
Dasatinib

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Abstract

Dasatinib is an orally available short-acting dual ABL/SRC tyrosine kinase inhibitor (TKI). It potently inhibits BCR-ABL and SRC family kinases (SRC, LCK, YES, FYN), but also c-KIT, PDGFR- α and PDGFR- β , and ephrin receptor kinase. Dasatinib is an effective treatment for chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Both diseases are characterized by a constitutively active tyrosine kinase; BCR-ABL. Dasatinib inhibits BCR-ABL with greater potency compared with other BCR-ABL inhibitors and is active in CML resistant or intolerant to imatinib. Dasatinib is approved for the treatment of CML (all phases) and for the treatment of Ph+ ALL, resistant or intolerant to prior imatinib treatment. Randomized trial data in CML show that first-line dasatinib provides superior responses compared with imatinib and enables patients to achieve early, deep responses, correlated with improved longer-term outcomes. A once-daily dose of 100 mg in chronic phase CML results in high hematologic and molecular remission rates and prolongation of survival. In accelerated and blastic phase of CML, as well as in Ph+ ALL, complete hematologic and cytogenetic remissions frequently occur. Remissions however are very short. In these patients, once-daily 140 mg is the recommended dose. The effect of dasatinib in other malignancies including solid

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tumors is subject of clinical studies. Regardless of many clinical trials in different tumor types and in different combinations of dasatinib with other agents, the role of dasatinib in the treatment of solid tumors has not yet been defined. Side effects of dasatinib are frequent but mostly moderate and manageable and include cytopenias and pleural effusions. The review presents the preclinical and clinical activity of dasatinib with a focus on clinical studies in CML.

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1 Introduction

Chronic myeloid leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells caused by a chromosomal aberration, the Philadelphia (Ph) chromosome. The Ph chromosome is formed by the chromosomal translocation t(9;22)(q34;q11). This translocation juxtaposes the ABL gene (chromosome 9) and the BCR gene (chromosome 22) creating a BCR-ABL fusion gene. The resulting chimeric protein is a constitutively active ABL tyrosine kinase (Hehlmann et al. 2007). Knowledge of the molecular pathogenesis of CML has allowed development of molecular targeted therapy, which has considerably changed the management and outcome of patients (Wong and Witte 2004; Hehlmann et al. 2007). Treatment options for CML include BCR-ABL tyrosine kinase inhibitors (TKIs), interferon alpha, chemotherapy, stem cell transplantation, or clinical trials of novel therapies (Baccarani et al. 2013; NCCN v4 2013).

Dasatinib is a potent multikinase inhibitor targeting BCR-ABL, the SRC family of kinases (SRC, LCK, HCK, YES, FYN, FGR, BLK, LYN, FRK), receptor tyrosine kinases (c-KIT, PDGFR, DDR1 and 2, c-FMS, ephrin receptors), and TEC family kinases (TEC and BTK). Most important is dasatinib's potent, short-acting inhibition of BCR-ABL. Dasatinib demonstrates activity against most imatinib-resistant BCR-ABL mutations (Karaman et al. 2008; Shah et al. 2004; Branford et al. 2009). The compound is indicated for the treatment of adults with newly diagnosed Philadelphia-chromosome-positive (Ph+) CML in all phases of the disease, e.g., chronic (CP), accelerated (AP), blast phase (BP; myeloid or lymphoid) Ph+ CML, and Ph+ ALL with resistance or intolerance to prior therapy, including imatinib (Sprycel® BMS 2012; EMA 2012; Hochhaus and Kantarjian 2013).

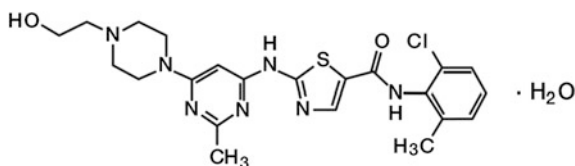
In malignancies, in which BCR-ABL is not the critical kinase, the role of dasatinib has still to be defined. Dasatinib inhibits the c-KIT receptor tyrosine kinase, which is involved in proliferation, differentiation, and survival of cells. Activating mutations of c-KIT are associated with different human neoplasms, including the majority of patients with systemic mast cell disorders, acute myelogenous leukemia (AML), and gastrointestinal stromal tumors (GISTs). Gain-of-function mutations of c-KIT are inhibited by dasatinib (Schittenhelm et al. 2006). Clinical studies to explore the clinical relevance of c-KIT inhibition by dasatinib are underway in acute myeloid leukemia.

SRC family kinases, involved in signal transduction, are potently inhibited by dasatinib. The drug blocks cell duplication, migration, and invasion, and it triggers apoptosis of tumor cells. It also diminishes metastatic spread of tumor cells and acts on the tumoral microenvironment. In addition, it sensitizes and resensitizes tumor cells to chemotherapy, antiangiogenic, antihormonal, or epidermal growth factor receptor (EGFR) inhibitor therapy (Montero et al. 2011). The effect of dasatinib monotherapy in clinical trials is modest. Many clinical studies with dasatinib in solid tumors in different treatment lines and combinations are ongoing. Results are summarized in this review.

2 Structure and Mechanism of Action

Dasatinib (former BMS 354825), or *N*-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide monohydrate (C22H26ClN7O2S), is an orally available small-molecule multitargeted kinase inhibitor (Fig. 1). Dasatinib was discovered by and named after Jagabandhu Das (Lombardo et al. 2004; Das et al. 2006) as part of an effort to develop potent inhibitors of SRC family kinases (SFKs).

The compound targets the SRC family of kinases (SRC, LCK, HCK, YES, FYN, FGR, BLK, LYN, FRK). In addition, and clinically more significant, dasatinib inhibits BCR-ABL with greater potency compared to other BCR-ABL inhibitors.

Fig. 1 Chemical structure of dasatinib**Table 1** Inhibitory activity of dasatinib on selected tyrosine kinases and potential clinical applications

Kinase	IC ₅₀ (nmol)	Neoplasias
<i>Nonreceptor tyrosine kinases</i>		
ABL	0.6	CML, Ph+ ALL
SRC	0.5	Several tumors, hematopoietic neoplasias
BTK	5	CLL, B-cell lymphomas
TEC	14	
<i>Receptor tyrosine kinases</i>		
c-kit	5–10	GIST, CML, breast cancer, AML, systemic mastocytosis
Ephrin A2 receptor kinase	17	Breast cancer, lung cancer
PDGFR-β	4	GIST, breast cancer, head and neck cancer chronic eosinophilic leukemia, hypereosinophilic syndrome

It also inhibits receptor tyrosine kinases (c-KIT, PDGFR, DDR1 and 2, c-FMS, ephrin receptors) and TEC family kinases (TEC and BTK) (Table 1).

Preclinical studies suggest that dasatinib induces apoptosis in only a small subset of cell lines. Inhibition of migration, invasion, and cell adhesion by dasatinib is reported more frequently (Johnson et al. 2005; Nam et al. 2005; Serrels et al. 2006). It has been demonstrated that dasatinib induces defects in spindle generation, cell cycle arrest, and centrosome alterations in leukemic cells, tumor cell lines, and also in normal cells. These effects are not attributable to the inhibition of a single kinase; rather it is expression of nonspecific effects on multiple kinases (Fabarius et al. 2008).

In a nude mouse model of prostate cancer, tumor growth and the development of lymph node metastasis were inhibited by dasatinib (Park et al. 2008). In addition, Dasatinib acts also on the tumoral microenvironment, especially in bone, where dasatinib inhibits osteoclastic activity and favors osteogenesis, exerting a bone-protecting effect (Metcalf et al. 2002).

Although immunosuppressive effects were initially observed in preclinical studies of dasatinib, recent evidence suggests that dasatinib may activate and mobilize antileukemic immune responses which may improve efficacy. These immunomodulatory effects may also be implicated in the clinically relevant side effects observed with dasatinib treatment (Mustjoki et al. 2010; 2011; 2013; Kreutzman et al. 2010; 2011).

3 Preclinical Data

3.1 Inhibition of ABL

Abelson kinase (ABL) is the constitutively active tyrosine kinase of the BCR-ABL fusion protein. It is a cytoplasmic nonreceptor tyrosine kinase. Human ABL has a number of structural domains critical for its activity. The major isoform of c-ABL has three SRC homology (SH) domains. SH1 domain contains the tyrosine kinase activity, while SH2 and SH3 domains allow interaction with other proteins. Under normal conditions, the activity of the ABL tyrosine kinase is tightly regulated.

Like many tyrosine kinases, ABL regulates its catalytic activity via conformational changes, switching between active and inactive forms by opening and closing an activation loop. The sequence available for binding in the inactive conformation varies dramatically between different kinases and provides a potential for binding specificity.

As demonstrated by X-ray crystallography, dasatinib, unlike imatinib, nilotinib, and ponatinib, binds the ATP-binding pocket of the SH domain 1 of BCR-ABL in both the active and inactive conformations (Tokarski et al. 2006; Vajpai et al. 2008; O'Hare et al. 2005; 2009; Weisberg et al. 2005; Levinson and Boxer 2012; Zhou et al. 2011; Radaelli et al. 2009; Cortes et al. 2010a).

Dasatinib has been shown to be 325-fold more potent than Imatinib for inhibiting unmutated BCR-ABL. The concentration required for 50 % inhibition [IC₅₀] is 0.6 nmol/L for dasatinib and 280 nmol/L for imatinib (O'Hare et al. 2005). It is suggested that this stronger binding activity of dasatinib over imatinib is at least partially due to its ability to bind to active and inactive conformations of the ABL protein.

Crystal structures of the inhibitors bound to ABL show that dasatinib has fewer interactions with the P-loop, the activation loop, and α -helix compared with imatinib (Tokarski et al. 2006). Mutations resistant to imatinib but sensitive to dasatinib can be found in these regions (Tokarski et al. 2006). This is the basis for the activity of the drug in imatinib-resistant disease, caused by mutated BCR-ABL. Dasatinib demonstrates activity against most imatinib-resistant BCR-ABL mutations (Karaman et al. 2008; Shah et al. 2004; Branford et al. 2009).

Based on in vitro assays, outcomes in patients treated with second-line dasatinib after developing a BCR-ABL mutation on imatinib, and emergence of mutations during dasatinib treatment, dasatinib has little or no activity against T315I/A

F317L/I/C/V, or V299L, and lower activity against Q252H, E255V/K, and possibly G250E (O'Hare et al. 2005; Redaelli et al. 2009; Branford et al. 2009; Hochhaus et al. 2012a; Müller et al. 2009; Soverini et al. 2009; Shah et al. 2007; Cortes et al. 2007b).

ABL inhibition has a role also in chronic lymphocytic leukemia (CLL). Resistance to alkylating agents in CLL cells is accompanied by relatively high ABL levels. Dasatinib, through inhibition of ABL, sensitizes CLL cells to chlorambucil and fludarabine (Amrein et al. 2008). In addition, CD40-induced anti-apoptotic pathways in CLL are mediated by LYN (Ren et al. 1994) and ABL (Hallaert et al. 2008). Since ABL and LYN are targets for dasatinib, the drug is expected to be active in CLL. Clinical trials with dasatinib in CLL so far have shown only moderate activity (Amrein et al. 2011).

3.2 Inhibition of SRC

SRC is a member of a nine-gene family that includes YES, FYN, LYN, LCK, HCK, FGR, BLK, and YRK.

SRC family kinases are membrane-associated and involved in signal transduction. They integrate and regulate signaling from multiple transmembrane receptor-associated tyrosine kinases, such as the EGFR receptor family or PDGFR.

SRC family kinases (SFK) consist of a unique NH2-terminal region, two SRC homology domains (SH2 and SH3), a highly conserved kinase domain, and a COOH-terminal tail containing a negative regulatory tyrosine residue. SRC and SFK cooperate in several cellular processes including migration, adhesion, invasion, angiogenesis, proliferation, differentiation, and immune function. They play a major role in the development, growth, progression, and metastasis of a wide variety of human cancers (Kopetz et al. 2007; Montero et al. 2011).

Elevated levels of SRC kinase activity and/or protein expression levels have been found in a variety of human epithelial cancers, including colon, breast, pancreatic and lung carcinomas, in brain tumors, but also in osteosarcomas and Ewing sarcomas. The levels of expression or activation generally correlate with disease progression.

Dasatinib inhibits SRC with an IC_{50} of 0.5 nmol/L (Lombardo et al. 2004). Inhibition of SRC activation by dasatinib can suppress tumor growth in human breast cancer cell lines, in human prostate cancer cells, in head and neck, in lung cancer, and in osteosarcoma cell lines (Johnson et al. 2005; Finn et al. 2007; Shor et al. 2007). Pathologic SRC family kinase activity may contribute to BCR-ABL-independent imatinib resistance in CML (Donato et al. 2003; Pene-Dumitrescu and Smithall 2010).

Nuclear translocation of EGFR is mediated by SRC family kinases and may contribute to acquired resistance to cetuximab in solid tumors. Dasatinib treatment of cetuximab-resistant lung cancer cell line samples was found to be associated with loss of nuclear EGFR and resensitization to cetuximab (Li et al. 2009). In a similar manner, SRC is involved in coordinating signaling from the steroid

receptors, including estrogen and androgen receptors. SRC inhibition may overcome endocrine resistance in hormonally driven cancers (Mayer and Krop 2010). Akin, dasatinib improves p53-mediated targeting of human acute myeloid stem cells by chemotherapy (Dos Santos et al. 2013).

Regarding the tumor microenvironment, SRC is involved in bone metabolism. Increased SRC activity has a net bone resorption result, as a consequence of inhibition of osteoclast generation, together with osteoclast stimulation (Metcalf et al. 2002; Garcia-Gomez et al. 2012).

3.3 Inhibition of KIT

KIT (CD117) is a 145-kD transmembrane glycoprotein, which is a member of the type III receptor tyrosine kinase family. Following ligand binding, the receptor dimerizes, is phosphorylated, and activates downstream signaling pathways involved in proliferation, differentiation, and survival. Normally, c-KIT is activated when bound to its ligand, the stem cell factor (SCF). Ligand-independent activation of c-KIT can be caused by gain-of-function mutations that have been reported in several malignancies, including GIST (Hirota et al. 1998), systemic mastocytosis (SM), acute myeloid leukemia (AML) especially core binding factor-AML (CBF-AML), lymphomas, and germ cell tumors (Schittenhelm et al. 2006). Imatinib, which is a potent inhibitor of KIT, has become the treatment of choice for advanced GIST. Comparable with its binding properties to ABL, imatinib only binds the inactive conformation of KIT.

Imatinib-resistant KIT mutants are frequent and often occur in the activation loop of KIT, resulting in a constitutive active conformation of c-KIT, to which imatinib cannot bind. These mutations have relevance in mast cell disorders, seminoma, and AML and are always resistant to imatinib. Dasatinib inhibits c-KIT 10–20-fold stronger than imatinib with an IC_{50} for inhibition of autophosphorylation and cellular proliferation of 5–10 nmol/L (Schittenhelm et al. 2006). In addition, dasatinib is a potent inhibitor of many clinically relevant mutated forms of c-KIT, including imatinib-resistant KIT activation loop mutations in vitro (Shah et al. 2006). In core binding factor (CBF)-AML, KIT mutations cluster most frequently within exon 17, which encodes the KIT activation loop in the kinase domain. In addition, CBF-AML is characterized by a higher KIT expression compared with other AML subgroups (Bullinger et al. 2004). Clinical trials with dasatinib in CBF-AML are ongoing.

3.4 Inhibition of Platelet-Derived Growth Factor Receptor (PDGFR) α and β Tyrosine Kinases

PDGFR- α and PDGFR- β are receptor tyrosine kinases. They are activated by binding of platelet-derived growth factor (PDGF). PDGF-signaling has a significant role in the formation of connective tissue and is also important during wound

healing in the adult. PDGFR- α and PDGFR- β are expressed mainly on fibroblasts and smooth muscle cells (Heldin and Westmark 1999). Dasatinib inhibits PDGFR- β with an IC_{50} of 4 nmol/L (Chen et al. 2006).

PDGFR- α tyrosine kinase activating mutations have been described in the pathogenesis of some GISTs (Heinrich et al. 2003). Fusion proteins consisting of the fibroblast growth factor receptor 1 (FGFR1) and PDGFR- α and PDGFR- β receptor tyrosine kinases have constitutive transforming activity. They are found in a subgroup of myeloproliferative disorders associated with eosinophilia (Cross and Reiter 2008). In intima sarcoma, amplification of PDGFR- α is a common finding. Dasatinib was shown to inhibit PDGFR- α in intima sarcoma in vitro (Dewaele et al. 2010).

3.5 Inhibition of Ephrin Receptor Tyrosine Kinases

The ephrin family of receptor tyrosine kinases constitutes the largest subfamily of receptor tyrosine kinases. They are divided into two subclasses (ephrin A and ephrin B) based on sequence similarity and their preferential binding to ligands, which are tethered to the cell surface either by a glycosylphosphatidylinositol-anchor (ephrin A) or by a single transmembrane domain (ephrin B) (Kullander and Klein 2002). Eph receptor tyrosine kinases have important functions in development and diseases. In tumorigenesis, they have been implicated in cellular transformation, metastasis, and angiogenesis. EphA2 is frequently overexpressed and functionally altered in many invasive cancers including metastatic melanoma, as well as cancers of the mammary gland, cervix, ovary, prostate, colon, lung, kidney, esophagus, and pancreas.

Dasatinib was shown to be a potent inhibitor of ephrin A2 receptor kinase with an IC_{50} of 17 nmol/L in various cell lines (Huang et al. 2007; Chang et al. 2008).

3.6 Inhibition of TEC Family Kinases and BTK

TEC kinases are a large group of nonreceptor TKs and are closely related to SRC and ABL. TEC kinases play a pivotal role in the development and signaling of hematopoietic cells (Smith et al. 2001). Bruton tyrosine kinase (BTK) is a member of the TEC family kinases with a well-characterized role in B-cell receptor signaling and B-cell activation. Dasatinib has been shown to inhibit BTK with an IC_{50} of 5 nM and TEC with an IC_{50} of 14 nM (Hantschel et al. 2007). The irreversible strong BTK inhibitor ibrutinib, former PCI-32765, with an IC_{50} of 0.5 nM (Pan et al. 2007) has been shown to be very effective in CLL in a phase I–II clinical trial (Byrd et al. 2013). Clinical trials with dasatinib in CLL are ongoing.

4 Clinical Data

4.1 Pharmacokinetic Profile

Dasatinib is administered orally. The drug is rapidly absorbed, peak plasma concentrations occur 0.5–3 h after administration. The intake of food is not relevant for pharmacokinetics of dasatinib. In a dose range of 25–120 mg twice daily, the area under the plasma concentration–time curve (AUC) increased proportionally. The drug is extensively metabolized in the liver, predominantly by cytochrome P 450 (CYP) 3A4, only 30 % remain unchanged. The metabolites of the compound are unlikely to play a pharmacologic role. There were linear elimination characteristics over the above-mentioned dose range with a terminal elimination half-life of 5–6 h.

Elimination occurs mostly in the feces (85 %) only little in urine (4 %). Dasatinib is excreted as metabolites, only 19% of a dose was recovered as unchanged drug in the feces (Sprycel[®] BMS 2012).

4.2 Clinical Trials with Dasatinib

More than 200 clinical trials in almost all tumor entities have been performed so far with dasatinib, about 70 are still ongoing. Dasatinib treatment is most effective in the BCR-ABL-driven diseases CML and Ph+ ALL. Dasatinib is approved for the treatment of all phases of CML and Ph+ ALL, and therefore, treatment of these diseases will be discussed in more detail, followed by an overview of trials in other malignancies.

4.3 Clinical Trials with Dasatinib in CML Patients: Overview

The clinical efficacy of dasatinib in CML patients resistant or intolerant to imatinib was assessed in a phase I trial (Talpaz et al. 2006). Five phase II trials, termed START (SRC-ABL Tyrosine kinase inhibition Activity Research Trials), were consecutively performed in all phases of CML in patients resistant or intolerant to imatinib (Kantarjian et al. 2007; Hochhaus et al. 2007; Ottmann et al. 2007; Guilhot et al. 2007a; Cortes et al. 2007a).

Dose-optimization phase III trials have been performed in chronic phase CML (Shah et al. 2008a) and in advanced phases of the disease (Kantarjian et al. 2009b, Saglio et al. 2010).

First-line treatment of CML patients with dasatinib was assessed in two phase II trials (Pemmaraju et al. 2011; Radich et al. 2012) and one phase III trial (Kantarjian et al. 2010; 2012).

4.3.1 Phase I Clinical Trial of Dasatinib in CML, All Phases and Ph+ ALL

The efficacy of oral dasatinib was first assessed in a phase I, open-label, dose-escalation study. Patients ($n = 84$) with various phases of CML or Ph+ ALL intolerant or resistant to imatinib, received oral dasatinib (15–240 mg/d) once or twice daily in 4-week treatment cycles (Talpaz et al. 2006). Dasatinib had clinical activity in all CML phases and Ph+ ALL. Complete hematologic response (CHR) was achieved in 92 % of patients (37/40) with CML-CP, and major hematologic response (MHR) was seen in 70 % of patients (31/44) with CML-AP, CML-BP, or Ph+ ALL. The rates of major cytogenetic response (MCyR) were 45 % in patients with CML-CP (18/40) and 43 % in patients with CML-AP (19/44), CML-BP, or Ph+ ALL. Of note, imatinib-associated side effects including muscle cramps and nausea were infrequently observed with dasatinib and patients intolerant to imatinib did not have recurrence of the same nonhematologic adverse events (AEs) (e.g., rash and liver-function abnormalities) with dasatinib treatment. The major AE associated with dasatinib was reversible myelosuppression.

4.3.2 Phase II Clinical Trials in Chronic Phase CML

A series of phase II trials, the pivotal START trial program, followed the phase I dose-escalation study. The primary objective for these trials was to treat patients with resistance or intolerance to imatinib treatment and who therefore had a life-threatening medical need. As the pharmacokinetics of the dasatinib 70 mg twice-daily regimen were better understood, it was selected for these trials. These open-label, multicenter trials established the efficacy and safety of second-line dasatinib (70 mg twice-daily) in the treatment of imatinib-resistant or imatinib-intolerant patients with CML (all phases) or Ph+ ALL (Table 2). Data from this program led to the initial approval of dasatinib in these indications.

Two START studies assessed second-line dasatinib 70 mg twice daily in patients with CML-CP. START-C trial was a single-arm study and START-R was a randomized, parallel-arm study of dasatinib versus high-dose imatinib (800 mg/day) in patients resistant to standard dose imatinib (Hochhaus et al. 2008; Kantarjian et al. 2009c). In START-C ($n = 387$), dasatinib-induced MCyR (primary endpoint) in 62 % of patients after a minimum follow-up of 24 months (Mauro et al. 2008). The corresponding CCyR rate was 53 %. In START-R, rates of MCyR were 53 % in the dasatinib 70 mg twice daily arm ($n = 101$) and 33 % in the high-dose imatinib arm ($n = 49$) ($P = 0.017$) after a minimum follow-up of 24 months (Kantarjian et al. 2009a). CCyR rates were 44 and 18 %, respectively ($P = 0.0025$). Although no formal statistical comparison between the study arms was planned, the data are suggestive of better efficacy for dasatinib compared with imatinib (Kantarjian et al. 2009a). These responses were also durable, as a pooled analysis ($n = 387$) of the START-C and START-R studies showed that 90 % of patients achieving a CCyR maintained this level of response after 24 months (Baccarani et al. 2008).

Table 2 Efficacy of dasatinib in chronic phase CML second line

Trial	No. patients/ Type of treatment	CHR (%)	MCyR (%)	CCyR (%)	MMR (%)	OS	PFS (%)	Reference
START-C ^a	387 (dasatinib 70 mg BID)	90	62	53	–	94 %	80	Hochhaus et al. (2008)
START-R ^a	101 (dasatinib 70 mg BID)	93	53	44	29	nr	86	Kantarjian et al. (2009c)
	49 (high-dose imatinib 400 mg BID)	82	33	18	12	nr	65	
CA180-034 ^a	167 (dasatinib 100 mg QD)	92	63	50	37	71 % ^b	49 ^b	Shah et al. (2008a), (2010), Rea et al. (2012)
	168 (dasatinib 70 mg BID)	88	61	53	43	70 % ^b	47 ^b	
	167 (dasatinib 140 mg QD)	87	63	50	42	77 % ^b	40 ^b	
	168 (dasatinib 50 MG BID)	92	61	49	41	74 % ^b	51 ^b	

QD once daily; BID twice daily, CHR complete hematologic remission, MCyR major cytogenetic response: $\leq 35\%$ Ph+ cells in metaphase in bone marrow, CCyR complete cytogenetic response: 0% Ph+ cells in metaphase in bone marrow, MMR major molecular response: defined as a BCR-ABL transcript level of 0.1 % or lower, corresponding to a reduction in the BCR-ABL transcript level by at least 3 log from the standardized baseline level, OS overall survival, PFS progression-free survival, ^aat 2-year follow-up, ^bat 6-year follow-up

4.3.3 Dose-Optimization Study

The recommended starting dose for dasatinib in patients with CML in chronic phase is 100 mg once daily (Sprycel[®] BMS 2012; EMA 2012). This dose is the result of a phase III dose-optimization study (NCT00123474; CA180-034) showing that 100 mg once daily was associated with similar efficacy as the twice daily regimen, but with a reduction in toxicity (Shah et al. 2008a). The rationale for this study was based on observations from the phase I study that once-daily and twice-daily dose schedules were associated with similar response rates (Talpez et al. 2006). Although dasatinib has a half-life of 3–5 h (Sprycel[®] BMS 2012), transient exposure of CML cell lines to dasatinib has been demonstrated to induce apoptosis (Shah et al. 2008b), supporting once-daily dosing. Furthermore, due to dose reductions in the START-C and START-R studies, the median total daily dose delivered to patients approximated 100 mg/day (Hochhaus et al. 2007; Kantarjian et al. 2007). It was therefore proposed to compare the 100 mg once schedule with other schedules. In this dose-optimization study, patients ($n = 670$) were randomized to receive dasatinib at 100 mg once daily ($n = 167$), 140 mg once daily ($n = 167$), 50 mg twice daily ($n = 168$), or 70 mg twice daily ($n = 168$) (Shah et al. 2008a) (Table 2). After a minimum follow-up of 2 years,

rates of CCyR and MMR were similar across the different dosing schedules (CCyR 50–54 %; MMR 37–38 %) (Shah et al. 2010). In the 100 mg once daily arm, the 24-month rates of CCyR and MMR were 50 and 37 %, respectively. Rates of progression-free survival (PFS), overall survival (OS), and transformation to AP/BP by 24 months were 80, 91, and 3 %, respectively. The 100 mg once daily arm was associated with improved safety. Rates of all-grade pleural effusion ($P = 0.049$), grade ≥ 3 thrombocytopenia ($P = 0.003$), all-grade neutropenia ($P = 0.034$), and all-grade leukocytopenia ($P = 0.017$) were significantly lower for patients treated with dasatinib 100 mg once daily compared with other schedules (Shah et al. 2010). After a minimum follow-up of 6 years, PFS, OS, and rates of transformation to AP/BP were 49, 71, and 5 %, respectively, in the 100 mg once daily arm (Shah et al. 2012).

4.3.4 First-Line Treatment of CML with Dasatinib

First-line treatment of CML with dasatinib was investigated in the MDACC phase II trial (Pemmaraju et al. 2011), one phase III study (Kantarjian et al. 2010; 2012), and a second randomized phase II trial, the SWOG S0325 study (Radich et al. 2012) (Table 3).

The first trial investigating dasatinib as first-line treatment was a phase II, open-label study (Cortes 2010b). Patients with newly diagnosed CML-CP were randomized to receive dasatinib 100 mg once daily ($n = 66$) or 50 mg twice daily ($n = 33$) (Pemmaraju et al. 2011). Because of results from a phase III multinational randomized study of first-line dasatinib (discussed in the previous section) and trends in favor of the 100 mg once-daily schedule of dasatinib seen in this study, the 50 mg twice daily arm of this trial was closed after 66 patients were enrolled and all subsequent patients were randomized to the 100 mg once daily arm. The study continued with the once daily schedule (Cortes et al. 2010b; Pemmaraju et al. 2011). After a median follow-up of 29 months, in patients with ≥ 3 months follow-up ($n = 87$), rates of CCyR and MMR were 95 and 86 %, respectively. BCR-ABL levels of ≤ 0.0032 % (≥ 4.5 log reduction; $MR^{4.5}$) were achieved in 67 % of patients. Responses were achieved rapidly with 94 and 95 % of patients achieving a CCyR after 6 and 12 months, respectively. Similarly, MMR rates at 6 and 12 months were 68 and 73 %, respectively. These data compare favorably with historic response data for imatinib (Pemmaraju et al. 2011).

Dasatinib in the first-line setting was further investigated in the pivotal, open-label, multinational, randomized phase III trial of Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION) (Kantarjian et al. 2010). In this study, 519 patients newly diagnosed with CML-CP were randomized to receive dasatinib 100 mg once daily ($n = 259$) or imatinib 400 mg once daily ($n = 260$) (Kantarjian et al. 2010). Efficacy data are shown in Table 4. The primary endpoint of this study was confirmed CCyR (cCCyR; CCyR on two consecutive assessments) by 12 months. For the dasatinib versus imatinib arms, the rate of cCCyR by 12 months was 77 versus 66 % ($P = 0.007$), respectively (Kantarjian et al. 2010). Cumulative CCyR, MMR, and $MR^{4.5}$ rates were higher for dasatinib across a

Table 3 Efficacy of dasatinib in chronic myeloid leukemia as first-line treatment

Trial	n	Treatment	CHR	CCyR (%)	MMR (%)	OS (%)	PFS (%)	Reference
MDACC	31	Dasatinib 50 mg BID	98 %	95	73	100	100	Pemmaraju et al. (2011)
(3-year follow-up)	62	Dasatinib 100 mg QD						
DASISION	295	Dasatinib 100 mg QD	nr	80	64	95	94	Kantarjian et al. (2012)
(2-year follow-up)	265	Imatinib 400 mg QD	nr	74	46	95	92	
SWOG-S0325	123	Dasatinib 100 mg QD	81 %	84	59	97	93	Radich et al. (2012)
(3-year follow-up)	123	Imatinib 400 mg QD	82 %	69	44	97	90	

QD once daily, *BID* twice daily, *CHR* complete hematologic remission, *CCyR* complete cytogenetic remission, *MMR* major molecular response: defined as a BCR-ABL transcript level of 0.1 % or lower, corresponding to a reduction in the BCR-ABL transcript level by at least 3 log from the standardized baseline level, *OS* overall survival, *PFS* progression-free survival

24-month period ($P = 0.0002$, $P < 0.0001$, and $P = 0.002$, respectively) (Kantarjian et al. 2012). Responses to dasatinib were rapid and prolonged; median times to CCyR were 3.2 and 6.0 months and median times to MMR were 15 and 36 months in the dasatinib and imatinib arms, respectively (Kantarjian et al. 2012). At 24 months, for dasatinib versus imatinib, cumulative rates of MMR were 64 versus 46 % ($P < 0.0001$), rates for BCR-ABL ≤ 0.01 % (MR^4) were 29 versus 19 % ($P = 0.0053$), and rates of $MR^{4.5}$ were 17 versus 8 % ($P = 0.0032$) (Hochhaus et al. 2012a; Kantarjian et al. 2012). After 2-year follow-up, transformation to AP/BP throughout study follow-up (including on study and after discontinuation) occurred in nine patients (3.5 %) receiving dasatinib and 15 (5.8 %) receiving imatinib (Hochhaus et al. 2012a; Kantarjian et al. 2012). At 2-year follow-up, survival data for this study remain immature. No difference was observed between dasatinib and imatinib for PFS (93.7 and 92.1 %) and OS (95.3 and 95.2 %). A small difference in failure-free survival for dasatinib versus imatinib was observed (including protocol defined progression; 91.2 vs. 87.8 %) (Hochhaus et al. 2012a; Kantarjian et al. 2012).

Rapid molecular responses were associated with lower transformation rates and better long-term outcomes. An early molecular response (BCR-ABL levels of ≤ 10 %) at 3 months was associated with lower transformation rates (dasatinib 1.5 vs. 8.1 %; imatinib 2.6 vs. 9.4 %), better long-term outcomes (24-month PFS: dasatinib 97 vs. 83 %, imatinib 96 vs. 85 %) and improved response (24-month MMR rates: dasatinib 76 vs. 16 %, imatinib 66 vs. 19 %) in both treatment arms (Hochhaus et al. 2012b). Deeper levels of response were achieved earlier with dasatinib compared with imatinib as equivalent BCR-ABL levels were achieved

Table 4 Efficacy of dasatinib second line after imatinib in phase II single-arm clinical studies in advanced stages of CML including blast crisis and Ph+ ALL (START trials)

Trial	Disease/ Phase	n	Follow-up (months)	Mutated BCR- ABL (% pts.)	Response (% of patients)				Survival		References	
					MHR	CHR	MCyR	CCyR	1 year PFS (%)	1 year OS (%)		Median PFS (mo)
Start-A	Accelerated phase	174	14.1		64	45	39	32	66	82	Guilhot et al. (2007a)	
Apperley et al. (2009)												
Start-B	Myeloid blast phase	109	>12	42	34	27	33	26		6.7	11.8	Cortes et al. (2008)
Start-L	Lymphoid blast phase	49	>12	65	35	29	52	46		3.0	5.3	Cortes et al. (2008)
Start-L	Ph+ ALL	46	>12	78	41	35	57	54			3	Porkka et al. (2007)
Ottmann et al. (2007)												

CHR complete hematologic response: normal white blood cell count, platelets <450.000/ μ l, no blasts or promyelocytes in peripheral blood, <5 % myelocytes and metamyelocytes in peripheral blood, normal basophil count, no extramedullary involvement, MHR major hematologic response: CHR or neutrophil count between 500 and 1,000/ μ l, and/or platelets between 20.000 and 100.000/ μ l. MCyR major cytogenetic response: <= 35 % Ph+ cells in metaphase in bone marrow, CCyR complete cytogenetic response: 0 % Ph+ cells in metaphase in bone marrow, PFS progression-free survival, OS overall survival

6 months earlier with dasatinib and a higher proportion of patients receiving dasatinib achieved BCR-ABL levels of $\leq 10\%$ at 3 months compared with patients receiving imatinib (84 vs. 64 %) (Hochhaus et al. 2012b; Saglio et al. 2012).

In total, 23 % of dasatinib-treated patients and 25 % of imatinib-treated patients discontinued treatment in DASISION; 5 and 7 % due to study-defined disease progression (defined as any of the following: doubling of white cell count to $>20 \times 10^9/L$ in absence of CHR; loss of CHR; increase in Ph-positive metaphases to $>35\%$; transformation to AP/BP; death from any cause), 3 and 4 % due to treatment failure, and 7 and 5 % due to drug-related AEs, respectively (Kantarjian et al. 2012). In patients who discontinued treatment, BCR-ABL mutations were found in 10 patients in each arm with a narrower spectrum of mutations seen with dasatinib versus imatinib (three versus nine different amino acids affected). Mutations associated with discontinuation in the dasatinib arm were T315I ($n = 7$), F317L ($n = 2$), and F317I/V299L ($n = 1$) (Kantarjian et al. 2012).

Similar levels of response have been observed in additional studies of first-line dasatinib. In the SWOG S0325 phase II study, newly diagnosed patients were randomized to receive dasatinib 100 mg once daily ($n = 123$) or imatinib 400 mg once daily ($n = 123$) (Radich et al. 2012). At 12 months, median reductions in BCR-ABL transcript levels were greater with dasatinib compared with imatinib (3.3 vs. 2.8 log, $P = 0.063$), as were the rates of >3 -log BCR-ABL reductions (59 vs. 44 %, $P = 0.059$). Rate of CCyR was significantly different between the dasatinib and imatinib arms (84 and 69 %, respectively, $P = 0.040$), although cytogenetic responses were only assessed in 53 % of patients (Radich et al. 2012).

In the phase II OPTIM study, association of dasatinib (100 mg once daily) pharmacokinetics with safety and response is being investigated. Dose adjustments were made as needed to achieve optimal minimal dasatinib concentrations (C_{\min}) in order to reduce the rates of AEs. Interim data for the first 125 patients are available (Rousselot et al. 2012). For all patients enrolled with at least 12 months follow-up, the rates of CCyR at 3, 6, and 12 months were 60, 82, and 95 %, and rates of MMR were 21, 46, and 62 %, respectively. At 12 months, the rate of MR^{4.5} was 25 %, of which 80 % had undetectable BCR-ABL transcript levels (Rousselot et al. 2010; 2012).

4.3.5 Treatment of Advanced Stages of CML

Three studies out of the START program, assessing dasatinib in imatinib-resistant disease, were dedicated to advanced stages of CML. START-A, START-B, and START-L were single-arm studies of second-line dasatinib 70 mg twice daily in patients with CML-AP, CML-BP, and CML-BP/Ph+ ALL, respectively (Apperley et al. 2009; Guilhot et al. 2007b; Cortes et al. 2008; Porkka et al. 2007; Ottmann et al. 2007; Saglio et al. 2008). In the START-A trial, including 174 patients with CML in accelerated phase (CML-AP), after a median follow-up of 14.1 months, 64 % of patients achieved the primary endpoint of MHR (Apperley et al. 2009). START-B included patients with myeloid blast phase (CML-BP) ($n = 109$) and START-L included patients with lymphoid CML-BP ($n = 48$) and a subset of

patients with Ph+ ALL (Cortes et al. 2008; Porkka et al. 2007; Ottmann et al. 2007). After a minimum follow-up of 24 months, a CHR was achieved in 26 % of patients with myeloid CML-BP, in 29 % of patients with lymphoid CML-BP, and in 35 % of patients with Ph+ ALL. The median overall survival in myeloid blast phase, lymphoid blast phase, and Ph+ ALL was 11.8 months, 5.3 months, and 3 months, respectively (Table 4).

A phase III dose-optimization study in patients with CML-AP (Kantarjian 2009b) and CML-BP (Saglio et al. 2010) led to a recommended dasatinib dose of 140 mg once daily in these indications (Sprycel® BMS 2012; EMA 2012). Patients were randomized to receive dasatinib 70 mg twice daily ($n = 159$, AP; $n = 74$, myeloid BP; $n = 28$, lymphoid BP) or 140 mg once daily ($n = 158$, AP; $n = 75$ MBP; $n = 33$, LBP). In patients with CML-AP, similar rates of MHR (68 vs. 66 %) and MCyR (43 vs. 39 %) were observed in both treatment arms after a median follow-up of 15 months. Significantly fewer patients in the once-daily arm had pleural effusion compared with the twice-daily arm ($P < 0.001$) (Kantarjian et al. 2009b). After 2 years of follow-up, for patients with myeloid BP, the MHR rates in both arms were 28 %; for those with lymphoid BP, the corresponding rates were 42 % in the once-daily arm and 32 % in the twice-daily arm. AE rates were suggestive of improved safety for dasatinib 140 mg once daily (Saglio et al. 2010).

4.4 Dasatinib in Ph+ Acute Lymphoblastic Leukemia (Ph+ ALL)

The effect of dasatinib in the treatment of Ph+ ALL was examined further in two phase II studies. Two more phase III studies with dasatinib in children with PH+ ALL are still active.

One phase II study in adults evaluated the combination of dasatinib with alternating hyper-CVAD (hyper-fractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone) and high-dose cytarabine and methotrexate. Dasatinib was administered for the first 14 days of 8 cycles.

Thirty-five patients were treated with a median age of 53 years and 94 % of them achieved complete remission, whereas two patients died due to infections before the evaluation of response. Twenty-seven patients achieved a cytogenetic response after the first cycle, whereas four patients had persistent Ph+ metaphases. Twenty patients achieved complete molecular remission at a median of 14 weeks, and additional seven patients achieved a MMR at a median time of 11 weeks. Monitoring of residual disease was negative by flow cytometry in 29 of 33 patients at a median of 3 weeks. After a median follow-up of 14 months, median disease-free survival and median OS were not reached with an estimated 2-years OS of 64 % (Ravandi et al. 2010). Side effects included 16 episodes of bleeding and 8 episodes of pleural effusions, in addition infections, deep vein thrombosis and pulmonary emboli, diarrhea and metabolic abnormalities.

In a second study, dasatinib as single agent was combined with steroids for 84 days and free post-remission therapy (Foa et al. 2011). Of 53 evaluable patients, all achieved complete hematologic remission, of which 92.5 % at day 22 and at this time point, 10 patients achieved 3-log reduction in the BCR-ABL transcript. Twenty-months OS and DFS were 69 and 51 %, with better results in terms of DFS for patients who showed a molecular response at day 22. No deaths or relapses occurred during induction therapy: 23 out of 53 patients relapsed after completing induction and of these 12 with the T315I mutation, resistant to most TKIs. Overall, treatment was well tolerated: four patients discontinued due to toxicity (only one case of pleural effusion grades 1–2). Another case of pleural effusion was recorded in one patient who continued therapy with the drug (Foa et al. 2011).

Central nervous system disease of Ph+ blast phase CML or Ph+ ALL

Substantial activity of dasatinib in patients with Ph+ ALL or blast phase CML and central nervous system (CNS) involvement has been shown. Eleven adult and pediatric patients were treated with dasatinib as first-line treatment for CNS leukemia, whereas three patients experienced a CNS relapse while on dasatinib therapy for other reasons. All of the eleven patients responded with seven complete responders, four after dasatinib monotherapy. Three patients achieved a partial response. Responses were generally durable, and response durations of more than 26 months have been reported (Porkka et al. 2008).

4.5 Dasatinib in Philadelphia-Chromosome-Negative Acute and Chronic Myeloid Diseases, Including Systemic Mastocytosis

Few studies have been reported with dasatinib in Philadelphia-chromosome-negative myeloid diseases. The largest study included a total number of 67 patients, with various hematologic disorders including 33 patients with SM, nine patients with AML, six patients with myelodysplastic syndromes, five patients with hypereosinophilic syndrome (HES), three patients with chronic eosinophilic leukemia (CEL), and 11 patients with primary myelofibrosis (PMF) (Verstovsek et al. 2008).

Most patients with SM presented with the D816V KIT mutation, which confers imatinib resistance. Since dasatinib has been shown to be active against the KIT D816V mutation in vitro, activity of the drug in SM was expected. The D816V was present in 28 of the 33 patients with SM. Patients were treated with dasatinib with different doses and schedules. In SM patients, an overall response rate of 33 % was reported, mostly symptomatic improvements including two complete responses, none of them with the D816V.

The authors concluded that it is questionable, whether the use of dasatinib provides any advantage over other treatment options in SM and that dasatinib therapy does not seem to have significant activity in patients with MDS, PMF, and HES/CEL (Verstovsek et al. 2008).

Table 5 Summary of phase II trials with dasatinib in hematologic malignancies other than CML and Ph+ ALL

Indication	No. of pts	Treatment	Outcome	Reference
Ph- acute and chronic myeloid disease, including systemic mastocytosis	67	Dasatinib 140 mg	Overall response rate in systemic mastocytosis 33 %	Verstofsek et al. (2008)
	33 with systemic mastocytosis		CR in AML and hyper-eosinophilic syndrome, no responses in MDS and myelofibrosis	
CLL	13	Dasatinib 50 mg twice daily	1 SD for 12 weeks	Garg et al. (2008)
CLL	15	Dasatinib 140 mg	PR in 3 of 15 Pts Additional 5 Pts with clinical response	Amrein et al. (2011)
High-risk MDS	18	Dasatinib 100 mg	3 PR	Duong et al. (2008)
			4 SD 10 progressive disease	

However, complete remissions were reported in the same study for a patient with HES, and one patient with AML. The patient with HES had a complex karyotype with an aberrant signaling via PDGFR- β . The patient with AML was KIT mutation positive.

An additional case with HES, characterized by the FIP1L1-PDGFR- α gene fusion, intolerant to imatinib was successfully treated with dasatinib 20 mg/day (Imagawa et al. 2011).

Patients with high-risk MDS have been treated with dasatinib monotherapy in another phase II clinical study. Few responses to dasatinib monotherapy were reported (Table 5). The authors conclude that the treatment was save but with only limited clinical efficacy (Duong et al. 2008).

4.5.1 Dasatinib in the Treatment of Chronic Lymphocytic Leukemia (CLL)

Dasatinib monotherapy has modest clinical activity in CLL, as shown in two phase II studies and one case report, documenting dasatinib-induced CR in a CLL-patient (Garg et al. 2008; Pittini et al. 2009; Amrein et al. 2011). Clinical trials, combining dasatinib with alkylating agents in CLL, are still ongoing. One study requires dasatinib sensitivity in vitro as an inclusion criterion (NCT01441882).

4.5.2 Dasatinib in the Treatment of Acute Myeloid Leukemia (AML)

Since mutated c-KIT is overexpressed in 26 % of core binding factor (CBF)-AML and dasatinib inhibits both mutated and unmutated forms of KIT, clinical studies

are ongoing evaluating dasatinib in CBF-AML. Individual cases have been reported so far with promising results (Ustun et al. 2009; Verstofsek et al. 2008). A phase II trial (NCT00850382) found beneficial effects by the addition of dasatinib to standard chemotherapy in CBF-AML. Based on these results, a phase III clinical trial in patients with CBF-AML is ongoing, randomizing patients to standard AML therapy with or without addition of dasatinib. Patients in the dasatinib arm will receive one year of dasatinib maintenance treatment.

4.6 Dasatinib in the Treatment of Solid Tumors

Up to now dasatinib is only approved for diseases where BCR-ABL is the critical kinase. Due to its ability to inhibit SRC family kinases and other kinases, dasatinib has been investigated in a huge number of phase I and phase II clinical trials in different cancers, few selected studies are summarized in Table 6. In Clinicaltrials.gov, more than 200 clinical trials with dasatinib are registered, with more than 70 studies still recruiting patients in various indications, the magnitude in solid tumors.

In summary, dasatinib as monotherapy has only modest activity in solid tumors. Combinations of dasatinib and other agents have been investigated intensively. Only few remissions have been reported in singular patients, even in combination with dasatinib and other treatments.

Since SRC is involved in bone metabolism and has the potency to resensitize tumor cells to antihormonal treatment, the SRC inhibitor dasatinib was expected to be effective in metastatic castration-resistant prostate cancer (CRPC). Results of a phase II clinical trial with dasatinib in combination with docetaxel have suggested clinical benefit with PSA decreases of more than 50 % from baseline for at least 6 weeks in almost half of the patients (Araujo et al. 2009, 2012).

Based on these data, the recently published multinational, double-blinded, placebo-controlled READY trial randomized 1,522 patients with metastatic CRPC 1:1 to receive either docetaxel 75 mg/m² every three weeks plus prednisone with dasatinib 100 mg every day ($n = 762$) or docetaxel plus prednisone with placebo ($n = 760$). The primary endpoint was overall survival (Table 7) (Araujo et al. 2013).

Despite the large number of patients, the study failed to show any significant improvement in dasatinib-treated patients with respect to overall survival, progression-free survival, or reduction of pain. Treatment-related AEs were more frequent in the dasatinib arm: 18 versus 9 % for placebo. Serious AEs were reported in 30 % of patients in both arms of the study. The rate of death occurring within 30 days of the last study drug was 10 % in the dasatinib arm versus 6 % in the placebo arm (Araujo et al. 2013). Results of this study were disappointing. Unselected patients with mCRPC did not have any advantage from the addition of dasatinib to standard treatment. The probability, that this would be the case in other cancers is fading, despite the large number of ongoing clinical trials. Eventually, there will be subgroups of patients with solid tumors, selected by appropriate biomarkers, benefitting from dasatinib.

Table 6 Clinical trials of dasatinib in solid tumors

Indication	Clinical phase	n	Treatment	Outcome	Reference
<i>Breast cancer</i>					
Advanced breast cancer	I	52	Capecitabine 1,000 mg/m ² , d1-14, Dasatinib 100 mg daily	Clinical benefit in 56 % of patients	Somlo et al. (2013)
Metastatic breast cancer	I	15	Paclitaxel weekly 80 mg/m ² for 3 weeks Dasatinib 120 mg daily	Of 13 assessable patients responses in 4 (31 %)	Fornier et al. (2011)
Advanced HER2-positive and/or hormone receptor-positive breast cancer	II	70	Dasatinib 70 mg twice daily	Of 69 Pts, 3 PR, 6 SD, all 9 hormone receptor-positive Limited single agent activity	Mayer et al. (2011)
Triple-negative breast cancer	II	43	Dasatinib 70 mg twice daily, initially 100 mg twice daily	Overall response rate 4.7 % Limited activity	Finn et al. (2011)
<i>Ovarian cancer</i>					
Ovarian or primary peritoneal carcinoma	II	35	Dasatinib 100 mg	No objective responses	Schilder et al. (2012)
Advanced or recurrent ovarian cancer	I	20	Paclitaxel 175 mg/m ² , Carboplatin AUC 6, Dasatinib 150 mg	Remission rate 40 %, SD 50 %, PFS 7.8 months, OS 16.2 months	Secord et al. (2012)
<i>Colorectal cancer</i>					
Advanced colorectal cancer, first line	I	13	Capecitabine 850 mg/m ² , d1-14, every 3 weeks, oxaliplatin 130 mg/m ² , bevacizumab 7.5 mg/kg, Dasatinib 70 mg	3 PR, 6 SD,	Starodub et al. (2011) Strickler et al. (2011)
Previously treated metastatic colorectal cancer	II	19	Dasatinib monotherapy	No activity in metastatic colorectal cancer	Sharma et al. (2012)

(continued)

Table 6 (continued)

Indication	Clinical phase	n	Treatment	Outcome	Reference
<i>Lung cancer</i>					
Advanced nonsmall cell lung cancer, first line	II	34	Dasatinib 100 mg twice daily, later due to toxicity 100 mg-0-50 mg	Activity of dasatinib lower than that observed with chemotherapy, however marked activity in one patient and prolonged SD in 4 pts	Johnson et al. (2010)
Lung adenocarcinoma resistant to gefitinib or erlotinib	II	21	Dasatinib 70 mg twice daily	No activity in patients with EGFR-mutant adenocarcinoma resistant to erlotinib and gefitinib	Johnson et al. (2011)
Chemosensitive relapsed lung cancer	II	45	Dasatinib 70 mg twice daily	No activity	Miller et al. (2010)
Advanced nonsmall cell lung cancer	I/II	34	Erlotinib Dasatinib	Disease control rate 63 %	Haura et al. (2010)
<i>Glioma</i>					
Recurrent glioblastoma	I/II	26	CCNU 90-110 mg/m ² Dasatinib 100-200 mg	Significant hematologic toxicities, suboptimal exposure to both agents	Franceschi et al. (2012)
Recurrent malignant Glioma	I	47	Erlotinib 150-450 mg Dasatinib 180 mg	No radiographic responses, only one Pt SD after 6 months	Reardon et al. (2012)
<i>Melanoma</i>					
Advanced melanoma	II	39	Initial 100 mg twice daily, decreased to 70 mg twice daily	No activity	Kluger et al. (2011)
Melanoma	I	29	Dacarbazine 800 mg/m ² Dasatinib 70 mg twice daily	Objective responses in 13.8 % 12-month overall survival 34.5 %	Algazi et al. (2012)

(continued)

Table 6 (continued)

Indication	Clinical phase	n	Treatment	Outcome	Reference
<i>Prostate cancer</i>					
Castration-resistant prostate cancer	I/II	I: 16	Docetaxel 75 mg/m2 Q3 weeks	Durable 50 % PSA-decline in 26 of 46 Pts (57 %)	Araujo et al. (2012)
		II: 30	Dasatinib 100 mg	18 of 30 Pts with measurable disease PR	
<i>Other</i>					
Previously treated mesothelioma	II	46	Dasatinib 70 mg BID	No activity in mesothelioma	Dudek et al. (2012)
Head and neck squamous cell carcinoma	II	15	Dasatinib monotherapy	No remissions despite proven SRC inhibition	Brooks et al. (2011)

5 Toxicity

Dasatinib has a unique safety profile and since early clinical trials some AEs have been consistently reported in patients receiving dasatinib including myelosuppression, fluid retention, pleural effusion, gastrointestinal disorders, fatigue, headache, musculoskeletal disorders, rash, and infection (Table 8). Some bleeding events have also been reported. More recently, cases of pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH), have been reported in a small number of patients receiving dasatinib (Galie et al. 2009; McLaughlin et al. 2009; Fang et al. 2012). In clinical trials of first-line and second-line dasatinib, most AEs occurred within 12–24 months of treatment and were managed with dose modifications (Kantarjian et al. 2012; Shah et al. 2012; Sprycel® BMS 2012).

In the early phase I, open-label, dose-escalation study, the major AE was reversible myelosuppression, leading to dose interruption in 60 % of patients (Talpaz et al. 2006). Grade 3–4 neutropenia and thrombocytopenia were seen in 45 and 35 % of patients with CML-CP, respectively. Nonhematologic AEs included diarrhea, nausea, and peripheral edema. Treatment-related pleural effusion occurred in 13 % of patients with CML-CP (Talpaz et al. 2006). Rates of AEs in this study may be expected to be elevated as some patients received doses of dasatinib considerably higher than the current recommended dose of 100 mg once daily (range of dasatinib dose received: 15–240 mg/day). A maximum tolerated dose was not determined in this study and no patient withdrew from treatment as a result of toxic effects (Talpaz et al. 2006).

Table 7 Phase III study of dasatinib in combination with docetaxel and prednisolon in the treatment of metastatic castration-resistant prostatic cancer (mCRPC) (READY trial)

	Docetaxel–prednisolon– dasatinib	Docetaxel–prednisolon– placebo	HR
No. of patients	762	766	
Median overall survival	21.5 months	21.2 months	0.99
Overall response rate	31.9 %	30.5 %	
PFS	11.8 months	11.1 months	0.92
Median time to PSA progression	8.0 months	7.6 months	0.91
Pain reduction	66.6 %	71.5 %	

Median follow-up 19 months (Araujo et al. 2013)

In the following START-C phase II trial, in which patients with CML-CP received second-line dasatinib 70 mg twice daily, 9 % of patients discontinued treatment because of study-drug toxicity after 8 months of follow-up (Hochhaus et al. 2007). Cytopenias were common (grade 3/4: thrombocytopenia 47 %, neutropenia 49 %), but generally reversible and manageable with dose adjustments. Pleural effusion was observed in 19 % of patients (grade 3/4 in 3 %) (Hochhaus et al. 2007). Similar results were seen in the START-R phase II trial of dasatinib 70 mg twice daily (Kantarjian et al. 2007). After a median follow-up of 15 months, 28 % of patients had discontinued treatment, 16 % due to study drug intolerance. Cytopenias were common (grade 3/4: thrombocytopenia 56 %, neutropenia: 61 %) but reversible and manageable with dose modification. Pleural effusion occurred in 17 % of patients and was successfully managed with dose interruption, diuretics, or pulse steroid therapy (Kantarjian et al. 2007). Most cases of pleural effusion observed across the START studies were uncomplicated and resolved with temporary dose interruption, diuretics, or pulse steroid therapy. In the START-C and START-R trials, patients received dasatinib at 70 mg twice daily which is higher than the current recommended dose for CML-CP (100 mg once-daily). It may therefore be expected that the frequency of AEs and the rate of discontinuation due to study-drug intolerance might be higher than expected in these trials compared with patients receiving the current recommended dose for CML-CP.

A single institution analysis of 138 patients treated with dasatinib in the phase I dose-escalation study and phase II START trials showed that 29 % of patients with CML-CP developed pleural effusion (Quintás-Cardama et al. 2007). Patients receiving dasatinib 100 mg once daily had a lower incidence of pleural effusion compared with patients receiving 50 or 70 mg twice daily, or 140 mg once daily, while efficacy remained consistent across all four dosing schedules. Furthermore, a separate analysis indicated that intermittent dosing of dasatinib at 100 mg per day for five days per week, including a weekend drug holiday where dasatinib was not taken, led to reductions in the rate and severity of AEs including fluid retention and

Table 8 Adverse drug reactions reported $\geq 5\%$ in clinical trials ($n = 2,182$)

	All grades	Grades 3/4
<i>Gastrointestinal disorders</i>		
Diarrhea	32	4
Nausea	22	1
Vomiting	13	1
Abdominal pain	10	1
Gastrointestinal bleeding	8	4
Mucosal inflammation (including mucositis/stomatitis)	7	<1
Dyspepsia	5	0
Abdominal distension	5	0
<i>Respiratory, thoracic and mediastinal disorders</i>		
Pleural effusion	25	6
Dyspnoea	21	4
Cough	10	< 1
<i>Nervous system disorders</i>		
Headache	25	1
Neuropathy (including peripheral neuropathy)	6	<1
<i>Skin and subcutaneous tissue disorders</i>		
Skin rash	22	1
Pruritus	7	<1
<i>General disorders and administration site conditions</i>		
Superficial edema	21	<1
Fatigue	21	2
Pyrexia	13	1
Pain	7	<1
Asthenia	9	1
Chest pain	5	1
<i>Vascular disorders</i>		
Hemorrhage	15	2
<i>Musculoskeletal and connective tissue disorders</i>		
Musculoskeletal pain	14	1
Arthralgia	8	1
Myalgia	8	<1

(continued)

Table 8 (continued)

	All grades	Grades 3/4
<i>Infections and infestations</i>		
Infection (including bacterial, viral, fungal, nonspecific)	10	3
<i>Metabolism and nutrition disorders</i>		
Anorexia	9	<1
<i>Blood and lymphatic system disorders</i>		
Febrile neutropenia	5	5
Percent of patients		

pleural effusion while efficacy and disease control were maintained (La Rosée et al. 2013). An analysis of risk factors for pleural effusion in patients treated with second-line dasatinib identified prior history of cardiac disease ($P = 0.02$), hypertension ($P = 0.01$), and twice daily dosing schedule ($P = 0.05$), was associated with an increased risk of pleural effusion (Quintás-Cardama et al. 2007). In a separate analysis, older age was the only baseline characteristic associated with an increased risk of pleural effusion (Porkka et al. 2010). The development of lymphocytosis during dasatinib treatment was associated with a 1.7-fold increased risk of pleural effusion (95 % CI, 1.1–2.5) (Porkka et al. 2010).

The second-line, phase III dose-optimization study indicated that dasatinib 100 mg once daily was associated with reduced frequency of AEs in patients with CML-CP, while efficacy was maintained (Shah et al. 2008a; Porkka et al. 2010; Shah et al. 2012). With a minimum follow-up of 6 months, patients receiving dasatinib 100 mg once daily had lower rates of pleural effusion and grade 3–4 thrombocytopenia compared with patients receiving 70 mg twice daily (7 vs. 16 % and 22 vs. 37 %, respectively) (Shah et al. 2008a). Furthermore, fewer patients receiving dasatinib 100 mg once daily required dose interruptions (51 vs. 68 %), dose reductions (30 vs. 55 %), or discontinuation (16 vs. 23 %) (Shah et al. 2008a). With a minimum follow-up of 24 months, 14 % of patients receiving dasatinib 100 mg once daily developed pleural effusion, compared with 25 % of patients receiving 70 mg twice daily (Porkka et al. 2010). Improved tolerability of once-daily dosing may be due to intermittent dasatinib exposure, in comparison with continuous exposure achieved by twice-daily dosing (Porkka et al. 2010). After a minimum follow-up of 5 years, grade 3–4 hematologic AEs in the 100 mg once daily arm included neutropenia (36 %) and thrombocytopenia (24 %). Any-grade nonhematologic AEs included headache (33 %), diarrhea (28 %), fatigue (26 %), and pleural effusion (24 %) (Shah et al. 2012). Grade 3–4 cytopenias and any-grade nonhematologic AEs generally first occurred within 12–24 months of treatment (Shah et al. 2012).

In the first-line setting, similar AEs were observed. Treatment-related AEs led to the discontinuation of dasatinib in 7 % of patients (Kantarjian et al. 2012). Grade 3–4 hematologic AEs were common in patients with CML-CP receiving

dasatinib (100 mg once daily) or imatinib (400 mg once daily) (neutropenia 24 vs. 21 %, thrombocytopenia 19 vs. 11 %, anemia 11 vs. 8 %) (Kantarjian et al. 2012). Severe biochemical abnormalities were uncommon with the exception of grade 3–4 hypophosphatemia (dasatinib arm 7 %, imatinib arm 25 %) (Kantarjian et al. 2012). The most common nonhematologic AEs in DASISION (all grades, dasatinib versus imatinib) were myalgia (22 vs. 39 %), diarrhea (19 vs. 21 %), pleural effusion (14 vs. 0 %), headache (13 vs. 11 %), superficial edema (11 vs. 36 %), rash (11 vs. 17 %), and nausea (10 vs. 23 %) (Kantarjian et al. 2012). Grade 3–4 nonhematologic AEs associated with dasatinib were uncommon at 0–2 % (fluid retention 2 %, pleural effusion 1 %, diarrhea <1 %, fatigue <1 %) (Kantarjian et al. 2012). In DASISION, at 1-year follow-up, 26 patients (10 %) had pleural effusion; all events were grade 1 (2 %) or grade 2 (8 %) (Kantarjian et al. 2010). By 2-year follow-up, pleural effusion events had occurred in 37 patients (14.3 %) and were generally mild-to-moderate in severity (grade 1: $n = 9$, 3.5 %; grade 2: $n = 26$, 10.1 %; grade 3: $n = 2$, 0.8 %) with no grade 4 events observed. Events were largely manageable with treatment interruption ($n = 30$), dose reduction ($n = 19$), or the use of diuretics ($n = 17$) or corticosteroids ($n = 15$). Four patients required a therapeutic thoracentesis. At 2-year follow-up, five patients (1.9 %) had discontinued dasatinib due to pleural effusion. Notably, the occurrence and management of pleural effusion appeared not to affect the efficacy of dasatinib (Laneuville et al. 2011; Kantarjian et al. 2012).

In some patients receiving dasatinib, large granular lymphocyte (LGL) expansions carrying clonal T-cell receptor gene arrangements occur resulting in lymphocytosis (Kreutzman et al. 2010). Data from a retrospective analysis of patients enrolled in DASISION suggested that dasatinib-treated patients with lymphocytosis had higher rates of any-grade pleural effusion and lower rates of myalgias and arthralgias compared with patients without lymphocytosis (Schiffer et al. 2010a). In a separate analysis of pooled study data, 31 % of patients with CML-CP had lymphocytosis, which was associated with a higher rate of CCyR and longer PFS in patients with advanced disease (Schiffer et al. 2010b). However, no formal statistical testing has been reported for either of these analyses. A subanalysis of DASISION demonstrated no substantial effects of baseline cardiovascular conditions, other comorbidities, or use of baseline medications on the general safety profile of dasatinib (Khoury et al. 2010; Saglio et al. 2010c; Guilhot et al. 2010).

More recently, rare cases of PAH in patients receiving dasatinib for CML and Ph+ ALL have been reported in the literature ($n = 16$) (Mattei et al. 2009; Rasheed et al. 2009; Hennigs et al. 2011; Orlandi et al. 2011; Dumitrescu et al. 2011; Philibert et al. 2011; Montani et al. 2012; Sano et al. 2012). By 2-year follow-up of the phase III DASISION trial of dasatinib versus imatinib in newly diagnosed CML-CP, three patients receiving dasatinib developed PH; however, no cases of PAH diagnosed by RHC were recorded (Kantarjian et al. 2012). No patient in DASISION discontinued dasatinib therapy because of PH or PAH (Kantarjian et al. 2012). PAH observed in patients receiving dasatinib is not typical as this

disease is normally progressive, including cases with a drug-induced etiology which do not reverse on treatment withdrawal (Galie et al. 2009; McLaughlin et al. 2009). To date, however, the typical clinical course for dasatinib-associated cases of PAH is improvement or complete resolution in the majority of cases upon withdrawal of treatment.

Most AEs occurring in patients receiving dasatinib treatment are manageable through dose interruption or dose reduction (Sprycel® BMS 2012). If hematologic AEs occur in patients receiving dasatinib, treatment should be interrupted until the absolute neutrophil count is $\geq 1.0 \times 10^9/\text{L}$ and platelets $\geq 50 \times 10^9/\text{L}$. Dasatinib can then be resumed at the original dose if recovery occurs within 7 days or at a reduced dose of 80/50 mg/d if recovery takes longer than seven days or if the event was a second/third recurrence. Growth factor support may also be considered (Sprycel® BMS 2012). If a severe nonhematologic AE (grade 3/4) develops dasatinib should be withheld until resolution or improvement. Treatment can then be resumed at a reduced dose dependent on initial severity of the event (Sprycel® BMS 2012). Pleural effusion events are largely manageable through dose reduction or interruption, and/or corticosteroids and diuretics. Once resolved a reduced dasatinib dose can be resumed. Rare cases of severe pleural effusion may require thoracentesis and oxygen therapy (Laneuville et al. 2011; Kantarjian et al. 2012). Other fluid retention events can be managed with diuretics and supportive care. To reduce the risk of PAH, patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease before initiating dasatinib treatment. Upon confirmation of a PAH diagnosis based on RHC, dasatinib should be permanently discontinued (Sprycel® BMS 2012). PAH may be at least partially reversible upon treatment discontinuation. For bleeding events, management steps include dose interruption and transfusion (Quintás-Cardama et al. 2009; Sprycel® BMS 2012). Rash may be managed with topical or systemic steroids in addition to dose reduction, interruption, or discontinuation. In cases of gastrointestinal upset, the NCCN guidelines suggest that dasatinib be taken with a meal and a large glass of water. Specific supportive medication is also indicated in case of headache and diarrhea (Sprycel® BMS 2012; NCCN v4 2013). A subanalysis of DASISION showed that dose modifications taken to manage AEs had no apparent effect on response (Jabbour et al. 2011).

6 Drug Interactions

Dasatinib is a substrate and an inhibitor of CYP3A4. Therefore, there is a potential for interaction with other concomitantly administered drugs that are metabolized primarily by or modulate the activity of CYP3A4.

Systemic exposure to dasatinib is increased if it is coadministered with drugs that are inhibitors of CYP 3A4 (e.g., clarithromycin, erythromycin, itraconazole, ketoconazole).

If coadministered with drugs that induce CYP 3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort), dasatinib AUC is reduced. It was reduced by 82 % when coadministered with rifampicin.

Dasatinib AUC was reduced when coadministered with H2-blockers/proton-pump inhibitors, or antacids. Concomitant administration of famotidin reduced dasatinib AUC by 61 %, coadministration of aluminum hydroxide by 55 %.

Dasatinib is an inhibitor of CYP3A4. Substrates of CYP3A4 with a narrow therapeutic index should be administered with caution in patients receiving dasatinib. Drugs that rank among that list are alfentanil, astemizole, terfenadine, cyclosporine, fentanyl, pimozone, quinidine, sirolimus, tacrolimus, or ergot alkaloid (ergotamine, dihydroergotamine) (Sprycel® BMS 2012).

7 Biomarkers

Valid biomarkers that may predict the sensitivity of a disease to dasatinib are important.

In the case of the BCR-ABL-positive diseases CML and Ph+ ALL, the presence of the fusion gene not only determines the diagnosis. BCR-ABL transcript levels under TKI treatment are a good biomarker for prognosis. In chronic phase CML scheduled response, checkpoints have been published, describing minimal requirements, expressed as BCR-ABL transcript levels or the extent of cytogenetic response at a given time. Treatment results are categorized as “optimal response” or “failure,” in between an intermediate warning zone. Warnings imply that the patient should be monitored very carefully and may become eligible for other treatments. Failure implies that the patient should be moved to other treatments whenever available (Baccarani et al. 2013).

In diseases, where KIT plays a major role, KIT expression can be detected immunohistologically by the presence of the CD117 antigen. Moreover, the identification of activating KIT mutations might predict the efficacy of dasatinib.

Definition of an SRC oncogenic pathway signature can predict sensitivity to dasatinib (Bild et al. 2006; Huang et al. 2007). Attempts to find markers of dasatinib sensitivity and/or resistance have been carried out by analyzing gene expression profiles in 23 breast cancer cell lines. A six-gene profile was identified that predicted dasatinib sensitivity in breast and lung cancer cell lines. In addition, a gene expression signature related to dasatinib resistance was described (Huang et al. 2007). A SRC pathway activity index has been defined to establish patients that may respond to dasatinib (Moulder et al. 2010). In CLL, the activity of SYK and phospholipase C γ 2 (PLC γ 2) correlates with sensitivity to dasatinib (Song et al. 2010).

8 Summary and Perspectives

Dasatinib has superior efficacy over imatinib and an acceptable safety profile in first- and second-line treatment of patients with CML. The potent, multitargeted activity of dasatinib may contribute to the depth and speed of response achieved with this agent. Dasatinib's potential immune activity may play a role in the observed potency and requires further investigation. These factors may also play a role in the unique safety profile and the AEs observed in patients receiving dasatinib.

In exploratory analyses, a greater proportion of patients achieved early, deep molecular responses ($\leq 10\%$ BCR-ABL at 3 months) associated with improved response and survival, and decreased transformation to AP/BP, with dasatinib compared with imatinib. With significantly deeper levels of molecular response achieved at all time points with up to 2-years follow-up in DASISION; more patients receiving dasatinib versus imatinib may achieve undetectable levels of BCR-ABL transcripts and a complete molecular response. Second-generation BCR-ABL inhibitors have also demonstrated some activity against CML stem cells, providing support for future investigation of dasatinib in achieving a functional cure (Mustjoki et al. 2011; Bocchia et al. 2010; Hiwase et al. 2010).

With changing treatment goals supporting earlier, deeper responses, it is reasonable to suggest that dasatinib and other second-generation BCR-ABL inhibitors are likely to be used more frequently as a first-line treatment option in patients with newly diagnosed disease, dependent on existing patient comorbidities and BCR-ABL mutation status (if known). The speed of response achieved with second-generation BCR-ABL inhibitors may also allow the early identification of a subset of patients resistant to BCR-ABL inhibitor treatment who may benefit from alternate TKI, stem cell transplant or clinical trials.

The loss of patent exclusivity for imatinib in 2015 (US) and 2016 (EU) is likely to influence first-line treatment selection. With the potential for increased use of imatinib, it will be important to closely monitor patient response to ensure early milestones are achieved. Data are emerging to support a change in treatment for patients failing to reach certain levels of response ($\leq 10\%$ BCR-ABL by 3 months) (Marin et al. 2012; Hanfstein et al. 2012; Neelakantan et al. 2013). A phase II study comparing dasatinib 100 mg once daily to imatinib standard of care in patients failing to achieve an optimal response of $\leq 10\%$ BCR-ABL after 3 months of imatinib 400 mg/day is currently in progress. This study will prospectively test the hypothesis that changing to dasatinib treatment in this patient population will induce an improved response rate (primary endpoint, MMR at 12 months) compared with continuing imatinib at any dose.

With the growing number of BCR-ABL inhibitors available for patients with CML-CP and the lack of head-to-head clinical trials with second-generation BCR-ABL inhibitors, choosing a treatment requires consideration on a patient-to-patient basis and therefore information regarding the efficacy and use of these agents in the real-world setting is of increasing interest. An observational 5-year prospective

cohort study (SIMPLICITY: NCT01244750) has been initiated to further understand the use of dasatinib, imatinib, and nilotinib in patients with newly diagnosed CML-CP including real-world response, outcomes, treatment adherence, and patient quality of life. Data are anticipated to provide additional information to help guide initial treatment selection for CML patients.

The role of dasatinib in the treatment of other malignancies is not yet defined. The drug has only moderate effects on cell proliferation, but due to its activity on several TKIs, it is supposed to sensitize or resensitize tumors to chemotherapy, antiangiogenetic treatment, EGFR-inhibitor treatment or antihormonal treatment. The moderate effect in monotherapy studies was to be expected. By adding dasatinib to standard treatment in different tumors and lines of treatment, only few additional patients responding have been reported. The negative results of the first large phase III study with dasatinib in solid tumors, the READY-study, treating 1,522 patients with metastatic CRPC with standard chemotherapy in combination with dasatinib, dampen the expectations to treat other malignancies, not dependent on BCR-ABL, with dasatinib in the near future.

Studies are ongoing in AML and CLL, but also in several solid tumors including breast cancer and colorectal cancer. Testing for dasatinib sensitivity prior to study entry might be a way to select a patient population benefitting from dasatinib.

Signal transduction in solid tumors is getting more important for the choice of treatment, for example the use of EGF inhibitors in colorectal cancer dependent on K-RAS status (Van Cutsem et al. 2009) or the treatment of melanoma dependent on the B-RAF mutation status (Flaherty et al. 2012). In a concept of personalized medicine, the focus might switch from the histology of a given tumor to the oncogenic pathways involved in malignant transformation. Since dasatinib is a potent inhibitor of several TKs involved in oncogenic pathways, it is possible, that some patients might benefit from dasatinib, if their pattern of activated or over-expressed TKs is sensitive to dasatinib.

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