and its regulatory elements. Recent data obtained in a mouse model revealed that B- to plasma-cell differentiation is associated with major changes in chromosome topology that could be driven by PC biology or reflect enhancer-induced modifications in chromatin organization.[6] B- to plasma-cell transition is associated with compartmentalization changes along with gain in genomic interactions across the Prdm1 locus, increasing genomic interactions between promoter regions and regulatory elements, concurrent with transcriptional induction. In contrast, the early B-cell factor 1 (Ebf1) locus repositions to pericentromeric heterochromatin in association with transcriptional repression. Furthermore, the interchromosomal hubs reported during B- to plasma-cell maturation are associated with histone marks that define transcriptionally active or repressive hubs. The epigenetic landscape characterization together with nuclear architecture study of the human B- to plasma-cell differentiation model developed by Pignarre et al may provide important findings for the understanding of the molecular mechanisms driving B- to plasma-cell fate.

IL-4 production by T-follicular helper and STAT6 mutations activates and drives the IL-4/STAT6 axis in follicular lymphoma.[7] Recently, single-cell RNAseq characterization of purified GC B cells (GCBs) generated a new single-cell cell of origin classification that identified distinct prognostic subgroups within the GCB and activated B-cell–like diffuse large B-cell lymphoma subgroups.[8] The analysis of these single-cell transcriptomic resources derived from GC purified B cells, in light of the new data provided by Pignarre et al, may be of particular interest. The results provided by Pignarre et al provide new insights in the molecular mechanisms driving follicular lymphoma biology.

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LYMPHOID NEOPLASIA

Comment on Corre et al, page 1192

Deletion 17p: a matter of size and number?

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In this issue of *Blood*, Corre and colleagues provide solid evidence for a profound negative impact of del(17p) in patients with myeloma who have del(17p) in >55% of their plasma cells. This increased risk is independent of the presence of a *TP53* mutation.[1]

It is generally accepted that loss of the short arm of chromosome 17 [del(17p)], as determined by fluorescence in situ hybridization (FISH) analysis, is the most important high-risk factor in multiple myeloma, negatively impacting both progression-free survival (PFS) and overall survival (OS).[2,3] The loss of the *TP53* gene, encoding the tumor suppressor protein p53, is supposed to underlie this dismal outcome.[4] There are limited and conflicting data on the impact of mutations in the *TP53* gene, either to a single allele or when associated with del(17p), so-called double hit disease. In a recent DNA sequencing analysis of ~800 heterogeneously treated patients, including both transplant-eligible and noneligible patients, performed by Walker and colleagues, a dismal outcome was found only in patients with biallelic *TP53* inactivation with a median OS of 20.7 months. In contrast, copy number loss of 17p only or 1 mutation in *TP53* only lacked prognostic impact, showing a similar outcome as compared with patients with *TP53* wild type.[5]

Corre and colleagues used a different approach in this study. They first identified 121 newly diagnosed multiple myeloma patients (NDMM) with a del(17p) in >55% of plasma cells who were uniformly treated with intensive therapy, including an autologous stem cell transplantation (ASCT). One-third of these patients had an additional mutation in *TP53*. As in the study by Walker and colleagues, median OS in biallelic disease was short, only 36 months. However, OS was also significantly worse in patients with del(17p) without *TP53* mutation(s), compared with patients lacking del(17p) (52.8 vs 152.2 months, respectively). Therefore, the study of Corre and colleagues supports the continued use of FISH analysis to identify high-risk patients with a poor prognosis based on the presence of del(17p) in >55% of myeloma cells, without the need for additional genome sequencing. This is important, as FISH analysis is widely available and standardized. In addition, FISH data are available from contemporary clinical studies, whereas DNA sequencing data, and thus *TP53* status, are generally missing.

Therefore, detection of cytogenetic abnormalities by FISH alone enables comparison between studies and identification of promising therapeutic regimens for high-risk patents. Nevertheless, it is important to realize that the presence of del(17p) does not necessarily implicate an inferior outcome. Furthermore, we expect that changing the diagnostic approach to DNA sequencing will be of added value, revealing additional information.

First, the size of the clone probably matters. The authors previously set a specific cutoff of 55% as having the best discriminative capacity to predict outcome.[6] The dismal prognosis of del(17p), without the need for additional DNA sequencing, was only shown for this cutoff point. The possibility of drugs overcoming the negative impact of del(17p) may depend on the clone size. This is supported by an analysis of patients with relapsed multiple myeloma who were treated with ixazomib, lenalidomide, and dexamethasone. Using a cutoff of 5% or 20%, the negative impact of del(17p) was completely overcome [median PFS 21.4 in del(17p) vs 20.6 months in all patients]. However, when using a cutoff of 60%, PFS was reduced to 15.7 months.[7] In NDMM patients with del(17p), a double ASCT has been found to overcome the negative impact of del(17p). The 5-year OS was 80.2% with double vs 57.1% with single ASCT. Even more important, the PFS and OS of del(17p)-positive patients undergoing double ASCT were comparable to patients with standard risk cytogenetics. However, it is important to realize that in the EMN study the cutoff for del(17p) was only 20%.[8] Therefore, it will be crucial to report the outcome of patients using a consistent cutoff of 55% for high-risk del(17p). In addition, it will be interesting to confirm the most optimal cutoff in separate studies, as this might be affected by the type of therapy.

Second, although the authors showed a clear negative impact of del(17p) only, there is a pronounced difference in the clinical outcome between mono- or biallelic disease. This can be biologically explained by the observation that a single hit, either complete loss of one of the wild-type alleles or a mutation with expression of mutant p53, was found to functionally impair p53, resulting in resistance to melphalan. A second hit abolished the remaining p53 activity and increased resistance to genotoxic drugs even further.[9] As second hits are known to develop with longer disease duration, the incidence of double-hit disease will increase over time. This can only be detected by DNA sequencing allowing more precise, rolling prediction of prognosis. DNA sequencing will also provide information on the prognostic impact of isolated *TP53* mutations, which was not reported in the current study of Corre and colleagues, as well as the impact of clone size of del(17p) specifically in patients with wild-type *TP53* by sequencing. Such an impact could not be shown in the previous study by the authors, likely because of the small number of patients included in that study.[6] This highlights the need for assessment of *TP53* status in future studies by DNA sequencing.

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MYELOID NEOPLASIA

Comment on Shanmuganathan et al, page 1196

Should I rock the boat? When to stop TKIs in CML

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In this issue of *Blood*, Shanmuganathan et al used early BCR-ABL1 kinetics to predict the likelihood of treatment-free remission (TFR) in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors (TKIs).[1]

The overall survival of chronic myeloid leukemia (CML) patients was remarkably improved after the introduction of TKI therapy. TKI therapy was initially thought to mean that patients must continue on treatment indefinitely. Stopping treatment safely would reduce cost, improve quality of life, and allow younger patients to conceive safely. Thus, sustained TFR, defined as maintaining a major molecular response (MMR) with *BCR-ABL1* ≤0.1% for at least 12 months off TKI therapy, became an important goal.[2] Several studies have shown that TKIs can be discontinued