAS-mutated backgrounds, with preclinical efficacy and apparent HMA synergy *in vitro/in vivo*.⁶ A phase 1 trial is underway. Another promising candidate is lenzilumab, a monoclonal antibody targeting granulocyte-macrophage colony-stimulating factor, which demonstrated preferential efficacy in RAS-mutant CMML, possibly by disrupting cytokine-driven signaling that cooperates with RAS activation. A single-arm phase 2 trial in RAS-mutant CMML

reported impressive efficacy in combination with azacitidine, including marked OS improvement compared with historical cohorts and a particular signal for *CBL*-mutated cases.¹¹ Randomized trials are needed, but these agents offer real hope for future precision approaches.

We may still lack the tool kit to fully exploit it, but the work by Montalban-Bravo et al lays essential groundwork for this future. By clarifying the implications of RAS pathway mutations across CMML, it equips the field with both rationale and road map for improved patient stratification and trial design. As new agents emerge, these insights may help finally translate molecular understanding into meaningful therapeutic advances for this challenging disease.

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