Molecular mechanisms mediating relapse following ivosidenib monotherapy in patients with *IDH1*-mutant relapsed or refractory acute myeloid leukemia

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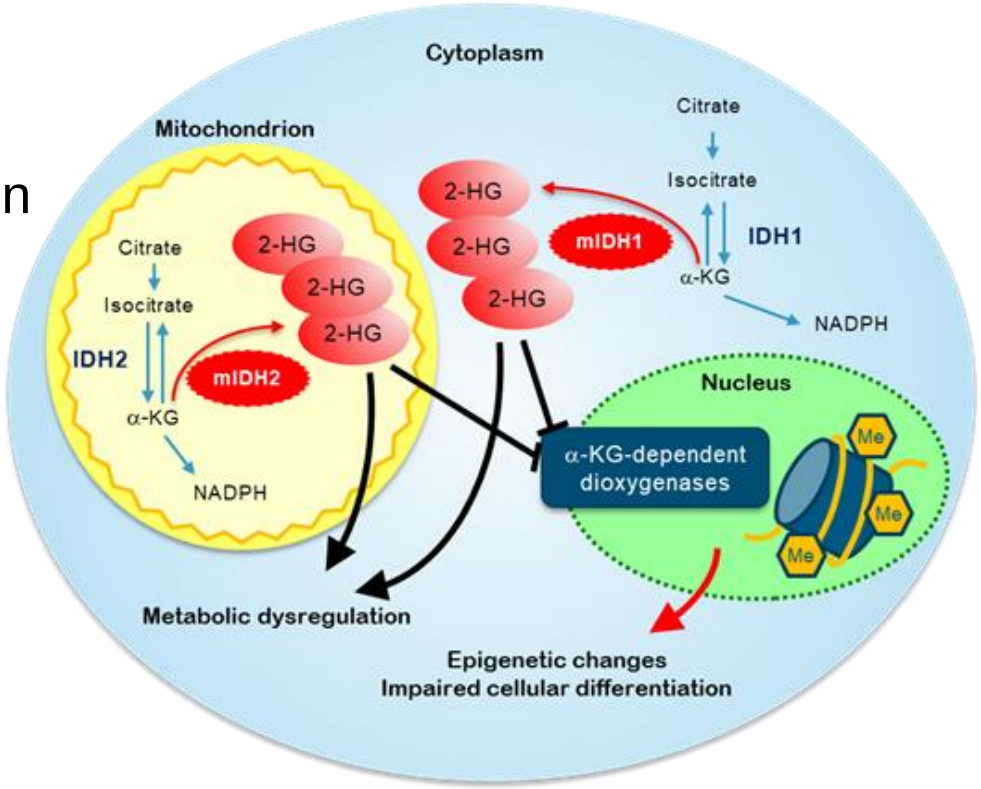
Background

- Somatic mutations in *IDH1* (*IDH2*) occur in 6–10% (9–13%) of patients with AML, resulting in production of the oncometabolite 2-HG

- Ivosidenib, a mutant IDH1 (mIDH1) inhibitor, is approved in the US for m*IDH1* R/R AML and newly diagnosed m*IDH1* AML in patients ≥75 years old or with comorbidities precluding intensive induction chemotherapy

- Durable remissions in m*IDH1* R/R AML were achieved with ivosidenib in a phase 1 study (NCT02074839)[1]
  - ORR 42%, CR rate 22%, and CR+CRh rate 30%
  - Median duration of CR+CRh response: 8.2 months



2-HG, D-2-hydroxyglutarate; α-KG, alpha-ketoglutarate; AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; IDH, isocitrate dehydrogenase; m, mutant; Me, methylation; ORR, overall response rate; R/R, relapsed or refractory

1. DiNardo CD et al. *N Engl J Med* 2018;378:2386-98.

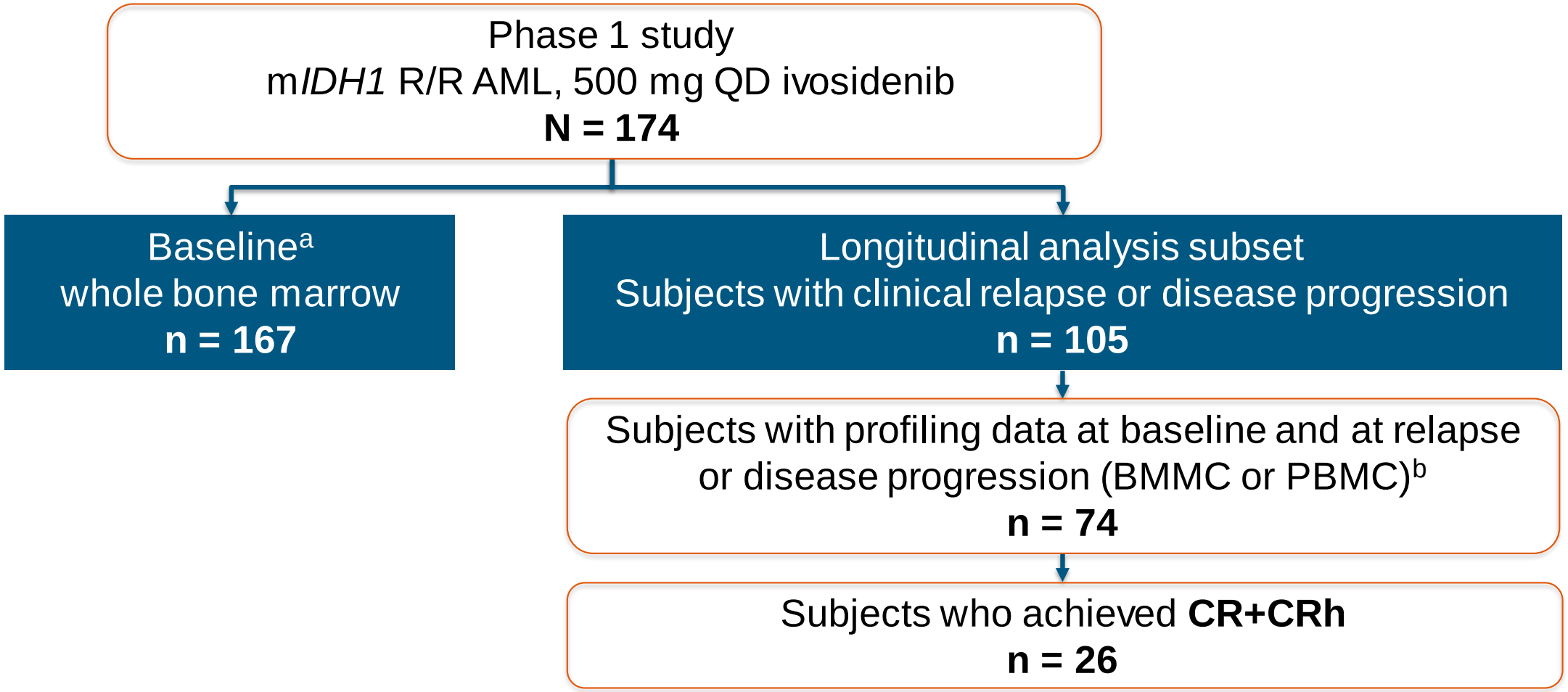
Objective

Characterize the molecular predictors of response and mechanisms of relapse to ivosidenib monotherapy in m*IDH1* R/R AML using comprehensive genomic profiling

- Hypothesis 1: Pre-therapy genetic profile predicts response
  - Mutations in single genes and pathways
  - Clonal vs subclonal status of m*IDH1*
- Hypothesis 2: Relapse is due to both *IDH*-dependent and *IDH*-independent mechanisms
  - Assess for *IDH2* and/or novel *IDH1* mutations at relapse[1,2]
  - Compare mutational profile before therapy and at relapse

1. Harding JJ et al. *Cancer Discov* 2018;8:1540-47. **2.** Intlekofer AM et al. *Nature* 2018;559:125-29.

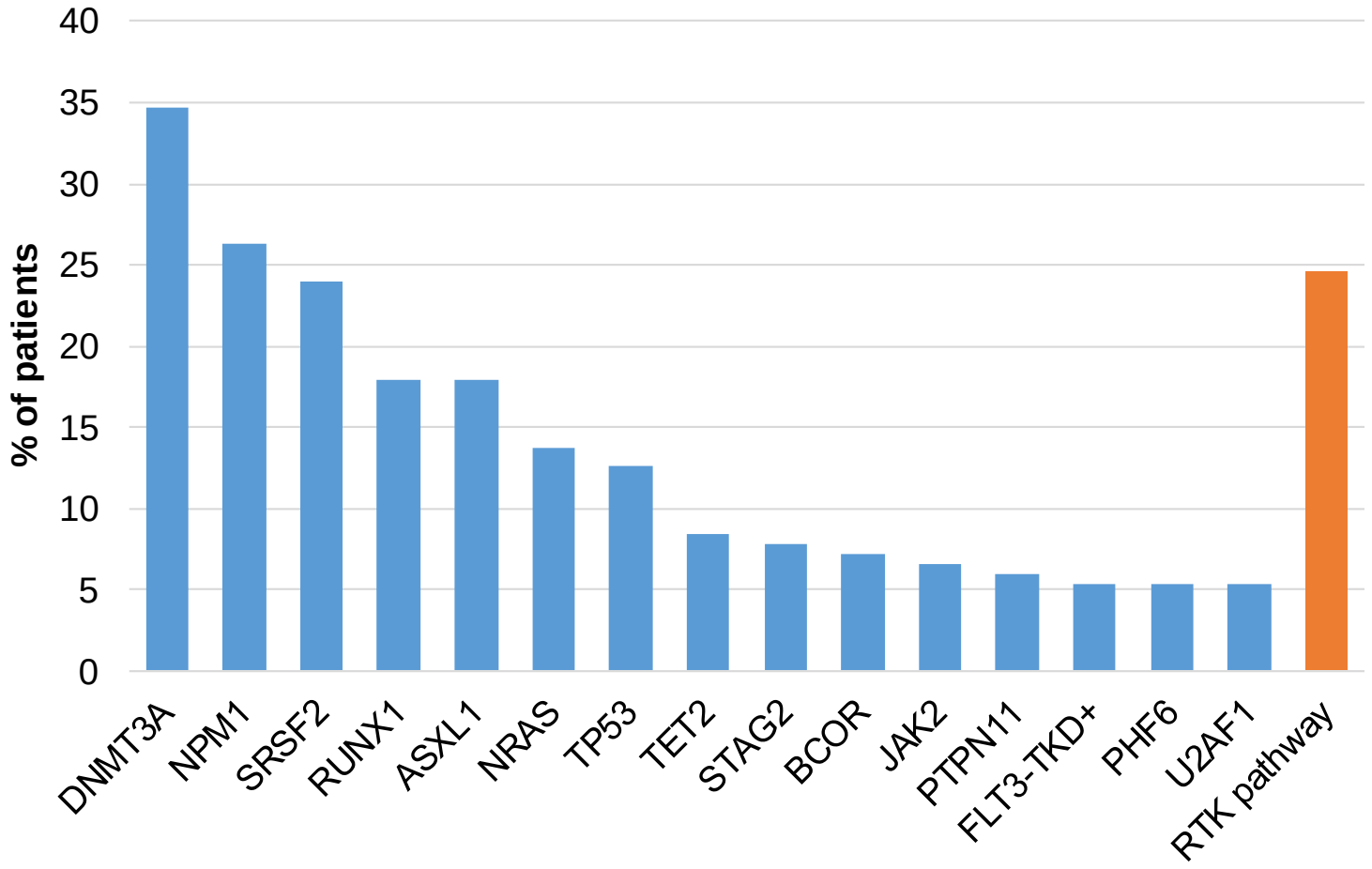
Molecular profiling by targeted next-generation sequencing (NGS)



[a]Genetic profiling was performed using the FoundationOne Heme (dose-escalation phase) or Brigham and Women's Rapid Heme (dose-expansion phase) panels
[b]Genetic profiling was performed with viably frozen BMMCs and/or PBMCs using the FoundationOne Heme (dose-escalation phase) or Personalis ACE Extended Cancer (dose-expansion phase) panels
Single nucleotide variants and short insertions/deletions are detected at allele frequencies of at least 2% (FoundationOne Heme, Personalis ACE) to 5% (Rapid Heme)

Clinical data cutoff: Nov 2, 2018
BMMC, bone marrow mononuclear cell; PBMC, peripheral blood mononuclear cell; QD, once daily

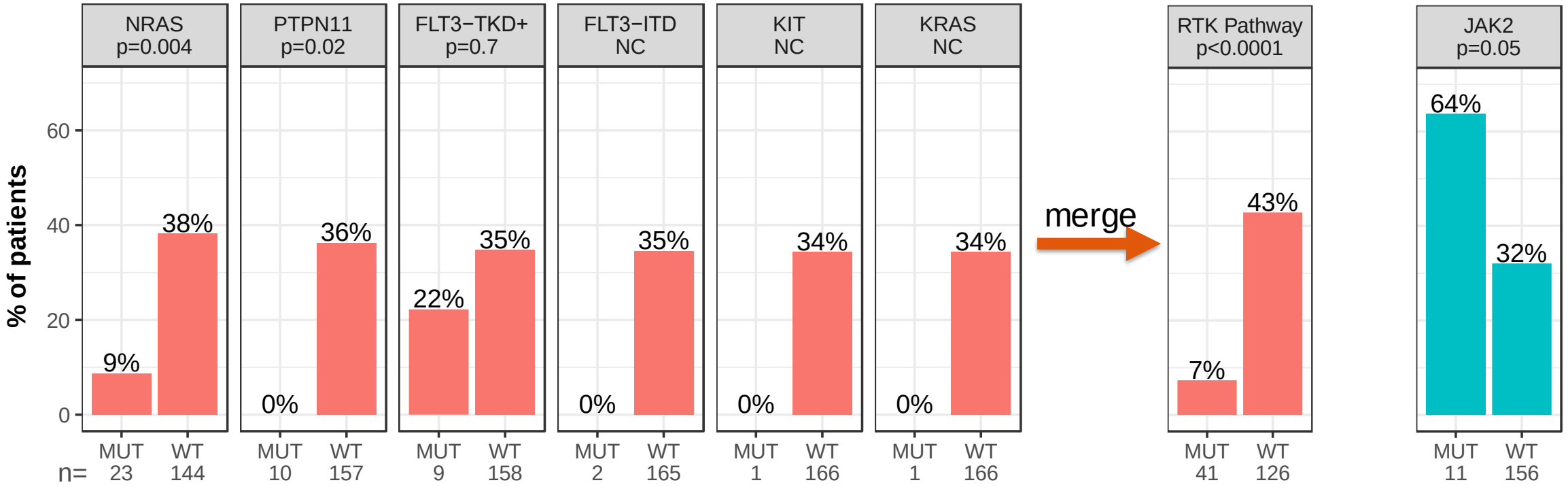
Most frequent co-mutations at baseline



- Included: gene mutations occurring at >5% frequency
- RTK pathway mutations (*NRAS*, *PTPN11*, *KRAS*, *KIT*, and *FLT3*) occurred in 25%
- *IDH2* mutations were infrequent at baseline (2%)

Data source: 167 patients with baseline NGS data from whole bone marrow
RTK, receptor tyrosine kinase

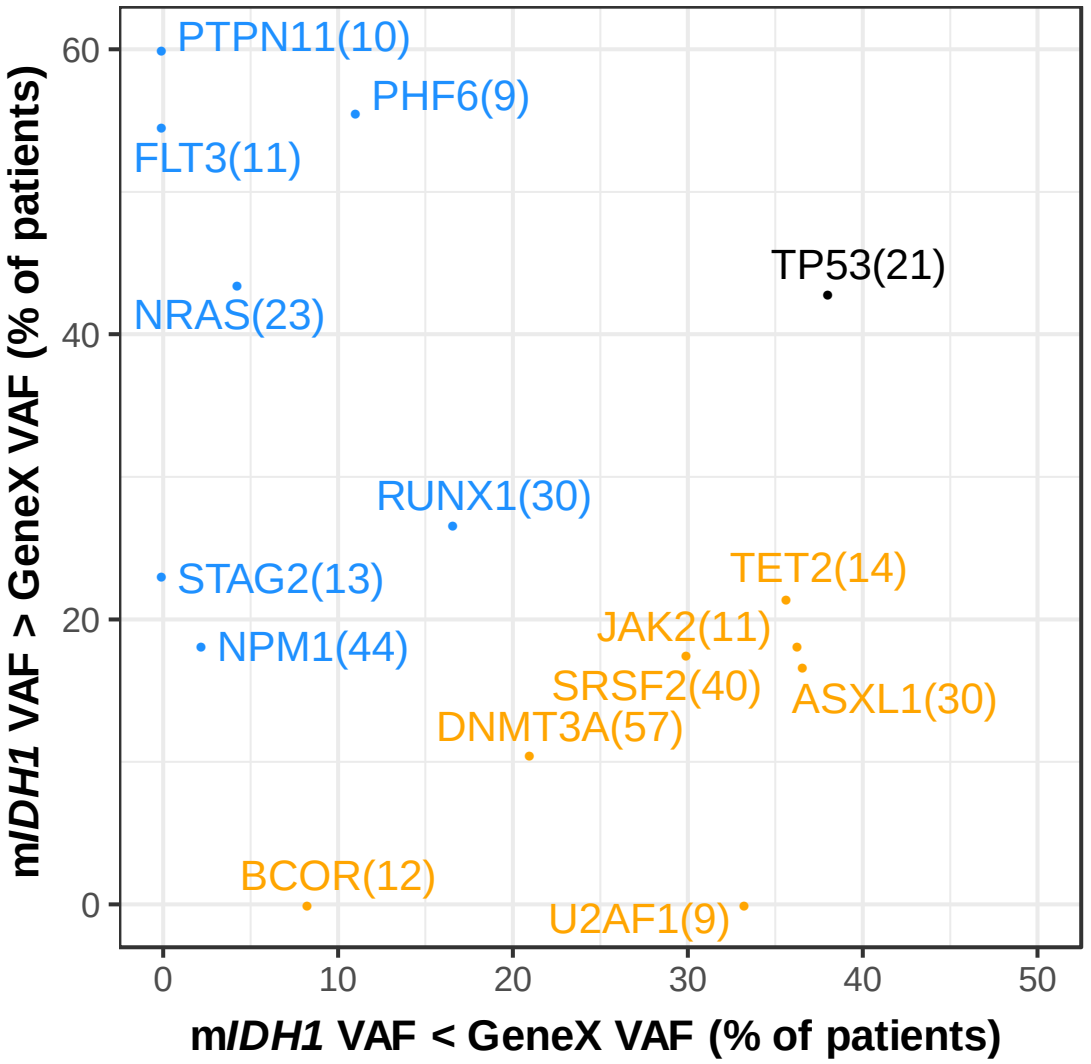
Significant association of baseline RTK pathway mutations with a lack of CR or CRh response



- RTK pathway mutations, and mutations in the individual genes *NRAS* and *PTPN11*, are significantly associated with a lack of CR or CRh response
- 64% of patients with *JAK2* mutations achieved CR or CRh

P-values: Fisher's exact test. NC denotes p-value not calculated owing to small number of patients with mutation
FLT3-TKD+ denotes FLT3-TKD or juxtamembrane domain point mutations
Data source: 167 patients with baseline NGS data from whole bone marrow; MUT = mutant; WT = wild type

Relationship of baseline m*IDH1* VAFs with co-mutation VAFs



- m*IDH1* VAFs are frequently higher than RTK pathway mutations (blue)
- m*IDH1* VAFs are often lower than co-mutations that are characteristic of MDS/MPN and clonal hematopoiesis (orange)

- m*IDH1* VAF is frequently greater than GeneX VAF
- m*IDH1* VAF is frequently lower than GeneX VAF
- No trend

Data source: 166 patients with baseline NGS data and m*IDH1* detection from whole bone marrow
MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; VAF, variant allele frequency

Clinical response is not predicted by the position of m*IDH1* within the clonal hierarchy at baseline

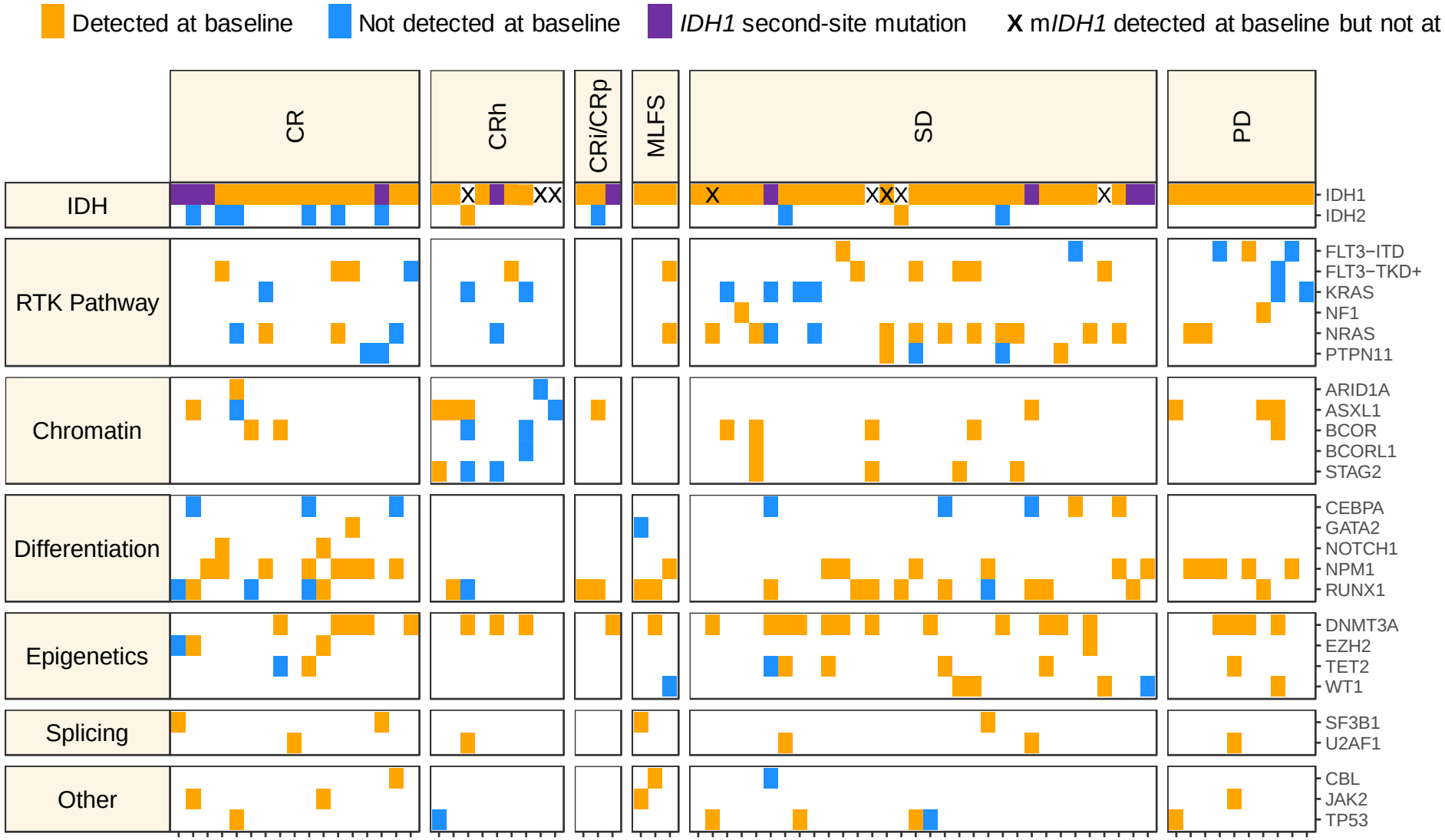
m*IDH1* status	n (%)	CR/CRh best response
Clonal	119 (72)	41/119 (34)
Subclonal	47 (28)	16/47 (34)
Total	**166**	

m*IDH1* was defined as subclonal if any co-mutation VAF was greater than m*IDH1* VAF +5%; otherwise, it was defined as clonal

Patients with clonal or subclonal m*IDH1* had the same frequency of CR/CRh response

Data source: 166 patients with baseline NGS data and m*IDH1* detection from whole bone marrow

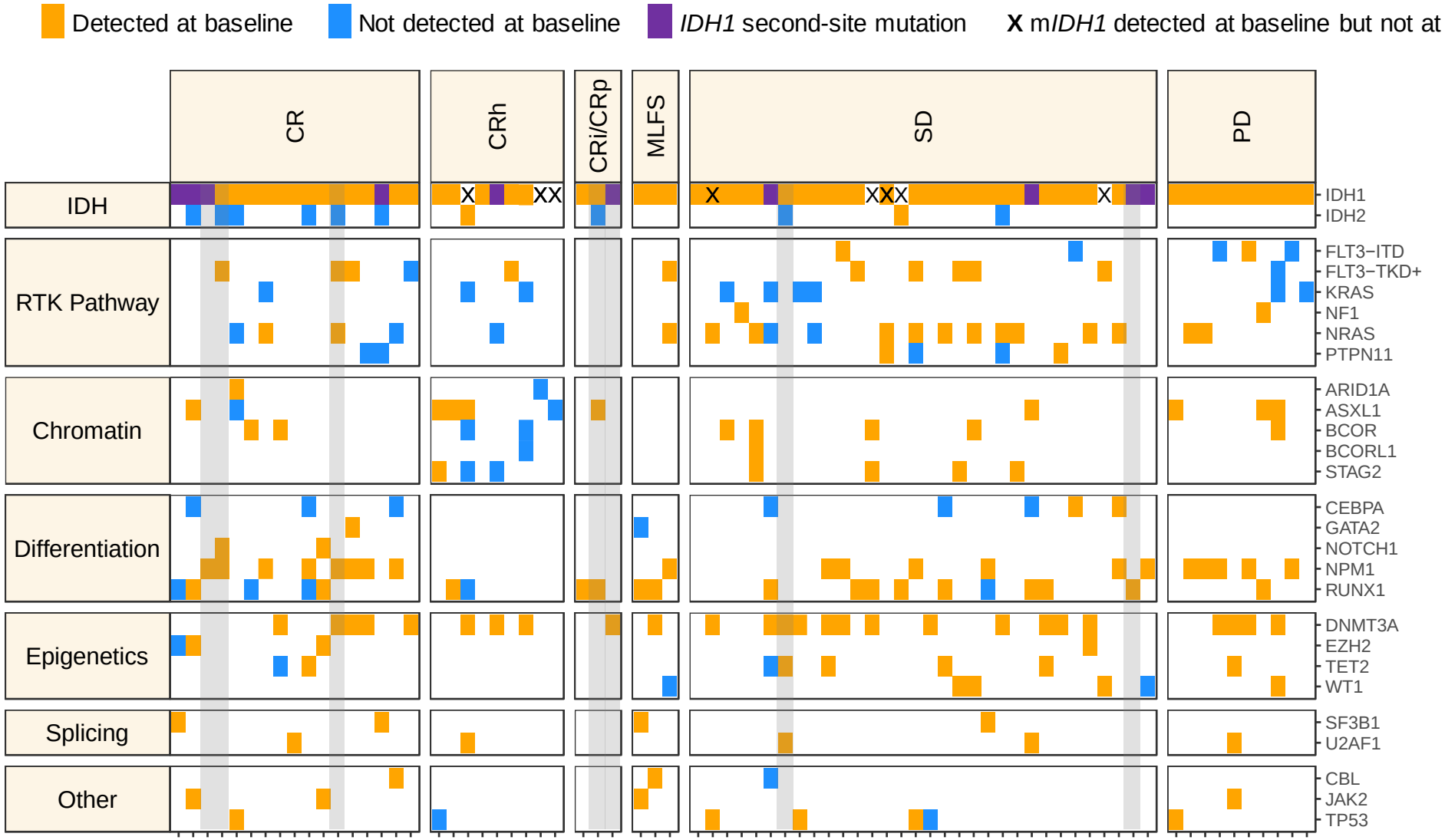
Multiple mechanisms contribute to relapse or progression



Heatmap showing variants detected at relapse or progression (n = 74)

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)
CRi/CRp, CR with incomplete hematologic or platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; RL, relapse; SD, stable disease

Multiple mechanisms contribute to relapse or progression



Heatmap showing variants detected at relapse or progression (n = 74)

IDH1/2 only

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)
CRi/CRp, CR with incomplete hematologic or platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; RL, relapse; SD, stable disease

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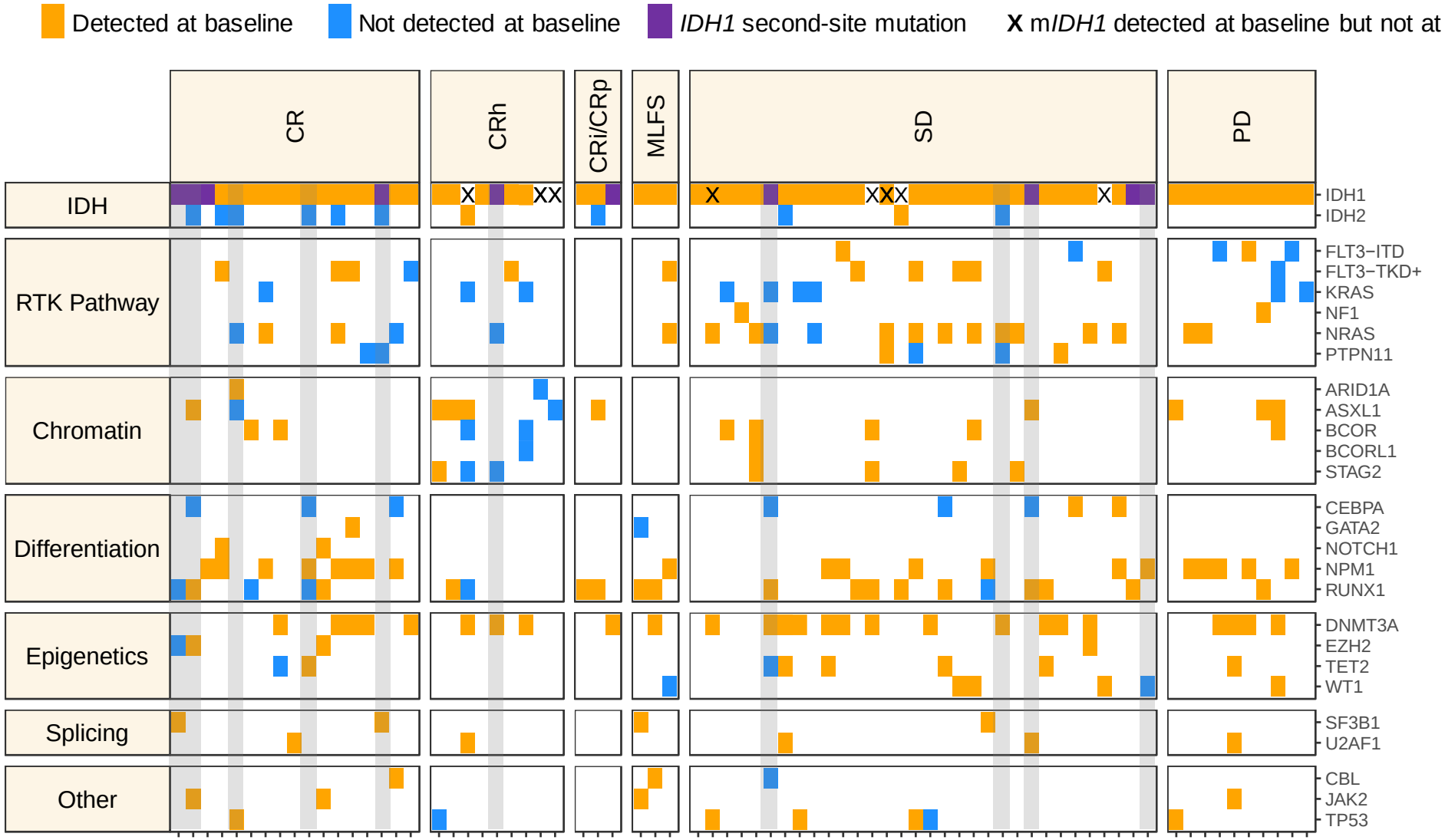


Heatmap showing variants detected at relapse or progression (n = 74)

IDH with other mechanisms

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)
CRi/CRp, CR with incomplete hematologic or platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; RL, relapse; SD, stable disease

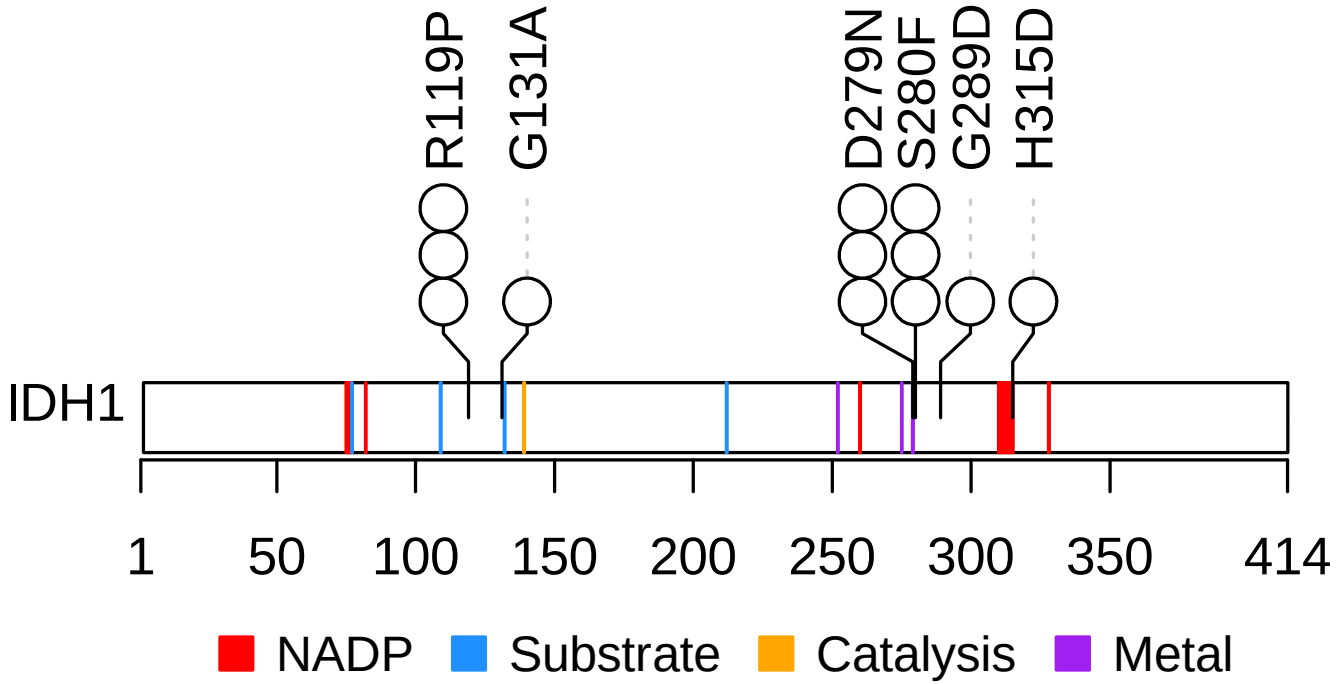
Summary of mutations observed at relapse

Pathway	Patients with mutations emerging at relapse or progression by pathway	
	All n = 74	Best response of CR or CRh n = 26
IDH-related	17 (23%)	9 (35%)
IDH1 second-site	10 (14%)	5 (19%)
IDH2-R140Q	9 (12%)	6 (23%)
Non–*IDH*-related		
RTK pathway	20 (27%)	9 (35%)
Differentiation	13 (18%)	8 (31%)
Chromatin	9 (12%)	8 (31%)
Epigenetics	6 (8%)	2 (8%)

Data source: 74 patients with NGS data at baseline and at relapse or disease progression (BMMC/PBMC, all evaluable response groups)

Novel *IDH1* second-site mutations observed on therapy

- *IDH1* second-site mutations were detected during ivosidenib treatment in 10 patients
- All of these second-site mutations were detected at relapse or disease progression, with concurrent increase in 2-HG



- Biochemical testing of S280F and R119P confirmed loss of ivosidenib potency

IDH1 mutant	Ivosidenib IC_{50}, μM
IDH1_R132C	0.019
IDH1_R132L	0.013
IDH1_R132C_**S280F**	>100
IDH1_R132C_**R119P**	0.15
IDH1_R132L_**R119P**	0.51

Other variants are not yet tested

The number of circles indicates the number of patients with detection of the mutation. Two of the 10 patients had detection of two *IDH1* second-site mutations IDH1_S280F was previously reported in one patient (Intlekofer AM et al. *Nature* 2018;559:125-29). IC_{50}, 50% inhibitory concentration

Conclusions

- RTK pathway mutations (including *NRAS* and *PTPN11*) were associated with a lower likelihood of clinical response to ivosidenib monotherapy in R/R AML
- Acquired resistance is mediated via diverse mechanisms
  - Mutations are acquired in multiple pathways, most frequently in RTK and 2-HG–restoring pathways (*IDH2* and second-site *IDH1* mutations)
  - These mechanisms are not mutually exclusive within an individual patient
  - 2-HG restoration at relapse underscores the key role of 2-HG production in m*IDH* AML
- These results inform the design of combination or sequential treatment strategies with ivosidenib in m*IDH1* AML, including, for example, enasidenib treatment at relapse, RTK pathway targeted agents, or standard of care
- Ongoing ivosidenib combination trials:
  - Ivosidenib + azacitidine: phase 1 (**Poster 2706,** NCT02677922), and phase 3 (AGILE, NCT03173248)
  - Ivosidenib + intensive chemotherapy: phase 3 (HOVON 150 AML/AMLSG 29-18, NCT03839771)

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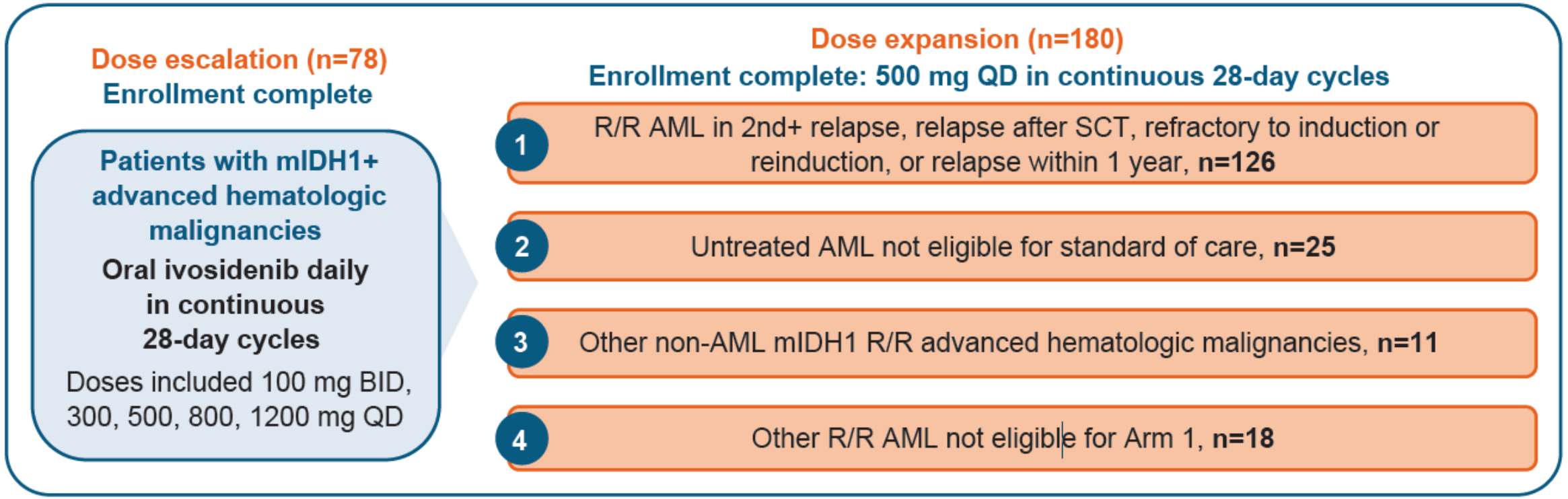
Clinical study design



BID, twice daily; SCT, stem cell transplant