To the editor:

Dasatinib may overcome the negative prognostic impact of *KIR2DS1* in newly diagnosed patients with chronic myeloid leukemia

Most chronic myeloid leukemia (CML) patients achieve complete cytogenetic response (CCyR) with tyrosine kinase inhibitors (TKI).[1] However, many relapse on therapy discontinuation.[2] The curative effect of allogeneic stem cell transplantation (allo-SCT) in CML is believed to be mediated through the donor-derived graft-versus-leukemia effect. Natural killer (NK) cells are important components of this allo-immune effect[3] and exert direct cytotoxicity against $CD34^+$ Philadelphia-positive cells in vitro.[4] The balance between signals from inhibitory and activating surface receptors determines NK-cell cytotoxicity.[5] These receptors include killer immunoglobulin-like receptors (KIR), which are specific for allotypic determinants shared by HLA-class I (KIR ligands).

We recently reported that newly diagnosed CML–chronic phase (CP) patients carrying the activating KIR gene, *KIR2DS1,* have significantly lower probability of achieving CCyR on imatinib, and lower 2-year progression-free (PFS) and overall survival (OS).[6] This effect was independent of Sokal and was validated in an independent cohort of 174 CML-CP patients treated with first-line imatinib in the multicenter United Kingdom SPIRIT-1 trial. The impact of *KIR2DS1* on CCyR was even greater in the absence of the ligand for the corresponding inhibitory KIR (KIR2DL1), suggesting that in the presence of the ligand, KIR2DL1 may neutralize the effect of KIR2DS1. We concluded that *KIR2DS1* may predict response to imatinib and identify patients at risk of treatment failure.

Here, we investigate whether *KIR2DS1* could also predict response to dasatinib, a second-generation TKIs with more potent BCR-ABL inhibitor activity than imatinib. Dasatinib also inhibits other kinases such as SRC and TEC,[7] key regulators of immune response, and may therefore exert an immunomodulatory effect.

We studied 130 CML-CP patients treated with first-line dasatinib on the United Kingdom multicenter SPIRIT-2 trial. All patients gave informed consent. Median follow-up was 18 months; 122 (93.8%) achieved CCyR and 94 (72.3%) achieved major molecular response (MMR).

KIR genotyping was performed as described previously.[8] In dasatinib-treated patients, we found no significant impact of KIR genotype on outcome (Table 1). Specifically, *KIR2DS1* was no longer a negative prognostic factor and the 2 year probabilities of CCyR and MMR for *KIR2DS1*-positive patients was not statistically different to *KIR2DS1*-negative patients, namely 100% versus 93.6% ($P = .09$) and 74.0% versus 74.9% ($P = .77$), respectively (Table 1). These data suggest that dasatinib may overcome the negative prognostic impact of *KIR2DS1* on CCyR in newly diagnosed CML-CP patients treated with imatinib. Longer follow-up is needed to assess whether dasatinib also overcomes the negative impact of *KIR2DS1* on PFS and OS.

Dasatinib suppresses NK-cell function in vitro,[9] although recent studies report the expansion of BCR-ABL–negative NK cells in dasatinib-treated patients.[10] The mechanism through which dasatinib may overcome the negative prognostic significance of *KIR2DS1* in imatinib-treated patients could be related to its off-target kinase inhibition. These data provide a rationale for genotyping CML patients at diagnosis to identify *KIR2DS1* positive patients at greater risk of treatment failure with imatinib. These patients who constitute nearly 30% of CML patients may benefit from upfront dasatinib treatment. Functional studies to determine the differential impact of imatinib and dasatinib on KIR2DS1-expressing NK-cell subsets are underway. A similar analysis in patients receiving upfront nilotinib, an analog of imatinib with minimal SRC kinase inhibition, would be of great interest.

Table 1. Frequencies and RR for response according to KIR genotype

	n (%)	RR for CCyR	RR for MMR
K2DL2		$P = .83$	$P = .50$
Negative	65 (50)	1	1
Positive	65 (50)	0.963	0.869
K2DL5A		$P = .17$	$P = .77$
Negative	94 (72.3)	1	1
Positive	36 (27.7)	1.313	0.936
K2DL5B002		$P = .17$	$P = .88$
Negative	98 (75.4)	1	1
Positive	32 (24.6)	1.318	0.951
K2DL5B003*		$P = .17$	$P = .78$
Negative	96 (73.8)	1	1
Positive	33 (25.4)	1.316	0.956
K2DS1		$P = .09$	$P = .99$
Negative	93 (71.5)	1	1
Positive	37 (28.5)	1.398	1.003
K2DS2		$P = .87$	$P = .61$
Negative	64 (49.2)	1	1
Positive	66 (50.8)	0.970	0.899
K2DS3		$P = .21$	$P = .10$
Negative	96 (73.8)	1	1
Positive	34 (26.2)	0.768	0.669
K2DS4 (alleles 0010101-0010103,00102/002)		$P = .97$	$P = .75$
Negative	73 (56.2)	1	1
Positive	57 (43.8)	0.994	0.935
K2DS4 (alleles 003/004/006/007)		$P = .65$	$P = .41$
Negative	27 (20.8)	1	1
Positive	103 (79.2)	1.106	1.247
K2DS5		$P = .26$	$P = .76$
Negative	96 (73.8)	1	1
Positive	34 (26.2)	1.256	1.073
K3DS1		$P = .08$	$P = .95$
Negative	89 (68.5)	1	1
Positive	41 (31.5)	1.413	1.013

The prognostic influence of an individual KIR gene was analyzed only if the gene prevalence was greater than 10% of the population. *P* values $< .003$ are considered as significant (multiple testing correction).

KIR indicates killer immunoglobulin-like receptors; MMR, major molecular response; CCyR, complete cytogenetic response; and RR, relative risk.

*One patient had missing data.

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To the editor:

The α4β7 integrin binds HIV envelope but does not mediate bystander killing of γδ T cells

Our previous study showed HIV envelope glycoprotein induces killing of CD4-negative Vγ2Vδ2 (referred as Vδ2) T cells by binding to CCR5 and α4β7.[1] Blocking either CCR5 with receptor antagonists or α4β7 with MAdCAM1 reduced Env binding and killing of Vδ2 cells. Signaling through p38 and caspase activation were responsible for envelope-dependent cell death. However, we could not determine which of these receptors mediated death signaling. We have now investigated effects of HIV envelope on the CD4-negative Vδ1 subset of γδ T cells, which express α4β7, but not CCR5 receptor. Comparing envelope receptors and responses on Vδ1 and Vδ2, cells showed the envelope-α4β7 interaction does not generate a death signal.