Dynamics of mutations in patients with essential thrombocythemia treated with imetelstat

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ABSTRACT

In a phase II study, the telomerase inhibitor imetelstat induced rapid hematologic responses in all patients with essential thrombocythemia who were refractory to or intolerant of prior therapies. Significant molecular responses were achieved within 3-6 months in 81% of patients with phenotypic driver mutations in *JAK2, CALR* and *MPL*. Here, we investigated the dynamics of additional somatic mutations in response to imetelstat. At study entry, 50% of patients carried one to five additional mutations in the genes *ASXL1, CBL, DNMT3A, EZH2, IDH1, SF3B1, TET2, TP53* and *U2AF1*. Three patients with baseline mutations also had late-emerging mutations in *TP53, IDH1* and *TET2*. Most clones with additional mutations were responsive to imetelstat and decreased with the driver mutation, including the poor prognostic *ASXL1, EZH2* and *U2AF1* mutations, while *SF3B1* and *TP53* mutations were associated with poorer molecular response. Overall, phenotypic driver mutation response was significantly deeper in patients without additional mutations (*P*=0.04) and correlated with longer duration of response. In conclusion, this detailed molecular analysis of heavily pretreated and partly resistant patients with essential thrombocythemia reveals a high individual patient complexity. Moreover, imetelstat demonstrates potential to inhibit efficiently co-incident mutations occurring in neoplastic clones in patients with essential thrombocythemia. (ClinicalTrials.gov number, NCT01243073).

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Introduction

Imetelstat is a 13-mer lipid-conjugated oligonucleotide that targets the RNA template of hTERC and can, therefore, inhibit activity of telomerase and cell proliferation in cancer cells.[1] hTERT, the catalytic subunit of telomerase that is generally not found in somatic cells, is expressed in megakaryocytes of patients with essential thrombocythemia (ET), a myeloproliferative neoplasm (MPN).[2] Previously, we demonstrated a dose-dependent inhibition of megakaryocytic colony-forming units from patients with ET but not from healthy individuals *in vitro*.[3] In a phase II study of ET patients who were refractory to or intolerant of prior treatment, imetelstat induced rapid and durable hematologic responses in all patients, and molecular responses were achieved in the majority of patients within 3-6 months.[4]

In ET, *JAK2* V617F*, CALR* and *MPL* mutations are phenotypic driver mutations present in around 90% of patients; the remaining cases are termed "triple negative". Non-canonical gain-of-function mutations have been identified in the *JAK2* and *MPL* genes in a minority of triple-negative patients.[5,6]

Additional recurrent somatic mutations occur at lower frequencies in a number

of genes in MPN, and clonality has been demonstrated.[7-9] In ET, mutations in *ASXL1, TET2* and *DNMT3A* genes are most frequent and are all involved in epigenetic regulation. Less frequent recurrent mutations are detected in *EZH2, TP53, IDH1, IDH2* and *CBL*, as well as in genes of the splicing machinery, such as *SF3B1, SRSF2, U2AF1* and *ZRSF2*.

So-called "adverse mutations" in *SF3B1, SRSF2, U2AF1, TP53, IDH2* and *EZH2* have been found to have negative effects on overall and myelofibrosis-free survival in ET, and *TP53* mutations predict leukemic transformation.[8-10,14] Furthermore, *ASXL1* mutations have been identified as a genetic risk factor for transformation to myelofibrosis in ET patients, as they are most frequently found in post-ET myelofibrosis.[11] Subsequently, genomic data were integrated in prognostic models to predict patients' outcomes.[13,14]

An influence of additional non-driver mutations on treatment response in MPN has been reported for interferon-α, ruxolitinib and imetelstat. In patients with *CALR*-mutated ET treated with interferon-α, the presence of additional mutations in *ASXL1, TET2, IDH2* and *TP53* correlated with a poorer molecular response.[15] *TET2*-mutated clones were resistant to interferon-α therapy in *JAK2*-mutated patients with polycythemia vera.[16] Resistance to ruxolitinib was reported in patients with myelofibrosis carrying three or more mutations.[17] Furthermore, in the first clinical trial with imetelstat in myelofibrosis patients, treatment response was reported to be negatively influenced by *ASXL1* mutations and favorably impacted by *SF3B1* and *U2AF1* mutations.[18]

In the present study, we assessed a panel of genes frequently mutated in MPN by next-generation sequencing at study entry and during treatment with imetelstat, and investigated the dynamics of additional mutations in ET patients and their association with hematologic and molecular response.

Methods

Patients and response criteria

A total of 18 patients with ET diagnosed according to the World Health Organization (WHO) 2008 criteria were treated with imetelstat in a phase II study.[4] The study was approved by the institutional review board at each participating site. All patients provided written informed consent. Diagnoses were re-evaluated according to the WHO 2016 classification.[19] Sequential blood samples were taken at baseline and at up to eight time-points during treatment with imetelstat through cycle 26 (28-day cycles), with approximately 12 weeks between samples. Mutational analysis was performed on all collected samples.

Clinical and hematologic responses were assessed according to the European LeukemiaNet criteria.[20] Molecular responses of phenotypic driver mutations were defined as follows: a major molecular response (MMR) was achieved when the mutant allele burden reduction was >50% from baseline value, and a partial molecular response (PMR) was present when a 25% to 49% reduction of the mutant allele burden was observed.

Genetic analysis

DNA was extracted from granulocytes or leukocytes from peripheral blood samples. The molecular response of *JAK2* V617F, *CALR* and *MPL* mutations was assessed using allele-specific real-time polymerase chain reaction, sequencing and fragment length analysis, respectively, as previously described.[4]

Targeted next-generation sequencing of all relevant exons and adjacent intronic sequences of 15 recurrently mutated genes (*ASXL1, CBL, DNMT3A, EZH2, IDH1, IDH2, JAK2, MPL, SOCS1, TET2, TP53, SF3B1, SRSF2, U2AF1* and *ZRSR2*) was performed using Ion Torrent™ semiconductor chip technology on the Ion Personal Genome Machine® PGM™ (Thermo Fisher Scientific Inc.). Genes were covered by two custom-designed amplicon libraries comprising 511 and 307 amplicons. In addition, a commercial panel for *TP53* was used for confirmation of *TP53* variants (Ion AmpliSeq™ Community Panel TP53, Thermo Fisher). For each primer pool, 10 ng of DNA were processed using the AmpliSeq™ chemistry for selective amplification of target sequences and library preparation according to the manufacturer's instructions. Libraries were diluted and combined according to the Ion PGM chip size to obtain a minimum coverage of 500x for all amplicons. Templates were prepared on the Ion Chef™ and sequencing was performed on the Ion PGM instrument. Variants were called using IonTorrent VariantCaller v4.3 software based on the human reference genome (GRCh37/hg19). Analysis of *TP53* was performed according to the manufacturer's instruction. Annotation was done using the Mutalyzer, dbSNP, COSMIC, ClinVar, UniProt and IARC TP53 databases and the functional *in silico* prediction algorithms PolyPhen-2 and SIFT.[21]

Fragment analysis was used to screen for insertions and deletions in ASXL1 exon 12 (NG_027868.1), which are frequently missed by next-generation sequencing. Primers were designed according to Pratcorona *et al.*[22] with small adaptations, and analysis was performed on a 3130 Genetic Analyzer using peak scanner software (Thermo Fisher). Sequences were confirmed by Sanger sequencing.

The limits of detection for real-time polymerase chain reaction analysis of *JAK2* and *MPL* mutations were 0.5%, whereas those for *CALR* and *ASXL1*, determined by fragment analysis, and all variants detected by next-generation sequencing were set at 2%.

Validation of genetic variants

All novel variants were confirmed by Sanger sequencing. For *ASXL1* and *TET2* analysis, published primers were used,[23,24] and primers for other genes were designed using Oligo7 and Primer3 software.[25,26] Low-level variants (<10%) were confirmed by a second round of next-generation sequencing analysis.

Statistics

Categorical patients' characteristics were summarized by frequencies and percentages and continuous characteristics by medians, means and an unpaired Student *t*-test. The efficiency of imetelstat treatment was analyzed by a paired Student *t*-test comparing percentages of mutant allele burdens before treatment and at best response. Smooth estimates of allele burdens over time were generated using running medians and smoothing splines. Standard errors and confidence intervals were computed by bootstrap.

Results

Characteristics of patients and phenotypic driver mutations

Of 18 patients with ET enrolled in the study, nine (50%) were refractory and 14 (78%) were intolerant of at least one prior therapy. Thirteen patients had received more than one prior therapy and the median time since diagnosis was 7.2 years (range, 0.3-24.9) (Table 1). The median age of patients at study entry was 59.5 years (range, 21-83) (*Online Supplementary Table S1*). Upon treatment with imetelstat, all patients had a hematologic response, with 16 patients achieving complete hematologic responses.[4]

Table 1. Characteristics of patients.

Pt.	Age at dg	Sex	Years since dg	Prior therapies, n.	HR	Duration of imetelstat therapy, months	Duration of response, months	Driver mutation	Reduction in allele burden at BR, %	Best MR	Additional mutations at study entry	Late-emerging mutations*
1	52	F	20.7	3	CR	18.5	18.3+	*JAK2* V617F	-96	MMR	*TP53* p.Arg249Lys	
2	43	M	4.6	2	CR	28.9	29.8+	*CALR* Type 1	-31	PMR	*TET2* p.Tyr1608Leufs*6	*TP53* p.Cys135Trp
3	60	M	3.3	3	CR	23.5	24+	*JAK2* V617F	-82	MMR		
4	67	F	19.9	3	CR	18.3	17.6	*CALR* Type 2	-38	PMR	*DNMT3A* p.Tyr735Cys *EZH2* p.Asp293Ala *SF3B1* p.Lys666Arg *TET2* p.Arg1465Ter *TP53* p.His179Leu	
5	55	F	0.3	1	CR	25.2	23.9+	*JAK2* V617F	-94	MMR		
6	69	M	7.7	2	CR	18.7	17.5+	*JAK2* V617F	-24	No		
7	83	F	1.8	2	CR	13.2	2.4	none	na	na	*SF3B1* p.Lys700Glu	
8	64	M	5.7	1	CR	14.5	16.5+	*CALR* Type 1	-48	PMR		
9	48	M	1.3	1	CR	10.8	9.7+	*JAK2* V617F	-100	MMR	*ASXL1* p.Gly646Trpfs*12 *U2AF1* p.Gln157Pro *CBL* c.1432-1G>A	
10	78	F	1.9	3	CR	15.9	14.5+	*JAK2* V617F	-90	MMR	*DNMT3A* p.M880V *TET2* p.Met1772Cysfs*48	
11	56	F	12.1	2	CR	12.1	10.9	none	na	na		
12	80	M	11.8	2	CR	33.2	31.3+	*CALR* del1092-1124	-55	MMR		
13	46	F	6.9	3	CR	36.7	29.5	MPL	-66	MMR		
14	77	M	1	2	CR	23.3	21.7+	*JAK2* V617F	-72	MMR	*DNMT3A* p.Ala644Thr *DNMT3A* p.Arg688His *DNMT3A* c.2597+1G>A	*IDH1* p.Arg132His
15	47	M	11.6	4	PR	7.8	3.8+	*CALR* Type 1	-15	No		
16	21	F	13.4	2	CR	24	22.4+	*JAK2* V617F	-96	MMR		
17	61	F	10.9	3	CR	16.6	10.7	*JAK2* V617F	-82	MMR	*ASXL1* p.Tyr591Ter	*TET2* p.Ser137Gly
18	59	F	24.9	3	PR	6.9	4.2	*MPL*	0	No	*DNMT3A* p.Gly722Asp	

Dg: diagnosis; HR: hematologic response; BR: best molecular response; MR: molecular response; MMR: major molecular response (>50% mutant allele burden reduction from baseline); PMR: partial molecular response (25% to 49% mutant allele burden reduction from baseline); No, no response; +, continued on treatment; * after best molecular response of the driver mutation.

Figure 1. Frequency and distribution of mutations by patient at study entry.

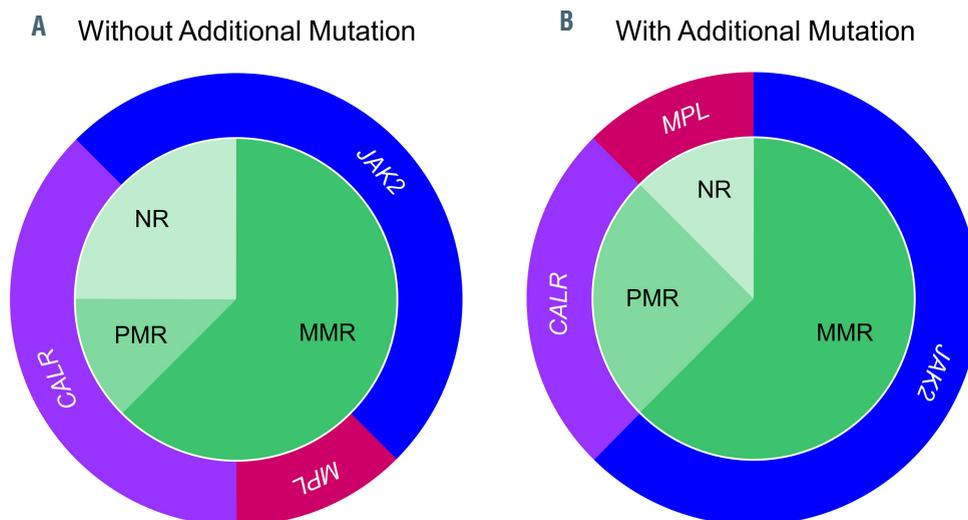3 = Patient with 3 *DNMT3A* mutations

Figure 2. Distribution of molecular response and driver mutations among patients with or without additional mutations. (A) Patients without additional mutations (n=8). (B) Patients with additional mutations (n=8). MMR: major molecular remission; PMR: partial molecular remission; NR: no remission; *JAK2: JAK2* V617F; *CALR: CALR* mutation; *MPL: MPL* mutation.

With regard to phenotypic driver mutations, nine (50%) patients had a *JAK2* V617F mutation, five (28%) patients had *CALR* mutations (type 1, n=3; type 2, n=1; a novel 33 bp deletion at position 1092, n=1) and two patients had *MPL* mutations (1 with W515L, 1 with W515K). Two patients (11%) were triple negative. Overall, there was a significant reduction of driver mutant allele burden, with a median decrease of 69% at best response during treatment ($P<0.001$). In detail, of 16 patients with a phenotypic driver mutation, ten (63%) reached a MMR (8 *JAK2*-mutated, 1 *CALR*-mutated, 1 *MPL*-mutated), three (19%) reached a PMR (3 *CALR*-mutated), and three (19%) patients did not reach a PMR (1 *JAK2*-mutated, 1 *CALR*-mutated, 1 *MPL*-mutated).

Additional mutations at study entry

At study entry, a total of 18 different additional somatic mutations (11 missense, 3 frameshift, 2 nonsense, 2 splice site) were identified in nine patients (50%), affecting the *DNMT3A* (n=6), *TET2* (n=3), *ASXL1* (n=2), *TP53* (n=2), *SF3B1* (n=2), *CBL* (n=1), *EZH2* (n=1) and *U2AF1* (n=1) genes (Figure 1). Details on mutations and variant allele frequencies at diagnosis and best response are given in *Online Supplementary Table S2*. Among the patients with any driver mutation, 40-56% carried up to five additional mutations (5/9 patients with *JAK2* V617F, 2/5 with *CALR* mutation, 1/2 with *MPL* mutation), and of two triple-negative patients one had an additional mutation.

Impact of additional mutations on molecular response and dynamics of mutant clones

Patients with or without additional mutations had similar molecular responses to imetelstat therapy with five (63%) patients reaching MMR in each group; one and two patients without and with additional mutations reached PMR, respectively (Figure 2). All patients with additional mutations who reached MMR had a *JAK2* V617F driver mutation. Regarding the reduction in mutant allele burden, phenotypic driver mutation response was significantly deeper in patients without additional mutations ($P=0.04$) (Figure 3).

Different dynamics of mutations in response to imetelstat were observed in individual patients (Figure 4). In five patients (#1, #2, #9, #10, #17), additional mutant allele burdens decreased with the driver mutation. In contrast, in two patients with three and five additional mutations (#4, #14), differential responses to imetelstat treatment were observed; i.e., the allele burden of some additional mutations decreased in parallel with the driver mutation while others persisted or increased (i.e., mutations in *TP53*, *SF3B1*, and *DNMT3A*) despite driver mutation response, suggesting the presence of at least two clones or subclones. Lack of response was observed in two patients: in patient #18, a *MPL* mutation did not respond while the *DNMT3A*-mutated clone expanded, and in patient #7 without a driver mutation (triple negative), a known hotspot mutation in *SF3B1* persisted at a high level. In total, non-responsive mutations were detected in *TP53, DNMT3A* and *SF3B1* genes.

Three patients (#2, #14, #17) acquired additional mutations in *TP53, IDH1* and *TET2* with low allele burden (mean 5%) after best molecular response of the driver mutation, at 10, 9 and 13 months of imetelstat treatment, respectively (Table 1). All three patients already had one to three preexisting additional mutations in other genes at study entry.

Clinical outcome in relation to additional mutations

Hematologic and molecular responses were equally reached independently of the presence of additional mutations (Table 2). Loss of response was, however, more frequent in patients with additional mutations. Namely, four patients with additional mutations lost their molecular response, including three patients with *DNMT3A* mutations and one patient with a *TET2* mutation, but none of the patients without additional mutations lost their molecular response ($P=0.025$). Patients with a higher burden of additional mutations at study entry had a shorter duration of clinical response compared to patients with no or a lower burden of additional mutations (10.2 *vs.* 22.1 months, median; cut-off at 10% mutant allele burden, $P=0.053$).

Table 2. Clinical outcome data.

	All (n=18)	No additional mutations (n=9)	With additional mutations (n=9)	P
Hematologic response	18 (100%)	9 (100%)	9 (100%)	n.s.
Hematologic complete response	16 (89%)	8 (89%)	8 (89%)	n.s.
Major molecular response[a]	10 (63%)	5 (63%)	5 (63%)	n.s.
Partial molecular response[a]	3 (19%)	1 (13%)	2 (25%)	n.s.
Median duration of treatment, months, (range)	18.4 (6.9-36.7)	23.5 (7.8-36.7)	16.6 (6.9-28.9)	n.s.
Median duration of response, months (range)	18.3 (2.4-31.3)	22.4 (3.8-31.3)	14.5 (2.4-29.8)	n.s.
Thromboembolic event	3 (17%)	1 (11%)	2 (22%)[c]	n.s.
Transformation to myelofibrosis	3 (17%)	1 (11%)	2 (22%)	n.s.
Loss of hematologic response	6 (33%)	2 (22%)	4 (44%)	n.s.
Loss of molecular response[b]	4 (31%)	0	4 (57%)	0.025

[a]n=16 for this analysis: two patients with no driver mutation were excluded; [b]n=13 for this analysis: two patients with no driver mutation and three patients with no molecular response were excluded; [c]one patient with two thromboembolic events. n.s.=not statistically significant.

	Cycle 2 Mean±SE (90%, CI)[1]	Cycle 6	Cycle 10	Cycle 14
Driver w/o additional	-21.7±4.97 (-29.4, -13)	-45.4±9.67 (-60.1, -28.2)	-56.6±12.02 (-74.2, -34.7)	-61.7±14.1 (-82.2, -35.8)
Driver w/additional	-15.9±6.72 (-28.9, -6.7)	-33.6±9.81 (-52.3, -19.9)	-41.5±8.55 (-56.4, -28.3)	-39.8±10.58 (-46.4, -13.4)

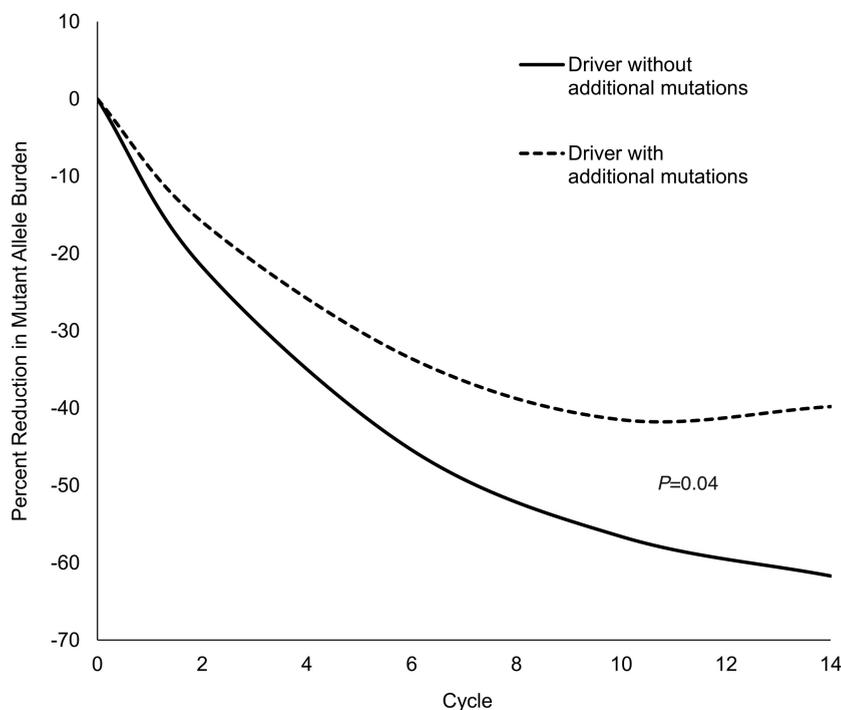1. Standard errors and confidence intervals computed by bootstrap

Figure 3. Mean phenotypic driver mutant allele burden over time. The solid line represents the driver mutant allele burden in patients without additional mutations (n=8). The dashed line represents the driver mutant allele burden in patients with additional mutations. Patients without additional mutations reached significantly lower mutant allele burdens (P=0.04).

Loss of response was associated with thromboembolic events (3/4 events unrelated to therapy), resistance to imetelstat treatment or progression to myelofibrosis. Transformation to myelofibrosis occurred in two patients with additional mutations during follow-up and 6 months after treatment termination (#4 and #17, respectively). The former, a *CALR*-mutated patient, carried five additional mutations in *DNMT3A, EZH2, SF3B1, TET2* and *TP53*, and the latter, a *JAK2*-mutated patient, had an *ASXL1* and a late-emerging *TET2* mutation. On retrospective evaluation, none of the patients fulfilled the criteria for prefibrotic myelofibrosis according to the newer WHO 2016 criteria.

Discussion

This is the first report on the mutational repertoire of refractory and/or intolerant ET patients after one to four prior therapies. Following treatment with imetelstat, a first-in-class, specific telomerase inhibitor, all patients achieved hematologic responses, and significant molecular responses were seen within 3-6 months, i.e., 63% and 19% of patients with driver mutations reached MMR or PMR, respectively.

At study entry, 50% of patients carried one to five somatic mutations in addition to the phenotypic driver mutation, including one triple-negative case. This frequen-
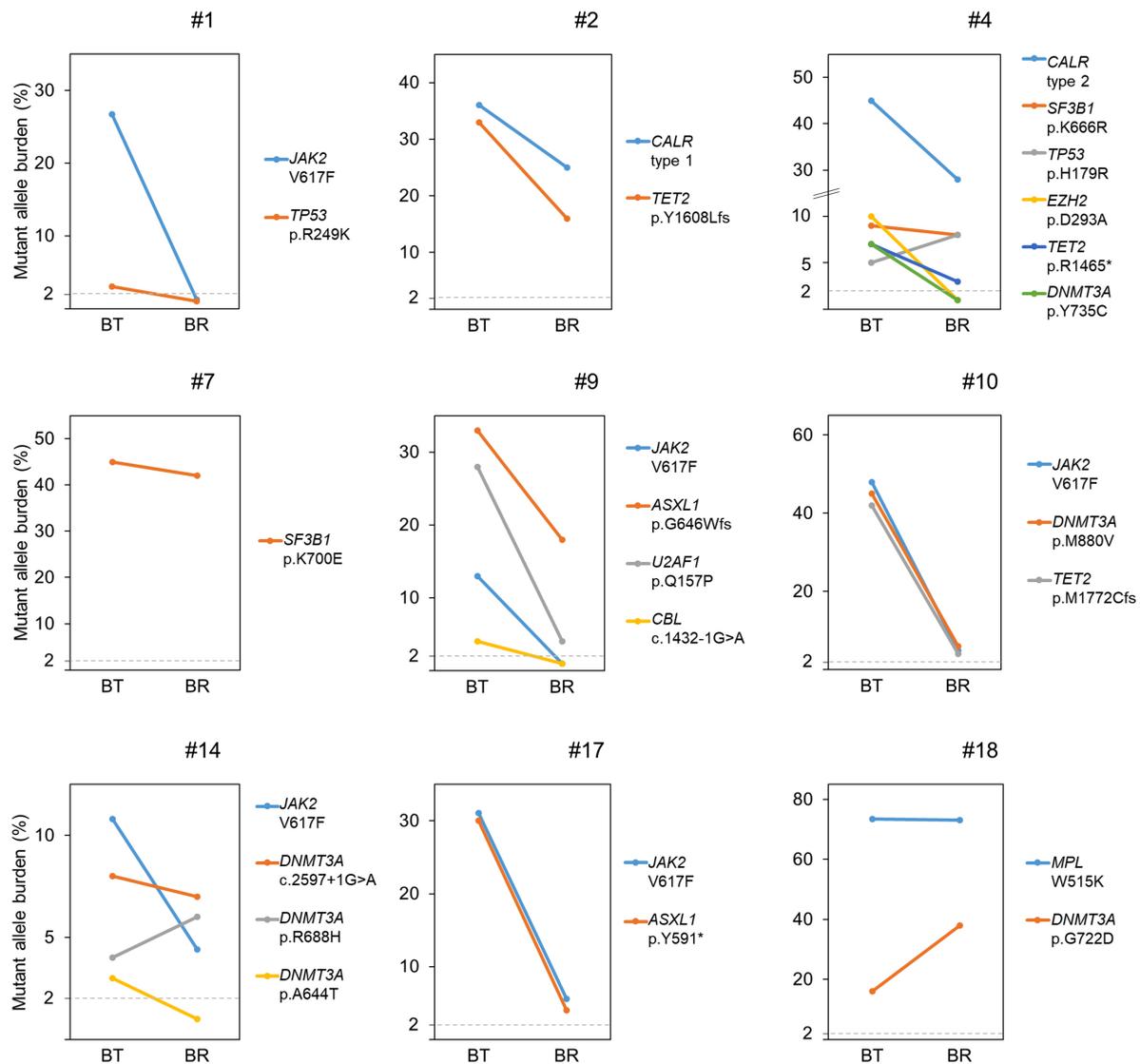
Figure 4. Best molecular response of patients with additional mutations. Mutant allele burdens of each mutation before imetelstat treatment and at best response. Driver mutations are depicted in blue. Limit of detection at 2%, dashed line. BT: before treatment; BR: at best response.

cy is higher than mutation rates reported from other cohorts of ET patients,[7,8,12] although still lower than the 86% and 98% overall rates of additional mutations detected in patients with myelofibrosis.[17,18] The high frequency of additional mutations in our ET cohort might reflect the concept of genetic instability in MPN and subsequent clonal evolution in a subset of these highly pretreated and partially resistant patients who had been diagnosed a median of 7.2 years previously. This concept is further supported by the finding that more than half of patients carried more than one additional mutation, as has also been reported by others.[27] In addition, only patients with additional mutations at study entry acquired even more somatic mutations late during treatment (n=3).

The most frequently mutated gene was *DNMT3A* followed by *TET2*. *DNMT3A* mutations co-occurred with other somatic mutations in three of four patients, in line with published data.[17] In ET, *DNMT3A* and *TET2* mutations are often early events involved in disease initiation, which may precede the *JAK2* V617F mutation and influence the phenotype.[9,28,29] Of the other genes mutated at

study entry, *TP53, SF3B1, U2AF1* and *EZH2* are part of a group of "adverse risk mutations" for ET, based on their significantly poor impact on overall, leukemia-free and myelofibrosis-free survival, and *ASXL1* mutations are known as molecular risk factors for transformation to myelofibrosis.[12,14]

Patients with or without additional mutations had similar molecular responses to imetelstat with 63% of MMR in both groups; however, the presence of additional mutations had a negative effect on the depth of response, as mutant allele burden reductions were significantly deeper in patients without additional mutations. Of interest, all patients with additional mutations who gained a deep response (MMR) had *JAK2* V617F driver mutations while patients with *CALR* or *MPL* driver mutations had poorer responses. In contrast, response depth in patients without additional mutations was not assigned to a specific driver mutation type. Further evidence from larger cohorts of patients is needed to support this observation.

The majority of cells with additional mutations were suppressed by imetelstat, and additional mutations

tracked with the driver mutation. Of note, *ASXL1* mutations were also responsive to imetelstat treatment, although one *ASXL1*-mutated patient later lost response and transformed to myelofibrosis with an acquired *TET2* mutation. This is in contrast to a study on imetelstat in myelofibrosis patients that reported a lack of response among patients with *ASXL1* mutations.[18]

With regard to the additional mutations, we observed several patterns of response. The parallel decrease of one or more mutations with the driver mutation in five of nine patients suggests that coexistence of mutations in the same clone or subclone was frequent in our cohort of patients. Unfortunately, we were not able to track the clonal architecture or coexistence of mutations within a cell due to the lack of additional cell material.

Discrepant patterns of response were seen in patients with multiple mutations that were responsive or persistent, with *DNMT3A, SF3B1* and *TP53* mutations persisting or increasing over time, suggesting the presence of independent clones. It has been reported that *DNMT3A* mutations are often present in preleukemic clones and persist during therapy in myeloid malignancies, e.g., in acute myeloid leukemia.[30,31] In this study, the four patients with *DNMT3A* mutations were 78, 80, 84 and 87 years old at study entry, and had had ET for 1, 2, 25 and 20 years, respectively. Since they were significantly older than the patients without *DNMT3A* mutations (mean age at study entry 82 years *vs.* 64 years, $P<0.05$), antecedent age-related clonal hematopoiesis (ARCH/CHIP) may be a contributing factor.[32-34] Individuals with ARCH/CHIP have a high risk of developing a hematologic malignancy. Experiments in mouse models carrying loss-of-function mutations in *DNMT3A* or *TET2* suggest a competitive advantage and enhanced self-renewal capacity of the mutant stem cells leading to clonal expansion.[34]

Of the other non-responsive mutations in this study, mutations affecting the splicing factor *SF3B1* are uncommon events in ET, reported to occur in 5% or fewer.[12,14,35] They have been considered as "adverse mutations" based on their negative impact on myelofibrosis-free and overall survival.[12,14] *TP53* mutations in MPN were described to be present for several years at low allelic burden and, after loss of the wild-type *TP53* allele, clones expanded rapidly resulting in leukemic transformation.[8,36] Hence, the presence of *TP53* mutations may be a warning of leukemic transformation in MPN.[10]

The presence of additional mutations *per se*, specific mutations and the total number of additional mutations have been associated with inferior response to treatment with interferon-α and ruxolitinib.[15-18,37] In contrast, imetelstat treatment led to a high proportion of MMR in patients with or without additional mutations, although the latter patients had more reduction of mutant allele burden.

Furthermore, initial mutant allele burden may have an impact on response as high-level additional mutations at study entry correlated with shorter duration of response.

Overall, this detailed molecular analysis of heavily pretreated and resistant ET patients reveals high individual patient complexity, with half of the patients harboring up to five additional somatic mutations at study entry. These results raise the question of whether additional mutations were acquired prior to diagnosis or whether mutational events were induced during treatment with prior therapies. Additional studies are needed to address this question.

In conclusion, treatment with imetelstat led to rapid and sustained hematologic and molecular responses and additional mutant allele burdens were also reduced. However, additional mutations significantly reduced the depth of response and had an impact on duration of response. Of acquired mutations with known adverse prognosis and/or risk for transformation to myelofibrosis or acute myeloid leukemia, *ASXL1, EZH2* and *U2AF1* mutations were responsive to imetelstat, while *SF3B1* and one of two *TP53* mutations persisted. These data emphasize imetelstat's potential to inhibit neoplastic clones in patients with ET.

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