Jefferson.

Thomas Jefferson University
Jefferson Digital Commons

Department of Medical Oncology Faculty Papers   Department of Medical Oncology

10-1-2012

Phase II evaluation of dasatinib in the treatment of recurrent or persistent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group study.

Russell J Schilder
Thomas Jefferson University, russell.schilder@jefferson.edu

William E Brady
Gynecologic Oncology Group Statistical & Data Center; Buffalo, NY

Heather A Lankes
Gynecologic Oncology Group Statistical & Data Center; Buffalo, NY

James V Fiorica
Dept. of Gynecologic Oncology; Sarasota Memorial Hospital; Sarasota, FL

Mark S Shahin
Hanjani Institute for Gynecologic Oncology; Abington Memorial Hospital, Abington, PA

Let us know how access to this document benefits you

See next page for additional authors

Follow this and additional works at: http://jdc.jefferson.edu/medoncfp

Part of the Medical Immunology Commons, and the Oncology Commons

Authors

Russell J Schilder, William E Brady, Heather A Lankes, James V Fiorica, Mark S Shahin, Xun C Zhou, Robert S Mannel, Harsh B Pathak, Wei Hu, R Katherine Alpaugh, Anil K Sood, and Andrew K Godwin

Russell J. Schilder MD[1*], William E. Brady MS[2], Heather A. Lankes PhD MPH[2],

James V. Fiorica MD[3], Mark S. Shahin MD[4], Xun C. Zhou MD[5], Robert S. Mannel MD[6],

Harsh B. Pathak PhD[7], Wei Hu MD, PhD[8], R. Katherine Alpaugh PhD[9], Anil K. Sood MD[8,10,11],

Andrew K. Godwin PhD[7]

1.   Dept. of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111

2.   Gynecologic Oncology Group Statistical & Data Center; Buffalo, NY 14263

3.   Dept. of Gynecologic Oncology; Sarasota Memorial Hospital; Sarasota, FL 34239

4.   Hanjani Institute for Gynecologic Oncology; Abington Memorial Hospital, Abington, PA 19001

5.   Dept. of Gynecologic Oncology; Hospital of Central Connecticut, New Britain, CT 06050

6.   Dept. of OB/GYN; University of Oklahoma; Health Sciences Center; Oklahoma City, OK 73190

7.   Dept. of Pathology & Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS   66160

8.   Dept. of Gynecologic Oncology; The University of Texas; MD Anderson Cancer Center, Houston, TX 77030

9.   Fox Chase Cancer Center, Protocol Support Laboratory, Philadelphia, PA 19111

10.   Dept. of Cancer Biology; The University of Texas; MD Anderson Cancer Center, Houston, TX   77030

11.   Center for RNAi and non-coding RNA, The University of Texas MD Anderson Cancer Center, Houston, TX 77030

Corresponding Author: Russell J. Schilder, MD

Thomas Jefferson University

Dept. of Medical Oncology

Philadelphia, PA   19107

Telephone: 215-503-3057

FAX: 215-503-3059

E-mail: russell.schilder@jefferson.edu

Running title: Dasatinib in Ovarian Cancer

Key Words: dasatinib, ovarian, cancer, SRC, inhibition

*Dr. Schilder is currently at Thomas Jefferson University, Dept. of Medical Oncology; Philadelphia, PA 19107

1 **ABSTRACT**
2

3 **Objective:** Preclinical data suggest an important role for the sarcoma proto-oncogene tyrosine

4 kinase (SRC) in the oncogenesis of epithelial ovarian cancer (EOC) or primary peritoneal

5 carcinoma (PPC). The Gynecologic Oncology Group (GOG) conducted a Phase II trial to

6 evaluate the efficacy and safety of dasatinib, an oral SRC-family inhibitor in EOC/PPC and

7 explored biomarkers for possible association with clinical outcome.

8 **Methods:** Eligible women had measurable, recurrent or persistent EOC/PPC and had received

9 one or two prior regimens which must have contained a platinum and a taxane. Patients were

10 treated with 100 mg orally daily of dasatinib continuously until progression of disease or adverse

11 effects prevented further treatment. Primary endpoints were progression-free survival (PFS) ≥6

12 months and response rate. Serial plasma samples were assayed for multiple biomarkers.

13 Circulating free DNA was quantified as were circulating tumor and endothelial cells.

14 **Results:** Thirty-five (35) patients were enrolled in a two-stage sequential design. Of the 34

15 eligible and evaluable patients, 20.6% (90% confidence interval: 10.1%, 35.2%) had a PFS ≥6

16 months; there were no objective responses. Grade 3-4 toxicities were gastrointestinal (mostly

17 nausea and emesis; n=4), pulmonary (dyspnea and/or pleural effusion; n=4) and pain (n=5),

18 and infrequent instances of anemia, malaise, insomnia, rash, and central nervous system

19 hemorrhage. Lack of clinical activity limited any correlation of biomarkers with outcome.

20 **Conclusion:** Dasatinib has minimal activity as a single-agent in patients with recurrent

21 EOC/PPC.

INTRODUCTION

23   Despite initially high remission rates, at least 75% of women diagnosed with advanced

24   stage epithelial ovarian carcinoma (EOC) will relapse and ultimately die of their disease [1].

25   Treatment of these patients once they develop recurrent disease remains a major problem. The

26   need for new therapeutic strategies is evident. The SRC family of kinases (SFK) is a nine

27   member group of membrane associated non-receptor tyrosine kinases that are involved in a

28   variety of cellular signaling pathways [2]. The SFK is involved in the oncogenesis of numerous

29   tumors including ovarian cancer. SRC regulates many intracellular signaling pathways

30   responsible for various important tumor cell functions such as proliferation, motility and invasion,

31   angiogenesis, and survival. SRC has been found to be overexpressed in a majority of late

32   stage ovarian tumors and cell lines [3].

33   SRC is a component of signaling pathways downstream of many growth factor

34   receptors, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor

35   receptor (VEGFR), and MNNG transforming gene product (c-MET) [4]. Increased resistance to

36   traditional chemotherapy is modulated by SRC through increased activity of RAS and AKT [5].

37   Inhibition of SRC enhanced the activity of cytotoxic agents, including cisplatin, gemcitabine, and

38   paclitaxel through the activation of caspase-3 in pre-clinical models [5-7]. In addition, tumor

39   growth was blunted when human ovarian cancer cells carrying an antisense SRC construct

40   were implanted into mice bearing these xenografts [8].

41   VEGF is an important growth factor for ovarian cancer cells [9]. VEGF was significantly

42   down-regulated by SRC inhibition and microvessel density was reduced [10]. Anti-VEGF

43   therapy has demonstrated activity in patients with recurrent and primary disease [11,12]. VEGF

44   stimulation of its receptor increased tyrosine phosphorylation of focal adhesion kinase, p130

45   CAS and paxillin [13]. Increased activity of these mediators leads to an increased epithelial-to-

46 mesenchymal transition (EMT), a crucial step to enhancing the metastatic potential of these

47 cancer cells [14]. SRC is a key intermediate in the EMT process [15,16]. In addition, caveolin-1

48 expression indirectly promotes cell-cell adhesion in ovarian cancer cells [17,18]. SRC interferes

49 with caveolin function also promoting EMT and encouraging tumor spread.

50   Dasatinib is a potent oral inhibitor of breakpoint cluster region-Abelson fusion protein

51 (BCR-ABL), c-KIT, ephrin type-A receptor 2 (EPHA2), c-FMS, and SFK [19,20]. These kinases

52 are implicated in oncogenic process and maintaining the metastatic phenotype of many

53 cancers. Dasatinib's mechasnism of action depends on itsuccessfully competing for the ATP

54 binding site contained in the kinase domain. The agent is widely approved for chronic

55 myelogenous leukemia and Ph+ acute lymphoblastic leukemia and is now under investigation

56 for treating various solid tumors [21].

57   Based on these observations, the evaluation of dasatinib in patients with recurrent EOC

58 was undertaken by the Gynecologic Oncology Group (GOG). Translational research objectives

59 were included to explore the association between biomarkers and patient outcome. Biomarkers

60 included cell-free DNA (cfDNA), circulating tumor cells (CTCs), circulating endothelial cells

61 (CECs), circulating endothelial precursors (CEPs), and seven plasma biomarkers relevant to

62 dasatinib treatment (EGF and its soluble receptor [sEGFR], VEGF and its soluble receptors

63 [sVEGFR1, sVEGFR2, sVEGFR3], and insulin like growth factor binding protein 2 [IGFBP2]).

PATIENTS AND METHODS

Eligibility

Eligible patients had a histologically-confirmed diagnosis of EOC or primary peritoneal carcinoma, measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [22], a GOG performance status of 0-2, and adequate bone marrow (absolute neutrophil count $\geq$1,500/μL, platelet count $\geq$100,000/μL), renal (serum creatinine $\leq$1.5 x the upper limit of normal), and hepatic function (total bilirubin $\leq$1.5 x the upper limit of normal, and transaminases and alkaline phosphatase $\leq$2.5 x the upper limit of normal). No biomarker based method was used for patient selection. Eligible patients were permitted to have up to two prior cytotoxic regimens, but if a patient had only one prior regimen, she was required to have a platinum-free interval of less than 12 months or to have progressed during or have persistent disease after platinum-based therapy. Prior biological agents were permitted other than those known to inhibit SRC. Patients with prior radiation to more than 25% of marrow bearing areas, therapeutic warfarin treatment, or signs and/or symptoms of bowel obstruction were excluded. Patients provided written informed consent consistent with federal, state, and local institutional review board at each participating GOG institution in accordance with assurances filed with and approved by the Department of Health and Human Services.

Treatment Plan and Dose Modifications

Dasatinib (Bristol-Myers Squibb, New York, NY) was administered orally at an initial dose of 100 mg once daily until disease progression or adverse effects required interruption, reduction or discontinuation of therapy. Dose level −1 was 70 mg daily and dose level +1 was 70 mg twice daily. Although dosing was continuous, a cycle was defined as 28 days. Dasatinib was supplied by Bristol-Myers Squibb, Inc.

87   Toxicity was graded using the National Cancer Institute Common Toxicity Criteria

88   version 3.0 (NCI-CTCAE v3.0). For first occurrence of febrile neutropenia and/or documented

89   grade 4 neutropenia, dasatinib was held until the absolute neutrophil count (ANC) was grade ≤ 2

90   then reduced by one dose level. Patients with grade 4 thrombocytopenia had their drug held

91   until grade ≤ 1 and then were reduced by one dose level. The next cycle of dasatinib did not

92   begin until the ANC was $\geq 1,500/\mu l$ and the platelet count was $\geq 100,000/\mu l$. Therapy was

93   allowed to be delayed up to a maximum of two weeks. Patients who failed to recover adequate

94   counts within this time were removed from study. Prophylactic use of myeloid growth factors

95   was prohibited. Patients who experienced grade ≥ 2 non-hematologic toxicity had therapy held

96   until resolution to grade 0-1 up to a maximum of 14 days. Dasatinib was then restarted at 70

97   mg daily. If toxicity recurred to grade 2 or worse, the patient would discontinue study drug.

98   Exceptions to the above modifications included: liver function tests were required to be grade 3

99   or worse toxicity before dose modification was required. There was no dose adjustment for

100   fatigue or alopecia. Doses were reduced for gastrointestinal toxicities only if they could not be

101   controlled with medical management. Fluid retention (pleural effusion and/or ascites) was

102   managed with early initiation of diuretic treatment (furosemide and/or spironolactone. Cavity

103   drainage was performed as clinically indicated. Once a patient's dose was reduced, no

104   subsequent increases were permitted.

105   Patients with no grade ≥ 1 toxicities after cycle 1 were escalated one dose level (70 mg

106   twice daily) beginning with cycle 2 of treatment. This dose escalation was included based on

107   early data that solid tumors may require higher doses of dasatinib to achieve clinical activity

108   compared with the doses used to treat patients with CML [23,24].

109   <u>Response Assessment</u>

110   Patients were evaluated clinically every four weeks and radiographically every eight

111   weeks. The same evaluation modality was used throughout for each patient on study.

112   Response criteria used were as defined by RECIST [22].

113

114   Translational Research

115   Plasma and whole blood specimens were collected for translational research prior to cycles 1, 2

116   and 3. Detailed methodology and references for isolating and phenotyping CTC and CEC/CEP

117   can be found in the supplemental material [online only]. Methods for determining circulating

118   levels of serum biomarkers and extraction and quantification of total plasma cell-free DNA

119   (cfDNA) are also summarized in the supplemental online material.

120   Statistical Methods

121   We anticipated that the effect of dasatinib might be either cytotoxic or cytostatic.

122   Therefore, the primary endpoint of this study included both objective tumor response and the

123   proportion of patients alive and progression-free after six months PFS-6). Time on study was

124   assessed from date of registration and included all eligible treated patients.

125   The null hypothesis, i.e. an "uninteresting" level of efficacy, was determined from

126   analysis of an historical GOG dataset, based on a similar patient population from clinical trials of

127   study drugs now considered inactive or minimally active. The null hypothesis jointly specified

128   the probability of a patient experiencing a tumor response to be ≤10% and the probability of a

129   patient being alive and free from PFS-6 to be ≤15%. For the purpose of study design, a 20%

130   increase (to 25% for tumor response or to 35% for PFS-6) were considered clinically significant.

131   The two-stage, bivariate, flexible method of Sill and Yothers [25] was used with a goal of limiting

132   patient exposure to inactive agents while restricting the probabilities of type I and type II errors

9

133   to about 10%. If the regimen were to demonstrate sufficient activity in the first stage (with 35

134   patients, this required $\geq$5 objective tumor responses or $\geq$8 patients with PFS-6), then the study

135   would target a total of 53 patients (cumulatively) in stage 2. Signed-rank tests were used to test

136   changes from baseline in biomarkers, and Wilcoxon rank sum tests were used to compare

137   changes or ratios for patients who had PFS for at least 6 months versus those who did not.

138   Proportional hazards models were used to compare PFS by high ($\geq$ median) versus low

139   ($<$median) baseline (pre-cycle 1) levels of each parameter; both unadjusted models and models

140   adjusted for age and performance status were examined.

RESULTS

142 <u>Patients and Eligibility</u>

143   Thirty-five patients were enrolled. One patient was deemed ineligible because

144 inadequate data were available. Patient characteristics are listed in Table 1. A majority of

145 patients (58.8%) received two prior regimens. All patients had a performance status of 0 or 1.

146 <u>Treatment and Response</u>

147   Patients received a median of two cycles (range, 1-12) of protocol therapy. Of the 23

148 patients who received two or more cycles, 15 were escalated to 140 mg of dasatinib daily (70

149 mg bid) and two were reduced to 70 mg daily.

150   There were no responders. Also, only seven patients (20.6%; 90% confidence interval:

151 10.1%, 35.2%) were PFS-6 (Table 2). Therefore, the protocol criteria for continuing to the

152 second stage of accrual were not met. Of the seven patients with PFS ≥6 months, five had two

153 prior treatment regimens while two had received one prior regimen, and all had platinum-

154 resistant disease (<6 months platinum-free interval) Median PFS was 2.1 months (first and third

155 quartiles: 1.8 and 4.9 months). Median overall survival (OS) was 17.7 months (first quartile:

156 10.8 months, third quartile has not been reached; Figure 1).

157 <u>Toxicity</u>

158   The most commonly observed grade 3 toxicities were gastrointestinal (mostly nausea

159 and emesis), pulmonary (dyspnea and/or pleural effusion), and pain (Table 3). There were

160 single cases of grade 3 or 4 anemia, malaise, insomnia, rash, and central nervous system

161 hemorrhage.

162

163 Translational research

164 *Dasatinib related biomarkers*

165   Bead-based immunoassays were used to measure circulating levels of seven dasatinib

166 related biomarkers in plasma collected pre-cycles 1 (n=27), 2 (n=23), and 3 (n=15). Fifteen

167 patients submitted samples at all three time points. Median biomarker levels (ng/mL) are

168 presented (Supplemental Table S1). There was a significant increase in the levels of

169 sVEGFR2, sVGEFR3, and IGFBP2 between baseline and pre-cycle three in these patients.

170 There was no association between baseline levels of plasma biomarkers and outcome (PFS

171 and OS) nor between changes in biomarker levels and six-month PFS outcome (data not

172 shown).

173 *Circulating cfDNA*

174   Total cfDNA from plasma collected pre-cycles 1 (n=28), 2 (n=23), and 3 (n=15) was

175 quantified using a real-time PCR TaqMan Assay and primers directed to β-actin, β-globin, and

176 GAPDH. Median cfDNA totals (GE/mL) are presented (Supplemental Table S2). cfDNA

177 increased from baseline to pre-cycle 2 and decreased between pre-cycle 2 and pre-cycle 3;

178 these changes were not significant. There were no statistically significant associations between

179 baseline measures of cfDNA and outcome (PFS and OS) nor between changes in biomarker

180 levels and six-month PFS outcome (data not shown).

181 *Circulating Tumor and Endothelial Cells*

182   Whole blood was collected pre-cycles 1 (n=26), 2 (n=21), and 3 (n=12) for CTC and

183 CEC enumeration; CEC VEGFR expression was examined. Twenty-six patients were

184 evaluated for at least one time point; nine patients submitted samples at all three time points.

185 Median biomarker values are presented (Supplemental Table 3). Sixteen patients had $\geq$1 CTC

186   at one of the three timepoints, with nine patients having $\geq$1 at baseline. All patients had CECs

187   (range 14-800) at each timepoint tested. There were no statistically significant associations

188   between baseline CTCs or CECs and outcome (PFS and OS) nor between changes in

189   biomarker levels and six-month PFS outcome (data not shown).

190   CEC VEGFR expression was used to examine whether dasatinib had an effect on

191   endothelial cell activation and whether activation correlates with outcome. We anticipated the

192   percent of VEGFR+ CEC to decrease with a positive anti-angiogenic treatment effect. There

193   was no significant association between baseline CEC VEGFR expression and outcome (PFS

194   and OS) nor between changes in biomarker levels and six-month PFS outcome (data not

195   shown).

196

DISCUSSION

198   Dasatinib was well tolerated but had minimal activity in patients with recurrent ovarian or

199   primary peritoneal carcinoma. With SRC reported to be overexpressed in approximately 90% of

200   ovarian cancers [3], no prescreening was performed to determine eligibility.

201   SRC occupies a strategic position in many cell signaling pathways affecting cell

202   proliferation, growth, and survival [4]. It has an important role in mediating the epithelial-to-

203   mesenchymal transition enhancing the metastatic potential of ovarian cancer cells [15,16].

204   Activated SRC is required for VEGF expression, which has already been shown to be important

205   in ovarian cancer biology and as an important therapeutic target. SRC expression was

206   associated with a drug resistant phenotype and SRC inhibition by transfecting SRC antisense

207   oligonucleotides (or by small molecule inhibitors) reversed drug resistance in preclinical models

208   [6]. Gene expression profiles of ovarian cancer tumors were able to identify with greater than

209   80% accuracy which tumors were likely to be resistant to primary platinum-based therapy

210   [26,27]. These profiles identified expression signatures consistent with activation of SRC which

211   in the future may be used to direct therapeutic strategies.

212   SRC protein expression usually correlated with the degree of SRC pathway

213   deregulation. The more deregulated the pathway, the higher the activated protein expression.

214   Platinum-resistant ovarian cancers have been shown to be more likely to have deregulation of

215   the SRC pathway [5,26]. Kaplan-Meier survival analysis showed that SRC pathway

216   deregulation is associated with a poor survival. Konecny and colleagues tested a panel of 34

217   ovarian cancer cell lines and reported that 71% were highly sensitive to dasatinib [28]. Teoh et

218   al, evaluated the *in vitro* activity of dasatinib alone and in combination with paclitaxel and

219   carboplatin in ovarian cancer cell lines [29]. Dasatinib demonstrated anti-proliferative activity

220   alone and synergistic activity with the cytotoxic in the cell lines with either SRC pathway

221   deregulation and/or high SRC protein expression. Dasatinib did not decrease SRC protein

222   expression, but completely abrogated the activation of SRC in all cell lines tested. These data

223   suggest dasatinib may help prime cells for apoptosis induced by cytotoxic chemotherapy.

224   Investigators at Duke University have conducted a phase I trial of carboplatin, paclitaxel, and

225   dasatinib [NCT00672295], but have yet to report these results.

226   It is not surprising that there was little single agent activity of dasatinib in this trial in light

227   of what has been learned about SRC since the conception and conduct of this trial. Preclinical

228   data support evaluating SRC inhibition in cancers with a predilection for developing metastases

229   to bone based on SRC's suppression of osteoclast function. A phase II trial of single agent

230   dasatinib investigated its activity in chemotherapy-naïve men with castrate resistant prostate

231   cancer (CRPC). A 43% stable disease rate (SDR) at 12 weeks and a 19 % SDR was

232   observed.(30) This level of activity was very similar to the results of current trial in patients with

233   recurrent ovarian cancer. A biochemical marker of drug activitywas identified with a decline in

234   N-telopeptide, a marker if bone resorption predictive of adverse skeletal events, in men with

235   CRPC treated with dasatinib. Dasatinib has been similarly studied in patients with triple

236   negative breast cancer, Her 2 positive/hormone receptor positive breast cancer with response

237   rates of 4-5%. No or minimal activity also was observed in phase II trials of monotherapy

238   dasatinib in patients with head and neck cancer, glioma and small cell lung cancer (21,31).

239   None of these trials pre-selected patients based on any predictive biomarkers of dasatinib

240   activity. While SRC may be effective (under some circumstances) in suppressing tumor growth,

241   it is not able as monotherapy to cause regression of established tumors. There are

242   compensatory pathways that can bypass blockade of SRC. For example, SRC silencing results

243   in significant increase in FGR levels (another member of the SFK) [32]. Alternatively, activation

244   of JAK may re-establish downstream STAT signaling after inhibition of SFKs [33].

245   The low activity of dasatinib as a single agent should not preclude evaluation as part of

246   combination regimens, either concomitantly or in sequence prior to chemotherapy if it is borne

247   out that dasatinib can serve a priming function in ovarian cancers with a high degree of SRC

248   pathway deregulation. In this regard, Pathak and Godwin have recently completed *in vitro* high-

249   throughput screening (HTS) using a siRNA library targeting signaling molecules related to

250   receptor tyrosine kinases in combination with dasatinib. Such screening would identify second-

251   site molecules that can be targeted in combination with SRC inhibition to synergistically improve

252   dasatinib efficacy in patients and to identify a potential gene signature predictive of response to

253   dasatinib therapy (personal communication). The clinical significance of these genes identified

254   through the HTS as being capable of synergizing with SRC inhibition is now being evaluated in

255   blinded tumor biopsy samples from the patients that participated in this trial.

256   Our correlative studies did not show any significance between the biomarkers tested and

257   patient outcome, mainly due to no clinical response on this study. There was a significant

258   increase in the levels of sVEGFR2, sVEGFR3, and IGFBP2 between baseline and pre-cycle 3

259   in the 15 patients submitting samples at all three time points similar to the data reported by

260   Strauss and colleagues [34]. There were no statistically significant changes in the three

261   housekeeping genes from baseline in these patients. The mechanisms of the occurrence of

262   cfDNA in blood under normal and pathological conditions are not yet fully understood. cfDNA

263   might be influenced by apoptosis, necrosis, decreased DNAase activity in circulating cancer

264   cells, as well as clearance by liver/kidney, and modification status of cfDNA. In this study, 16

265   patients had $\geq$1 CTC at one of the three time points; 9 had $\geq$1 at baseline. Further investigation

266   of the relationship between cfDNA and circulating CTCs and the predictive value of changes in

267   CTC in patients with ovarian cancer is needed..

CONFLICT OF INTEREST

The co-authors have no conflicts of interest to declare.

ACKNOWLEDGMENTS

REFERENCES

1. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin. 2011; 61:183-203.

2. Frame MC. Src in cancer: deregulation and consequences for cell behaviour. Biochim Biophys Acta. 2002; 1602:114-30.

3. Wiener JR, Windham C, Estrella BC, Parikh NU, Thall PF, Deavers MT, et al. Activated SRC protein tyrosine kinase is overexpressed in late-stage human ovarian cancer. Gynecol Oncol. 2003; 88:73-9.

4. Yeatman TJ. A renaissance for SRC. Nat Rev Cancer. 2004; 4:470-80.

5. Pengetnze Y, Steed M, Roby KF, Terranova PF, Taylor CC. Src tyrosine kinase promotes survival and resistance to chemotherapeutics in a mouse ovarian cancer cell line. Biochem Biophys Res Commun. 2003; 309:377-83.

6. Chen T, Pengetnze Y, Taylor CC. Src inhibition enhances paclitaxel cytotoxicity in ovarian cancer cells by caspace-9 independent activation of caspace-3. Mol Cancer Ther. 2005; 4:217-24.

7. Ceppi P, Papotti M, Monica V, Lo Iacono M, Saviozzi S, Pautasso M, et al. Effects of Src kinase inhibition induced by dasatinib in non-small cell lung cancer cell lines treated with cisplatin. Mol Cancer Ther. 2009; 8:3066-74.

8. Wiener JR, Nakano K, Kruzelock RP, Bucana CD, Bast RC Jr, Gallick GE. Decreased Src tyrosine kinase activity inhibits malignant human ovarian cancer tumor growth in a nude mouse model. Clin Cancer Res. 1999; 5:2164-70.

9. Martin L, Schilder R. Novel approaches in advancing the treatment of epithelial ovarian cancer: the role of angiogenesis inhibition. J Clin Oncol. 2007; 25:2894-901.

10. Han LY, Landen CN, Trevino JG, Halder J, Lin YG, Kamat AA, et al. Antiangiogenic and antitumor effects of SRC inhibition in ovarian cancer. Cancer Res. 2006; 66:8633-9.

11. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007; 25:5165-71.

12. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473-83.

13. Sood AK, Coffin JE, Schneider GB, Fletcher MS, DeYoung BR, Gruman LM, et al. Biological significance of focal adhesion kinase in ovarian cancer: Role in migration and invasion. Am J Path. 2004;165:1087-95.

14. Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002; 110:673-87.

15. Guarino M. Src signaling in cancer invasion. J Cell Physiol. 2010; 223:14-26.

16. Boyer B, Bourgeois Y, Poupon MF. Src kinase contributes to the metastatic spread of carcinoma cells. Oncogene. 2002; 21:2347-56.

17. Miotti S,Tomassetti A, Facetti I, Sanna E, Berno V, Canevari S. Simultaneous expression of caveolin-1 and E-cadherin in ovarian carcinoma cells stabilizes adherens junctions through inhibition of Src-related kinases. Am J Pathol. 2005; 167:1411-27.

18. Davidson B, Nesland JM, Goldberg I, Kopolovic J, Gotlieb WH, Bryne M, et al. Caveolin-1 expression in advanced-stage ovarian carcinoma – a clinicopathologic study. Gynecol Oncol. 2001; 81:166-71.

19. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004; 305:399-401.

20. Lombardo LJ, Lee FY, Chen P, Norris D, Barrish JC, Behnia K, et al. Discovery of *N*-(2-Chloro-6-methyl-phenyl-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src-Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem. 2004; 47:6658-61.

21. Araujo J, Logothetis C. Dasatinib: A potent SRC inhibitor in clinical development for the treatment of solid tumors. Cancer Treat Rev. 2010; 36:492-500.

22. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer. National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205-16.

23. Luo FR, Yang Z, Camuso A, Smykla R, McGlinchey K, Fager K, et al. Dasatinib (BMS-354825) pharmacokinetics and pharmacodynamic biomarkers in animal models predict optimal clinical exposure. Clin Cancer Res. 2006;12;7180-6.

24. Luo FR, Barrett YC, Yang Z, Camuso A, McGlinchey K, Wen ML, et al. Identification and validation of phospho-SRC, a novel and potential pharmacodynamic biomarker for dasatinib (SPRYCEL™),a multi-targeted kinase inhibitor. Cancer Chemother Pharmcol. 2008; 62:1065-74.

25. Sill MW, Yothers GA. A method for utilizing bivariate efficacy outcome measures to screen agents for activity in the 2-stage phase II clinical trials. Technical Report 06-08, Department of Biostatistics, University of Buffalo. Website: http:/sphhp.buffalo.edu/biostat/research/techreports/index.php

26. Dressman HK, Berchuck A, Chan G, Zhai J, Bild A, Sayer R, et al. An integrated genomic-based approach to individualized treatment of patients with advanced-stage ovarian cancer. J Clin Oncol. 2007; 25:517-25.

27. Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature. 2006; 439:353-7.

28. Konecny GE, Glas R, Dering J, Manivong K, Qi J, Finn RS, et al. Activity of the multikinase inhibitor dasatinib against ovarian cancer cells. Brit J Cancer. 2009; 101:1699-708.

29. Teoh D, Yeni TA, Tubatt JM, Adams DJ, Grace L, Starr MD, et al. Dasatinib (BMS-35482) has synergistic activity with paclitaxel and carboplatin in ovarian cancer cells. Gynecol Oncol. 2011; 121:187-92.

30. Yu EY, Wilding G, Posadas E, Gross M, Culine S, Massard C, et al. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res. 2009; 15:7421-8.

31. Puls LN, Eadens M, Messersmith W. Current status of Src inhibitors in solid tumors. The Oncologist, 2011; 16:566-78.

32. Kim HS, Han HD, Armaiz-Pena GN, Stone RL, Nam EJ, Lee JW, et al. Functional roles of Src and Fgr in Ovarian carcinoma. Clin Cancer Res. 2011; 17:1713-21.

33. Sen B, Peng S, Woods DM, Wistuba I, Bell D, El-Naggar AK, et al. STAT-5A-mediated SOCS2 expression regulates JAK2 and STAT3 activity following c-SRC inhibition in head and neck squamous carcinoma. Clin Cancer Res. 2012; 18:127-39.

34. Strauss L, Sy O, Fairchild J, Fu C, Rybicki A, Yoganathan S, et al. Biomarker analysis in phase 2 single-agent trials of dasatinib for breast cancer. SABCS, 2009 #2034.

Figure 1: Kaplan-Meier plots for overall and progression-free survival.