

#### REFERENCES

- Argiropoulos B, Humphries RK. Hox genes in hematopoiesis and leukemogenesis. Oncogene 2007; 26: 6766–6776.
- 2 Kroon E, Krosl J, Thorsteinsdottir U, Baban S, Buchberg AM, Sauvageau G. Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b. *EMBO J* 1998; 17: 3714–3725.
- 3 Fischbach NA, Rozenfeld S, Shen W, Fong S, Chrobak D, Ginzinger D et al. HOXB6 overexpression in murine bone marrow immortalizes a myelomonocytic precursor in vitro and causes hematopoietic stem cell expansion and acute myeloid leukemia in vivo. *Blood* 2005; **105**: 1456–1466.
- 4 Thorsteinsdottir U, Kroon E, Jerome L, Blasi F, Sauvageau G. Defining Roles for HOX and MEIS1 Genes in Induction of Acute Myeloid Leukemia. *Mol Cell Biol* 2001; **21**: 224–234.
- 5 Pineault N, Buske C, Feuring-Buske M, Abramovich C, Rosten P, Hogge DE et al. Induction of acute myeloid leukemia in mice by the human leukemia-specific fusion gene NUP98-HOXD13 in concert with Meis1. Blood 2003; 101: 4529–4538.
- 6 Li Z, Zhang Z, Li Y, Arnovitz S, Chen P, Huang H *et al.* PBX3 is an important cofactor of HOXA9 in leukemogenesis. *Blood* 2013; **121**: 1422–1431.
- 7 Pan Q, Zhu YJ, Gu BW, Cai X, Bai XT, Yun HY et al. A new fusion gene NUP98-IQCG identified in an acute T-lymphoid/myeloid leukemia with a t(3;11)(q29q13;p15)del (3)(q29) translocation. Oncogene 2008; 27: 3414–3423.

- 8 Zhu YJ, Xue YQ, Pan JL, Wu YF, Wang Y, Shen J. Clinical genetics research on a new case with hybrid acute leukemia involving NUP98 gene at 11p15. *Jiangsu Med J* 2006; **32**: 809–811.
- 9 Touw IP, Erkeland SJ. Retroviral insertion mutagenesis in mice as a comparative oncogenomics tool to identify disease genes in human leukemia. *Mol Ther* 2007; 15: 13–19.
- 10 Watanabe-Okochi N, Kitaura J, Ono R, Harada H, Harada Y, Komeno Y et al. AML1 mutations induced MDS and MDS/AML in a mouse BMT model. Blood 2008; 111: 4297–4308.
- 11 Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci USA 2005; 102: 15545–15550.
- 12 Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2009; 4: 44–57.
- 13 Sasaki YT, Sano M, Kin T, Asai K, Hirose T. Coordinated expression of ncRNAs and HOX mRNAs in the human HOXA locus. *Biochem Biophys Res Commun* 2007; 357: 724–730.
- 14 Wang KC, Yang YW, Liu B, Sanyal A, Corces-Zimmerman R, Chen Y et al. A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. Nature 2011; 472: 120–124.
- 15 Tanaka Y, Kawahashi K, Katagiri Z, Nakayama Y, Mahajan M, Kioussis D. Dual function of histone H3 lysine 36 methyltransferase ASH1 in regulation of Hox gene expression. *PLoS One* 2011; 6: e28171.

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### OPEN

## Low incidence of peripheral arterial disease in patients receiving dasatinib in clinical trials

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The oral tyrosine kinase inhibitors (TKI) dasatinib, imatinib, ponatinib, nilotinib and bosutinib each target BCR-ABL, yet are structurally distinct from one another.<sup>1–6</sup> The selection of BCR-ABL TKI treatment for an individual patient is influenced by factors including any previous treatment, likelihood of benefit, risk of toxicities and the potential for end-organ damage resulting from use, particularly as a long-term therapy is expected in chronic myeloid leukemia in chronic phase (CML-CP). Despite considerable overlap of safety profiles, there are distinct drug-specific adverse events associated with each TKI.<sup>2</sup>

Peripheral arterial disease (PAD) is often associated with claudication, and may result in critical limb ischemia, and increased risks of loss of limb or death.<sup>7</sup> We evaluated safety databases of dasatinib clinical trials in patients with Philadelphia chromosome-positive (Ph+) leukemias to identify PAD or PADrelated events. We also conducted a standardized incidence ratio (SIR) analysis to evaluate the rate of PAD or PAD-related events in the trials relative to the rate in external reference populations derived from administrative data sets, representing a general adult population in the United States and a CML population that did not receive dasatinib. This retrospective analysis used pooled safety data from 2712 adults with CML or Ph+ acute lymphoblastic leukemia (ALL) treated with dasatinib in 11 clinical trials, including two first-line trials (n = 324) and nine trials in imatinibresistant or -intolerant patients (n = 2388; Supplementary Table S1). The median duration of dasatinib treatment was 19 months (range: 0.03-93 months). The trial enrollment criteria permitted inclusion of patients with myocardial infarction >6 months prior, congestive heart failure >3 months prior and previously uncontrolled angina controlled  $\ge$  3 months.

Bristol-Myers Squibb safety databases for the included trials were examined to identify PAD or PAD-related events, using the following Medical Dictionary for Regulatory Activities preferred terms: arterial stenosis, arterial thrombosis, arteriosclerosis, arterial stenosis limb, intermittent claudication, femoral artery occlusion, necrosis ischemic and PAD.

For the SIR analysis (SIR = observed number of events/expected number of events; detailed description in Supplementary Materials), two external populations were extracted from Truven Health Analytics Marketscan Commercial Claims and Medicare Supplementary database (Ann Arbor, MI, USA) between 2008 and 2013. MarketScan consists of data from commercial health plans, Medicaid, Medicare, and self-insurance for Americans. Each reference population included individuals enrolled in the databases for  $\geq 60$  days before the index date. Adult patients were included in the general reference population ( $n = 90\ 000\ 000$ ), and the CML reference population had  $\geq 2$  diagnostic codes for CML and were not using dasatinib ( $n = 15\ 000$ ). To obtain the expected number of cases, the age and gender-specific person-time of dasatinib-treated patients in the trials were multiplied by the age and gender-specific rates of events in the external populations.

PAD or PAD-related events were detected in 11 patients during dasatinib treatment among 2712 individuals with a cumulative dasatinib exposure of 6421 patient-years, which corresponds to a cumulative incidence of 0.4% and an incidence rate (per 100 patient-years) of 0.2%. Of the 11 patients, all were previously treated with a TKI; 8 were resistant and 3 were intolerant to prior imatinib therapy (Table 1). No cases of PAD or PAD-related events were identified among the 258 patients treated with first-line dasatinib in DASatinib versus Imatinib Study In treatment-Naive CML patients (DASISION) (median duration of 60 months (range: 0.03–73 months)). Characteristics, comorbidities and risk factors of the 11 patients with PAD or a PAD-related event are shown in

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Table 1.	Characteristics, outcomes, risk factors and management of	PAD and PAD-related	d adverse	events						
Age/CMI phase	. Pre-existing comorbidities and risk factors present at baseline		Ac	lverse event chara	cteristics		Outcor	nes (best r at any tim	e) esponse	Adverse event management
		Preferred term	CTC grade <sup>a</sup>	Dasatinib starting dose	Time on dasatinib before onset, days	First occurrence:	MMR	CMR <sub>4.5</sub>	CCyR	Dasatinib dose modification
73/CP	Pre-existing heart disease, previous smoker	Femoral artery occlusion	1	25 mg BID, 5 d per wk	2227	Yes	NR	NR	No	Interrupted
68/AP	Previous smoker	Intermittent claudication	2, 2	70 mg BID	NR, 42	Yes	Yes	Yes	Yes	None
80/AP <sup>b</sup>	Pre-existing noncardiac atherosclerosis, hypertension, hypercholesterolemia	Femoral artery occlusion	2	70 mg BID	m	No	No	No	No	Interrupted
63/CP	Diabetes mellitus	PAD	1, 3	70 mg BID	343, 657	Yes	No	No	No	None
74/CP	Pre-existing ischemic heart disease, hypertension, diabetes mellitus	Intermittent claudication	2	70 mg BID	868	Yes	No	No	No	None
71/CP	Hypertension	Peripheral artery thrombosis	3, 3	50 mg BID	777, 870	Yes	Yes	No	Yes	Interrupted
54/LBP	Deep vein thrombosis	Intermittent claudication	2	70 mg BID	151	Yes	NR	NR	Yes	None
67/CP <sup>c</sup>	Pre-existing ischemic heart disease, pre-existing noncardiac atherosclerosis, hypertension	PAD	m	70 mg BID	367	Yes	NR	NR	No	None
75/CP	Arterial bypass surgery, pre-existing ischemic heart disease	Intermittent claudication	-	50 mg BID	1177	Yes	NR	NR	No	None
		Peripheral vascular disorder	m		1323					Interrupted
65/CP	PAD on a pre-existing lesion, hypertension, previous smoker	Peripheral ischemia	3, 3, 3	100 mg QD	1229, 1361, 1447	Yes	No	No	No	None
44/CP	History of angioplasty and stent, hypertension, hypercholesterolemia, smoker	Peripheral ischemia	m	50 mg BID	1692	Yes	Yes	Yes	Yes	Interrupted
Abbrevia Criteria; c the sole p	tions: AP, accelerated phase; BID, twice daily; CCyR, complete cyt ; day: IBP, lymphoid blast phase; MMR, major molecular respons patient for whom the PAD-related adverse event was not a first	genetic response; CN ;; NR, not reported; P <sup>p</sup> occurrence. <sup>c</sup> The chrc	lL, chronic \D, periph onic phase	: myeloid leukemia eral arterial disease disease of this pa	ı; CMR, complete mole e; QD, once daily; wk, v atient had clonal evolu	cular respons veek. <sup>a</sup> Nationa ition.	e; CP, chro al Cancer	onic phase Institute C	; CTC, Co TCAE v.3	mmon Terminology .0. <sup>b</sup> This patient was

Table 2. Incidence of PAD and PAD-related events in patients receiving treatment for Ph+ leukemia in clinical trials							
	Dasatinib	Imatinib	Nilotinib	No BCR-ABL inhibitor			
Dose	15–240 mg per day	400 mg QD or BID	300 or 400 mg BID	IFN $5 \times 10^6$ U/m <sup>2</sup> per day; Ara-C 20 mg/m <sup>2</sup> per day for 10 days per month			
Trial	11 dasatinib trials	TOPS, IRIS, ENESTnd	ENESTnd	IRIS			
Study population	Ph+ leukemia <sup>a</sup>	Newly diagnosed CML-CP	Newly diagnosed CML-CP	Newly diagnosed CML-CP			
Patients treated (n)	2712	1301	556	533			
PAD cases <sup>b</sup> ( <i>n</i> )	11	2	7	3			
Cumulative incidence (%)	0.4	0.2	1.3	0.6			
Exposure, patient-years	6421	4523	1464	534 <sup>c</sup>			
Incidence rate (per 100 patient-years), %	0.2	0.1	0.5	0.6			
Data source	Current analysis		Adapted from Giles et al.7,	8			
Abbreviations: Ara-C, cytarabine; BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; ENESTnd, Evaluating Nilotinib Efficacy and Safety ir							

Abbreviations: Ara-C, cytarabine; BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; ENESTnd, Evaluating Nilotinib Efficacy and Safety in clinical Trials-newly diagnosed patients; IFN, interferon; IRIS, International Randomized Study of Interferon and ST1571; PAD, peripheral arterial disease; Ph+, Philadelphia chromosome-positive; QD, once daily; TOPS, Tyrosine Kinase Inhibitor Optimization and Selectivity Study. <sup>a</sup>Includes newly diagnosed CML-CP (n = 324) and imatinib-resistant or -intolerant CML (any phase) and Ph+ ALL (n = 2388). <sup>b</sup>In Giles *et al*,<sup>7</sup> PAD included atherosclerotic and thrombotic events, excluding functional (vasoreactive), embolic or aneurysmal disorders, in the arteries of lower and upper extremities. Terms indicative of PAD included: arterial disorder, peripheral ischemia, arterial insufficiency, arterios obliterans, peripheral vascular disorder, arterial occlusive disease, femoral artery angioplasty, arterial stenosis limb, intermittent claudication, peripheral revascularization, arterial thrombosis limb and PAD.<sup>8</sup> <sup>c</sup>Patients treated with IFN+Ara-C had shorter median duration of therapy (8 months) compared with nilotinib (36 months) and imatinib (45 months) cohorts, because of early crossover to imatinib.

Table 1. For these patients, median age at baseline was 68 years (range: 44–80 years) and median duration of dasatinib before diagnosis of PAD or PAD-related event was 777 days (range: 3–2227 days). Median duration of prior imatinib therapy amongst these patients was 29 months (n=9; range: 2–74 months). Of the 11 patients, 8 had CML-CP, 2 had CML in accelerated phase (CML-AP) and one had CML in blast phase (CML-BP) of lymphoid phenotype. Ten of the 11 patients were on BID (twice daily) dosing regimens. Of the eight patients with CML-CP, only one started at a dose of 100 mg QD (once daily), the current recommended dose of dasatinib for CML-CP.<sup>2</sup> Dosing regimens for the other seven patients with CML-CP ranged from 25 to 70 mg BID. The current recommended dose for CML-AP or CML-BP is 140 mg QD;<sup>2</sup> however, the patients with CML-AP (n=2) and CML-BP (n=1) received a 70 mg BID starting dose of dasatinib.

All 11 patients had pre-existing comorbidities/conditions that potentially increased the risk of developing PAD (Table 1), including one patient who had prior arterial bypass surgery, one with a history of angioplasty and stent, and one who had pre-existing PAD. Furthermore, six patients had hypertension, four had pre-existing ischemic heart disease, four were former or current smokers, two had pre-existing noncardiac atherosclerosis, two had hypercholesterolemia, two had diabetes mellitus and one had deep vein thrombosis (DVT). Of nine patients with PAD or a PAD-related event with available data, all were receiving other medications at baseline. The PAD or PAD-related events in the 11 cases included intermittent claudication (four patients), femoral artery occlusion (two patients), PAD (two patients), peripheral ischemia (two patients), peripheral artery thrombosis (one patients) and peripheral vascular disorder (one patient), with one patient experiencing two of these events (Table 1). All events identified were Common Terminology Criteria grade  $\leq$  3. Of seven patients with available molecular response data, best responses at any time included 27% (n=3) with a major molecular response, 18% (n=2) achieving complete molecular response (CMR<sub>4 5</sub>) and 36% (n = 4) achieving a complete cytogenetic response. Dasatinib treatment was interrupted in five patients due to PAD or a PAD-related event, and no patients discontinued dasatinib because of PAD or PAD-related events (Table 1).

SIR analysis showed that the observed number of PAD or PADrelated events (n = 11) in the pooled population did not exceed the expected number of events (n = 20) in the general population (SIR (95% confidence interval; CI), 0.56 (0.31–1.01)). Similarly, the observed number of PAD or PAD-related events (n = 11) in the pooled population did not exceed the expected number (n = 43) based on rates in the reference CML population (SIR (95% Cl), 0.26 (0.14–0.46); Supplementary Table S2).

The current analysis investigated the incidence of PAD or PADrelated events in patients treated with dasatinib to test the hypothesis that PAD might be a class effect among second- and third-generation BCR-ABL TKIs. Previous reports have described an association of PAD with either ponatinib or nilotinib treatment.<sup>4,5</sup> The cumulative incidence and incidence rate (per 100 patientyears) reported here are higher than those previously published in a retrospective analysis by Giles and colleagues for imatinib (0.2% and 0.1%, respectively); however, they are lower than cited for nilotinib (1.3% and 0.5%, respectively) and interferon- $\alpha$ plus cytarabine (0.6% and 0.6%, respectively; Table 2).<sup>8</sup> No PAD or PAD-related events were identified in newly diagnosed CML patients treated with dasatinib in the DASISION trial, which has the longest median exposure time to dasatinib of any study.

Generally, risk factors for cardiovascular disease are also risk factors for PAD or PAD-related events.<sup>7,9</sup> The prevalence of PAD increases with age and concomitant cardiovascular disease risk factors.<sup>8,10</sup> Some clinical trials report a lower incidence of PAD in CML and Ph+ ALL compared with published rates for the general population; however, this may be affected by the study entry criteria that exclude patients with significant cardiovascular disease.<sup>7,8,9,11</sup> The included dasatinib clinical trials (with the exception of CA180-002) allowed the participation of patients with diabetes and patients with a history of cardiac comorbidities. Ten of the 11 patients with PAD or PAD-related events had at least one potential risk factor for PAD (the remaining patient had DVT).

The extended survival of CML patients in the TKI era makes it important to understand the implications of long-term treatment and understand better the potentially irreversible and severe toxicities of some TKIs. The results presented here do not show an association between dasatinib treatment and development of symptomatic PAD in patients with CML or Ph+ ALL, and are consistent with the hypothesis that PAD observed in CML patients is not a class effect of second- and thirdgeneration BCR-ABL TKIs. Similar analyses evaluating cardiac and cerebrovascular adverse events in CML patients treated with BCR-ABL TKIs are warranted, based on the findings by Chai-Adisaksopha *et al.*<sup>12</sup> Second-generation TKIs, including dasatinib, have established higher rates of molecular remission in CML than reported with imatinib, with the hope for cure or at 1596

least treatment-free remissions. When selecting treatment for Ph+ leukemia, physicians should carefully assess overall cardiovascular health, as well as pre-existing comorbidities and risk factors present at baseline.

#### **CONFLICT OF INTEREST**

PDL has received honoraria from BMS, Novartis and Pfizer, and has received research funding from Novartis. TPH has received honoraria and research funding from BMS and Novartis, and has acted in an advisory role for both companies. F-XM has served as a consultant for and has received research funding from BMS and Novartis; he has served on advisory boards for BMS, Novartis, Pfizer and Ariad. D-WK has served as a consultant for and has received honoraria and research funding from Novartis, BMS, Pfizer and Ilyang. JLS has served as a consultant for and Pfizer. NPS has received research funding from BMS, Ariad and Pfizer, and serves as a DSMB member for Teva. KG and NW are employees of BMS. JEC has served as a consultant for Ariad, BMS, Novartis, Pfizer and Teva.

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#### **AUTHOR CONTRIBUTIONS**

All authors provided feedback and guidance on the analysis and interpretation of the results, critically reviewed the manuscript and approved the final draft for submission. The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise.

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#### REFERENCES

- 1 O'Hare T, Walters DK, Stoffregen EP, Jia T, Manley PW, Mestan J et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res* 2005; 65: 4500–4505.
- 2 Sprycel (dasatinib) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
- 3 Gleevec (imatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
- 4 Iclusig (ponatinib) [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc.; 2015.
- 5 Tasigna (nilotinib) [prescribing information]. Stein, Switzerland: Novartis Pharma Stein AG; 2015.
- 6 Bosulif (bosutinib) [prescribing information]. New York, NY: Pfizer Labs; 2015.
- 7 Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia* 2013; 27: 1310–1315.
- 8 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007; **45**: 55–567.
- 9 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM *et al.* Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; **382**: 1329–1340.
- 10 Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362: 2251–2259.
- 11 Hooi JD, Stoffers HE, Kester AD, Rinkens PE, Kaiser V, van Ree JW *et al.* Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral arterial occlusive disease. *Scand J Prim Health Care* 1998; **16**: 177–182.
- 12 Chai-Adisaksopha C, Lam W, Hillis C. Major arterial events in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: a metaanalysis. *Leuk Lymphoma* 2015; e-pub ahead of print 20 October 2015; ; doi: 10.3109/10428194.2015.1091929.

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# SOX11 defines two different subtypes of mantle cell lymphoma through transcriptional regulation of BCL6

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Mantle cell lymphoma (MCL) is an aggressive lymphoid neoplasm initially considered as derived from naive, pre-germinal center lymphocytes.<sup>1</sup> However, several studies have now shown that 15–40% of cases carry somatic mutations in the expressed

immunoglobulin (*IGVH*) gene, indicating that at least a subset of MCL is derived from antigen-experienced cells that have transitioned through the germinal center (GC).<sup>2</sup> The clinical impact of the *IGHV* mutational status on MCL has not been as well investigated as in chronic lymphocytic leukemia (CLL) but some studies have suggested a better outcome for patients with high load of *IGHV* mutations.<sup>3–5</sup> Intriguingly, the presence of

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