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IKZF1 deletions in pediatric acute lymphoblastic leukemia: still a poor prognostic marker?

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Improved personalized adjustment of primary therapy to the perceived risk of relapse by using new prognostic markers for treatment stratification may be beneficial to patients with acute lymphoblastic leukemia (ALL). Here, we review the advances that have shed light on the role of *IKZF1* aberration as prognostic factor in pediatric ALL and summarize emerging concepts in this field. Continued research on the interplay of disease biology with exposure and response to treatment will be key to further improve treatment strategies. (*Blood*. 2020;135(4):252-260)

Background

Pediatric acute lymphoblastic leukemia (ALL), the most common malignancy observed in children and adolescents, is characterized by broad clinical and biological heterogeneity that is largely sustained by a diverse background of disease-initiating and -maintaining recurrent structural and/or numerical genetic aberrations acquired by the leukemic clone.[1-5] Despite this heterogeneity, overall treatment results in pediatric ALL are one of the true success stories in clinical oncology with current cure rates exceeding 85%.[1,4] On modern clinical protocols, this is achieved by the application of risk-adapted therapy, reflecting the probability of treatment failure. For this purpose, prognostic factors are used to estimate an individual patient's risk of relapse and to adjust the required treatment intensity by patient stratification into different therapeutic risk groups, for example, standard, intermediate, high, and very high risk.[1,4,5] Unfortunately, despite all of these efforts, a significant proportion of patients with ALL still experiences relapse. Thus, further improved personalized adjustment of primary therapy to the perceived risk of ALL relapse by using new prognostic markers for treatment stratification is likely to be beneficial to patients and, therefore, of great interest to those involved in the diagnosis and treatment of pediatric ALL and beyond.

Technical advances in the "omics" field fueled multiple comprehensive exploratory studies, and a number of candidate prognostic markers for ALL risk stratification have been identified and published during the last 10 years.[1-5] Caregivers are thus faced with an ever-growing body of literature on new prognostic markers, unfortunately, mostly full of uncertainties about their clinical relevance. Therefore, it does not come as a surprise that the majority of newly described genetic or genomic markers are not regularly used to support decision-making procedures on current clinical protocols for ALL. General reasons for this lack of translation include (1) large heterogeneity across studies with differently sized, selected, and treated patient populations; (2) methodological differences in marker assessment and uncertainties regarding assay procedures; (3) differences in reported end points and conflicting outcomes; and (4) differences in the statistical analyses used, as well as other issues. One obvious difficulty in the practical implementation of new prognostic markers for ALL is the limited clinical significance conferred by many of the new high-risk markers, making it difficult to justify exposure to more intensive and toxic treatments for the potential benefit of a minority of patients among those identified by the marker.

The genetics of *IKZF1*

The *IKZF1* gene is located on chromosome band 7p12.2, consists of 8 exons, and codes for the transcription factor IKAROS with key regulatory functions in lymphopoiesis.[6,7] IKAROS harbors 6 zinc fingers. Four of these are located in the DNA-binding domain encoded by exons 4 to 6 and are essential to maintain IKAROS' tumor-suppressor function. The remaining 2 zinc fingers are encoded by exon 8 and mediate the dimerization of IKAROS either as a homodimer or with other transcription factors of its family (eg, AIOLOS and HELIOS).[6-8] *IKZF1* has remained in the spotlight of the leukemia field since 2008 when Mullighan et al first described that recurrent, mostly monoallelic, focal deletions affect the coding regions of *IKZF1*.[9,10] These deletions involve either the whole gene or only parts of *IKZF1* and are observed at an overall frequency of ~15% in pediatric and 40% in adult ALL cases.[2,11,12] Although some deletions (eg, those affecting the whole gene, intragenic deletions including exons 2 and/or 8, deletions of exon 1 and 5′ untranscribed regulatory regions) result in haploinsufficiency, other deletions, most commonly those affecting exons 4 to 7, lead to loss of the DNA-binding domain and generation of dominant-negative isoforms.[2,9-12] The latter compromise the tumor-suppressor function of IKAROS translated from the remaining wild-type allele. The frequency of somatic point mutations in *IKZF1* has been studied far less extensively. They are present to a much lower extent (Figure 1) and,

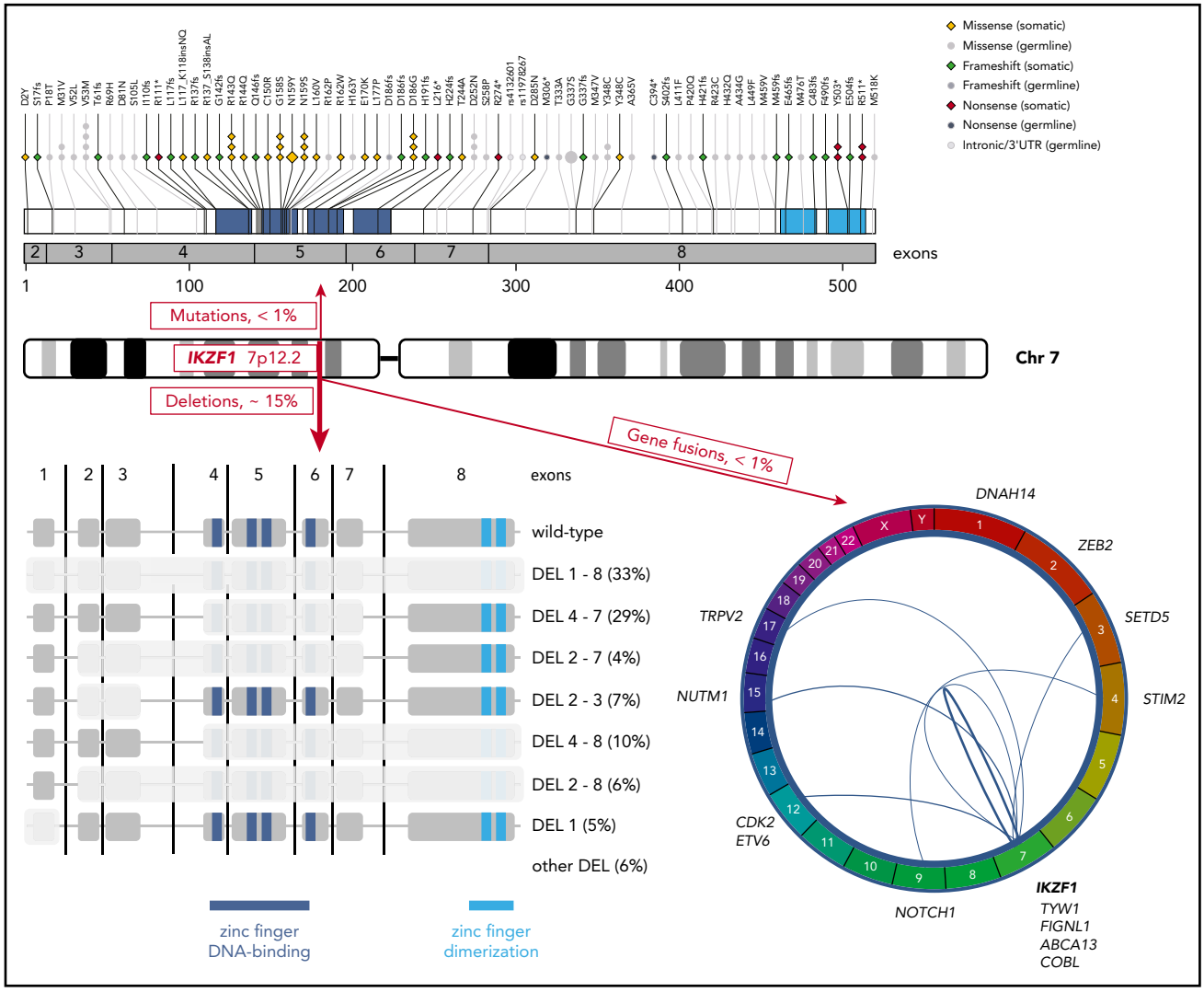

Figure 1. Genetic alterations of the *IKZF1* gene at chromosome band 7p12.2 in pediatric ALL. Red boxes indicate the observed approximate frequencies of the different types of genetic aberrations: deletions (bottom left), gene fusions (bottom right), and somatic as well as germline single-nucleotide variants (top). The 2 intronic germline risk variants identified in genome-wide association studies are indicated by their Reference SNP cluster ID. Frequencies (percentages) of the most common specific deletions (DEL) within the group of *IKZF1*-deleted ALL are indicated in black. Chr, chromosome; UTR, untranslated region.

as with deletions, their molecular consequence can be either haploinsufficiency (eg, truncating variants) or a dominant-negative effect (Figure 1).[10,13-19] Recently, a new B-cell precursor (BCP) ALL subgroup characterized by the *IKZF1* missense mutation p.Asn159Tyr (N159Y) affecting the DNA-binding domain was identified through a distinct gene-expression profile.[17,18] Of interest, the specific gene-expression profile also differed from those BCP ALL cases with other known *IKZF1* alterations. In addition, an increasing number of cases with fusion transcripts involving *IKZF1* have been described (Figure 1).[17-26] Besides the somatic alterations described earlier in this section, frequent intronic germline variants in *IKZF1* (rs11978267 and rs4132601) have been identified in genome-wide association studies and consistently described to modestly modulate the risk of pediatric BCP ALL (Figure 1).[27,28] Of major importance, Churchman et al recently characterized *IKZF1* as a leukemia predisposition gene by reporting mostly adverse germline *IKZF1* variation in familial pediatric ALL and 43 of 4963 (0.9%) unselected BCP ALL patients[29] (Figure 1).

Most of the published data on *IKZF1* deletions in pediatric ALL have been generated by multiplex ligation probe-dependent amplification (MLPA) analysis (Table 1).[13,30-44] Alternative techniques include polymerase chain reaction (PCR) or array techniques.[10,14,15,30,39,40,45,46] MLPA detects virtually all deletions targeting the coding sequence, and most large studies evaluating the prognostic effect of *IKZF1* deletion in patient cohorts relied on this technique (Table 1). However, like array techniques, it cannot reliably detect deletions present in <25% of cells. Thus, MLPA may fail to detect *IKZF1* deletions in samples showing a low leukemia burden or deletions that are limited to a leukemic subclone only. For recurrent intragenic deletions, this limitation can be overcome by quantitative PCR assays. This technique allows detection of intragenic *IKZF1* deletions with a higher sensitivity than classical techniques and, furthermore, allows minimal residual disease (MRD) monitoring.[47] However, it has to be emphasized that the prognostic impact of subclonal *IKZF1* deletions has not been specifically evaluated yet and may differ from that of full clone deletions. Another debated issue

Table 1. Summary of studies on the prognostic impact of *IKZF1* aberration in treatment trials of pediatric ALL

Trial	Ref.	Country	Trial period	No. of patients	Type of ALL	Frequency of aberrant *IKZF1* (method of detection)	EFS (DFS)	OS	Cumulative incidence of relapse	Comments
COG P9906, St. Jude Total XI, XII, XIII, XIV, XV, and Interfant-99	10	US	COG P9906: 2000-2003 St. Jude and Interfant: 1986-2007	COG P9906: 221 St. Jude and Interfant: 258	High-risk BCP BCP	28.6% (SNP array, Sanger sequencing) 18.6% (SNP array)	25% vs 73% (at 5 y), $P < .0001$ 40% vs 72% (at 10 y), $P < .001$		73% vs 25% (at 5 y), $P < .0001$ 48% vs 26% (at 10 y), $P = .004$	Groundbreaking first study demonstrating prognostic impact of *IKZF1* deletion; includes 5 patients with *IKZF1* point mutation in the COG cohort and 21 *BCR-ABL1*–rearranged cases in the St. Jude cohort
DCOG ALL9	13, 48	The Netherlands	1997-2000	131	BCP	13.0% (MLPA, Sanger sequencing)	39% vs 89% (at 8 y), $P < .001$	56.0% vs 91.0% (at 8 y), $P < .001$		Exemplifies the importance of *IKZF1* deletion as a prognostic factor, especially in non–high-risk patients; included 2 *BCR-ABL1*–rearranged cases; subsequent study in related population demonstrated the prognostic power of integrated use of aberrant *IKZF1* and MRD levels
TPOG-ALL-93, TPOG-97-VHR, TPOG-ALL-2002	14	Taiwan	1995-2009	242	BCP	10.7% (PCR)	15% vs 76% (at 10 y), $P < .0001$	38% vs 78% (at 10 y), $P = .0016$		First study indicating poor prognostic effect of *IKZF1* deletion in an Asian population
DCOG ALL8, ALL9, ALL10, UKALL 97, 97/99, 2003	30	The Netherlands, UK	1997-2006	DCOG: 34 UKALL: 85	Down syndrome ALL	DCOG: 35.3% (CGH array, MLPA, Sanger sequencing) UKALL: 27.1% (MLPA)	DCOG: 45% vs 95% (at 6 y), $P = .002$ UKALL: 21% vs 58% (at 6 y), $P = .002$	DCOG: 66% vs 95% (at 6 y), $P = .02$ UKALL: 15% vs 71% (at 6 y), $P = .002$	DCOG: 37% vs 5% (at 6 y), $P = .044$ UKALL: 37% vs 18% (at 6 y), $P = .06$	Strong prognostic effect of *IKZF1* deletion in Down syndrome ALL
Japan Childhood Leukemia Study ALL02	31	Japan	2002-2008	202	BCP	9.4% (MLPA)	63% vs 89% (at 5 y), $P = ..001$	72% vs 90% (at 5 y), $P = ..02$		Particularly strong prognostic effect of *IKZF1* deletion in the NCI high-risk group
JCCLSG ALL 2004	32	Japan	2004-2008	177	BCP	12.0% (MLPA)	68% vs 85% (at 4 y), $P = .04$			Prognostic effect of *IKZF1* deletion more pronounced in high-risk patients
ALL-REZ BFM 2002	33	Germany, Austria, Switzerland	2002-2009	204	BCP relapse	33.3% (MLPA)	30% vs 51% (at 5 y), $P = .002$	36% vs 60% (at 5 y), $P = .001$	41% vs 23% (at 5 y), $P = .006$	Prognostic impact of *IKZF1* deletion also in second-line treatment of relapsed ALL; one-quarter of *IKZF1* deletions was acquired at relapse
AIEOP-BFM ALL 2000	34	Germany	1999-2005	694	BCP and T ALL	12.0% (MLPA)	69% vs 85% (at 5 y), $P < .0001$	82% vs 92% (at 5 y), $P = .003$	21% vs 10% (at 5 y), $P = .001$	Pronounced prognostic effect of *IKZF1* deletion in the intermediate-risk group

AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; ALL-REZ, Acute Lymphoblastic Leukemia-Relapse Study; BFM, Berlin-Frankfurt-Münster; ALLR3, An International Collaborative Trial for Relapsed and Refractory Acute Lymphoblastic Leukaemia Combination Chemotherapy in Treating Young Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia; ANZCHOG, Australian & New Zealand Children's Haematology/Oncology Group; CGH, comparative genomic hybridization; COG, Children's Oncology Group; DCOG, Dutch Childhood Oncology Group; DFCI, Dana-Farber Cancer Institute; DFS, disease-free survival; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EsPHALL, Safety and Efficacy of Imatinib Added to Chemotherapy in Treatment of Ph+ Acute Lymphoblastic Leukemia in Children; I-BFM SG, International Berlin-Frankfurt-Münster Study Group; JCCLSG, Japanese Children's Cancer and Leukemia Study Group; MLPA, multiplex ligation probe-dependent amplification; MRD, minimal residual disease; NCI, National Cancer Institute; NOPHO, Nordic Society of Pediatric Hematology and Oncology; OS, overall survival; PCR, polymerase chain reaction; Ref., reference(s); Sanger sequencing, dye-terminator sequencing; SNP, single-nucleotide polymorphism; TKI, tyrosine kinase inhibitor; TPOG, Taiwan Pediatric Oncology Group; UK, United Kingdom; US, United States; VHR, very high risk; WBC, white blood cell.

Table 1. (continued)

Trial	Ref.	Country	Trial period	No. of patients	Type of ALL	Frequency of aberrant *IKZF1* (method of detection)	EFS (DFS)	OS	Cumulative incidence of relapse	Comments
AIEOP-BFM ALL 2000	35	Italy	2003-2005	410	BCP	13.2% (MLPA)	70% vs 85% (at 5 y), $P = .007$	87% vs 93% (at 5 y), $P = .100$	24% vs 13% (at 5 y), $P = .049$	Due to the modest effect of *IKZF1* deletion observed, the relevance of *IKZF1* deletion as a clinically useful stratification factor is debated
DCOG ALL8, ALL9, ALL10, COALL-97, COALL-03	36	The Netherlands, Germany	1991-2012	857	BCP	15.9% (MLPA)			34% vs 13% (at 5 y), $P = <.001$	Confirms and extends the strong prognostic effect of *IKZF1* deletion; *IKZF1* deletion remained predictive in intermediate risk patients on the MRD-guided DCOG ALL10 trial
EsPhALL and I-BFM SG studies (for pre-TKI assessment)	37	Austria, Czech Republic, France, Germany, The Netherlands, UK	1995-2005	Pre-TKI cohort: 84 EsPh-ALL cohort: 107	*BCR-ABL1*–rearranged BCP	66.0% (MLPA, CGH array, SNP array)	DFS pre-TKI: 30% vs 58% (at 4 y), $P = .013$ DFS EsPhALL: 54% vs 63% (at 4 y), $P = .168$ DFS EsPhALL TKI-treated good-risk patients: 56% vs 75% (at 4 y), $P = .051$	Pre-TKI: 49% vs 75% (at 4 y), $P = .075$ EsPhALL: 58% vs 83% (at 4 y), $P = .070$ EsPhALL TKI-treated good-risk patients: 66% vs 100% (at 4 y), $P = .039$	Pre-TKI: 57% vs 21% (at 4 y), $P = .026$ EsPhALL: 28% vs 31% (at 4 y), $P = .817$ EsPhALL TKI-treated good-risk patients: 29% vs 25% (at 4 y), $P = .249$	*IKZF1* deletion is demonstrated to be a poor prognostic marker in *BCR-ABL1*–rearranged pediatric ALL independent of imatinib treatment
UKALL trials ALL 97/99 and ALL 2003	38	UK, Ireland	UKALL 97/99: 1997-2002 UKALL 2003: 2003-2011	UKALL 97/99: 864 UKALL 2003: 782	BCP BCP	13.4% (MLPA) 11.1% (MLPA)	56% vs 80% (at 5 y), $P = <.001$ 80% vs 92% (at 5 y), $P = <.001$	70% vs 89% (at 5 y), $P = <.001$ 86% vs 95% (at 5 y), $P = <.001$	40% vs 18% (at 5 y), $P = <.001$ 16% vs 6% (at 5 y), $P = .002$	Integration of cytogenetic with genomic data including *IKZF1* deletion refines risk groups in a clinically meaningful way
NOPHO ALL-1992, NOPHO ALL-2000, NOPHO ALL-2008	39	Denmark, Finland, Norway, Sweden	1992-2013	334	BCP	15.0% (SNP array, MLPA)	60% vs 83% (at 10 y), $P < .001$	73% vs 89% (at 10 y), $P = .001$	35% vs 12% (at 10 y), $P < .001$	Prognostic impact independent of WBC count and MRD; co-occurrence of PAR1 deletion increased prognostic impact of *IKZF1* deletion
EORTC Children's Leukemia Group study 58951	40	Belgium, France, Portugal	1998-2008	1223	BCP	14.6% (PCR, MLPA)	68% vs 87% (at 5 y), $P = <.001$	87% vs 92% (at 5 y), $P = .035$		*IKZF1*-aberrant BCP ALL benefited from vincristine-steroid pulses during maintenance treatment

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Table 1. (continued)

Trial	Ref.	Country	Trial period	No. of patients	Type of ALL	Frequency of aberrant *IKZF1* (method of detection)	EFS (DFS)	OS	Cumulative incidence of relapse	Comments
ALLR3	41	UK, Ireland, The Netherlands, Australia, New Zealand	2002-2013	222	BCP relapse	23.0% (MLPA)		48% vs 53% (at 5 y), $P = .30$		No prognostic impact of *IKZF1* deletion at relapse
ANZCHOG ALL8	42	Australia, New Zealand	2002-2011	475	BCP standard and intermediate risk	10.5% (MLPA)	53% vs 83% (at 7 y), $P < .0001$	78% vs 94% (at 7 y), $P < .0001$	41% vs 15% (at 7 y), $P < .0001$	Strong prognostic effect of *IKZF1* deletion in non–high-risk BCP ALL
ALL-BFM 95	45	Germany	1995-2000	655	BCP intermediate risk	12.2% (PCR)	66% vs 82% (at 5 y), $P = .001$			Vincristine-dexamethasone pulses during maintenance were not of benefit to *IKZF1*-deleted intermediate-risk patients
DFCI ALL Consortium Protocol 05-001	43	US	2005-2010	385	BCP	16.0% (MLPA)	63% vs 88% (at 5 y), $P < .001$	79% vs 94% (at 5 y), $P < .001$	29% vs 8% (at 5 y), $P < .001$	*IKZF1* deletion was confirmed as an independent predictor of inferior outcome
Malaysia-Singapore ALL 2003, 2010	44	Malaysia, Singapore	2002-2017	665	BCP	15.9% (MLPA)			Without *IKZF1* as high-risk criterion: 30% vs 8% (at 5 y), $P < .001$ With *IKZF1* as high-risk criterion: 14% vs 5% (at 5 y), $P = .030$	Demonstrates that intensifying treatment of *IKZF1*-deleted BCP ALL patients reduces risk of relapse
COG Trial AALL0622	46	US, Canada	2008-2012	44	*BCR-ABL1*–rearranged BCP	56.8% (SNP array)	52% vs 82% (at 5 y), $P = .040$	80% vs 100% (at 5 y), $P = .040$		Confirms poor outcome for *IKZF1*-deleted *BCR-ABL1*–rearranged ALL on dasatinib-containing treatment regimen
AIEOP-BFM ALL 2000	61	Germany, Italy	1999-2009	1408	BCP	14.6% (MLPA)	*IKZF1*-deleted, but not *IKZF1*^{plus}: 77% vs 86% (at 5 y), $P = .0005$ *IKZF1*^{plus}: 51% vs 86% (at 5 y), $P < .0001$	*IKZF1*-deleted, but not *IKZF1*^{plus}: 89% vs 94% (at 5 y), $P = .023$ *IKZF1*^{plus}: 75% vs 94% (at 5 y), $P < .0001$	*IKZF1*-deleted, but not *IKZF1*^{plus}: 16% vs 11% (at 5 y), $P = .045$ *IKZF1*^{plus}: 44% vs 11% (at 5 y), $P < .0001$	Definition of a poor MRD-dependent prognostic pattern termed *IKZF1*^{plus} with *IKZF1* deletions co-occurring with deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or PAR1 in the absence of *ERG* deletion

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relates to isolated *IKZF1* exon 1 deletions and whether they should be considered in routine diagnosis or not. Their accurate detection can be complicated due to false MLPA positivity favored by a high guanine-cytosine content in this region. Molecular mapping of exon 1 deletions together with an adapted MLPA protocol with a reinforced denaturation step recently confirmed the frequency and impact of exon 1 deletions on *IKZF1* transcription[48] and suggest that these deletions should be considered for diagnosis when properly controlled. It is noteworthy that additional *IKZF1* deletions targeting the 5′ regulatory regions have been described and are not detected by current MLPA protocols.[9,48] *IKZF1* sequence mutations were mainly analyzed by Sanger sequencing and targeted or nontargeted next-generation sequencing strategies whereas the majority of fusion genes have been identified in transcriptomic studies.[10,13-26,29] The different qualities and sensitivities of these techniques need to be considered when comparing frequency and type of *IKZF1* aberrations in the literature.

IKZF1 as a prognostic factor in pediatric ALL

During the last 10 years, various studies have analyzed the clinical importance of *IKZF1* aberration in pediatric ALL treated on different treatment protocols.[10,13-16,30-46] The presence of *IKZF1* deletions has been associated with older age at diagnosis, higher presenting white blood cell counts, and higher levels of MRD after induction and consolidation.[10,31,32,34,35,43,44,49,50] Consequently, *IKZF1* deletions are overrepresented in high-risk patients with pediatric ALL. Importantly, the distribution of *IKZF1* aberrations within the subgroups of ALL is not homogeneous. Although approximately two-thirds of *BCR-ABL1*$^+$ pediatric BCP ALL carry an *IKZF1* deletion,[9,37,44,46] the frequency in *BCR-ABL1*$^-$ BCP ALL subgroups is lower. It ranges from roughly 20% in the B-other group, which lacks the "classical" recurrent acquired genetic aberrations of ALL, but includes Philadelphia-like and *BCR-ABL1*–like BCP ALL characterized by an activated kinase signature, and 15% in high hyperdiploid ALL to <5% in *ETV6-RUNX1*-, *TCF3*- or *KMT2A*-rearranged ALL as well as T-cell ALL.[10,31,34,35,38-40,44,51-53] Although very rare in *BCR-ABL1*$^-$ BCP ALL (~1%), *IKZF1* point mutations have been described in up to 10% of *IKZF1* deletion-negative *BCR-ABL1*$^+$ BCP ALL.[10,13-16] One unifying and important feature of a majority of prognostic studies in pediatric BCP ALL is that the different types of *IKZF1* deletions have been consistently linked to an unfavorable clinical outcome of frontline treatment (Table 1).[10,13,14,30-46,54] It is worth mentioning that *IKZF1* point mutations seem to have a similar impact on outcome.[10,13-16] As a consequence, some international study groups on treatment of ALL early on included *IKZF1* deletion status into their high-risk treatment-stratification strategies for BCP ALL patients whereas others did not follow this strategy because the prognostic effect of *IKZF1* deletions alone was considered not sufficiently strong enough to justify exposure to the toxic side effects of high-risk or even very-high-risk therapy.[38,53]

Of significance, although it has been clearly demonstrated that *IKZF1* aberrations exert an independent prognostic impact, some studies early on suggested the presence of effect modification or confounding by different levels of MRD, activated JAK-STAT signaling, or co-occurring deletions of the lymphoid transcriptional regulator gene *BTG1* or the ets family transcription factor *ERG*.[15,32,34,35,49,55-57] For example, integrated use of MRD and *IKZF1* deletion status predicted 79% of relapses in a Dutch study.[49] Such an epistatic effect of other genetic aberrations has been particularly documented for *ERG* deletions because *IKZF1* deletion surprisingly does not affect the prognosis of BCP ALL when co-ocurring with *ERG* deletion.[56,57] It is now known that *ERG* deletions almost exclusively occur in the recently described *DUX4*-rearranged BCP ALL subtype, which also bears *IKZF1* deletions in >20% of the cases.[19,58,59] In this respect, *ERG* deletion can be considered a surrogate marker for *DUX4* rearrangements, although approximately one-third of *DUX4*-rearranged BCP ALL lacks an *ERG* deletion.[60] So far, it is unclear whether the previously described prognostic effect of the *ERG* deletion[56,57] is mediated by itself or the association with the *DUX4* rearrangement. Of interest, there are hints that positivity for an *ERG* deletion also seems to confer an advantageous outcome within *DUX4*-rearranged BCP ALL.[60] Hence, the interrelationships of *ERG* deletion and *DUX4* rearrangements with *IKZF1* deletions and their impact on outcome are complex and not fully understood. Recently, a large study of the International Berlin-Frankfurt-Münster (I-BFM) Study Group refined the prognostic strength of *IKZF1* deletions in *BCR-ABL1*$^-$ pediatric BCP ALL by describing an extremely poor prognostic *IKZF1* deletion-associated genetic aberration profile termed *IKZF1*^{plus}.[61] It is defined by *IKZF1* deletions co-occurring with deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* in the absence of *ERG* deletion. Of interest, but unfortunately not yet understood, *IKZF1*^{plus} exerts its strong prognostic impact only in patients still carrying measurable MRD of a leukemic cell load exceeding 10^{-4} after induction treatment. This simple to assess profile in combination with MRD analyses has already been implemented as a high-risk stratification criterion in the current frontline AIEOP-BFM ALL 2017 trial for treatment of ALL, and its prognostic value has been confirmed by others.[62]

Lastly, the prognostic importance of *IKZF1* deletions for second-line treatment of BCP ALL is relatively underexamined in comparison with frontline protocols and, therefore, is less well understood. Despite differences in results of 2 published studies, 1 unifying conclusion is supportive of the idea that, similar to frontline therapy, the prognostic effect of *IKZF1* deletions seem to be context-dependent.[33,41]

Overall, these observations indicate that the complex interplay of exposure and response to treatment with the underlying disease biology is the key driver determining the prognostic impact of *IKZF1* aberrations. Thus, a greater understanding of the interrelationships between treatment, treatment response, and cooperating molecular lesions in *IKZF1*-aberrant ALL could help to develop improved treatments tailored to the different scenarios.

IKZF1 and mechanisms of treatment resistance

The suggested molecular mechanisms involved in drug resistance mediated by *IKZF1* alteration in BCP ALL are complex and not completely understood. However, there is evidence that loss of IKAROS in normal BCP cells or *BCR-ABL1*$^+$ BCP ALL leads to acquisition of a stem cell–like phenotype with increases

in self-renewal, upregulation of focal adhesion kinase (FAK), cell-adhesion molecules, and drug resistance through formation of a de novo superenhancer landscape of collaborating master transcription regulators and B-cell transcription factors.[63-65] Of interest, Churchman et al demonstrated reversal of such a phenotype in *IKZF1*-aberrant *BCR-ABL1*$^+$ BCP ALL by treatment with retinoid receptor agonists.[65] Retinoids induced selective expression of wild-type *IKZF1* and initiated expression of *IKZF1* target genes. Similar results were obtained through FAK inhibition and both treatments, retinoid receptor agonists and FAK inhibition, improved the sensitivity of *BCR-ABL1*$^+$ BCP ALL to tyrosine kinase inhibitor therapy.[65,66] In addition, there are intriguing data demonstrating that *IKZF1* controls energy metabolism in BCP ALL with a direct link to glucocorticoid response.[67,68] These important insights may allow the development of new specific therapeutic approaches targeting *IKZF1*-altered signaling networks in BCP ALL.

Perspective

Risk stratification and associated treatment strategies in trials on pediatric ALL are often not fully comparable. This may, at least in part, contribute to the partially different impact of aberrant *IKZF1* on outcome observed in some of the published trials (Table 1). However, these complicating issues may also bear chances, if we engage into more detailed and careful comparisons of the different treatment backgrounds and their variant stratification strategies in context with *IKZF1* aberrations and the relevant clinical end points. Following such strategies may allow us to nourish our knowledge on *IKZF1* aberration with a better understanding of the differential response of affected patients to specific parts of the applied treatment protocols. Cooperative approaches incorporating well-characterized trial populations from large study groups will likely be key to success in this regard and should also answer many additional open questions such as the importance of a truly comprehensive assessment of the molecular spectrum of *IKZF1* alterations (copy-number variation, nucleotide mutations, gene fusions), their prognostic importance in ALL subgroups, and the development of a full picture of the interplay of aberrant *IKZF1* with cooperating genetic aberrations (eg, *CDKN2A*, *PAX5*, *BTG1*, JAK pathway aberrations, RAS pathway aberrations, other kinase activating lesions, *ERG*, subclonality of cooperating lesions).

Therefore, by continuing our research on *IKZF1* in pediatric ALL, we will (1) be able to improve information for patients and/or their guardians regarding the risk of recurrence and final outcome of ALL; (2) very likely gain further insights into the biology of ALL; and (3) increase our ability to design and conduct clinical trials delivering optimized treatment strategies based on improved individual characterization of children and adolescents with ALL.

So, is *IKZF1* aberration still a prognostic factor? As it turns out, the answer is: yes, more than ever!

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Authorship

Contribution: M.S., H.C., and A.V.M. designed and performed research, analyzed and discussed data, and wrote the paper.

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Footnote

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