Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online May 18, 2015

DOI: 10.1634/theoncologist.2015-0105

Title: A Phase I Trial of Bortezomib and Sorafenib in Advanced Malignant Melanoma

Authors: Ryan J. Sullivan,[a] Nageatte Ibrahim,[b] Donald P. Lawrence,[a] Julie Aldridge,[b] Anita Giobbie-Hurder,[b] F. Stephen Hodi,[b] Keith T. Flaherty,[a] Christine Conley,[c] James W. Mier,[c] Michael B. Atkins,[d] David F. McDermott[c]

[a]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA; [b]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [c]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [d]Georgetown Lombardi Comprehensive Cancer Center, Washington, D.C., USA

ClinicalTrials.gov Identifier: NCT01078961

Sponsor(s): Dana-Farber/Harvard Cancer Center

Principal Investigator: Ryan J. Sullivan

IRB Approved: Yes

Disclosures

Ryan J. Sullivan: Astex Pharmaceuticals (C/A), Boehringer Ingelheim (Other: adverse event adjudication); **Nageatte Ibrahim:** GSK, Merck (E, OI); **F. Stephen Hodi:** Novartis, Merck, Genetech (C/A), Bristol Myers Squibb (RF, IP); **James W. Mier:** X4 Pharmaceuticals (RF), Acceleron (IP); **David F. McDermott:** BMS, Merck (C/A); **Julie Aldridge:** EMD Serono (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Lessons Learned

- This study is a rare example of effective doses of both targeted agents being both administered and tolerated.
- This combination should not be used in melanoma.

Author Summary: Abstract and Brief Discussion

Background

Sorafenib and bortezomib affect BCL family member expression. We previously demonstrated that bortezomib augmented sorafenib-mediated cytotoxicity in melanoma cell lines in vitro. We aimed to combine sorafenib 400 mg b.i.d. with increasing doses of weekly bortezomib.

Methods

Patients with metastatic melanoma were enrolled in dose-escalation cohorts to determine the maximum tolerated dose (MTD) of sorafenib (twice daily) in combination with bortezomib (weekly for 3 of 4 weeks). The MTD was defined as the highest dose level at which less than 33% of patients exhibited a dose-limiting toxicity (DLT). Efficacy, as measured by 6-month progression-free survival and response rate per RECIST, was documented.

Results

Eleven patients were enrolled at three dose levels. DLTs (fatigue and rash) were seen in two of three patients at the highest dose level. Five patients were enrolled for sorafenib 400 mg b.i.d. and bortezomib 1.0 mg/m^2 weekly for 3 of every 4 weeks;

none had DLTs, and this dose level was defined as the MTD. Of 10 evaluable patients, no responses were seen. Two of 11 patients (18%) remained progression free for longer than 6 months.

Conclusion

The combination of sorafenib and bortezomib is safe but not active in patients with melanoma.

Discussion

The combination of sorafenib and bortezomib had been tested in a phase I trial with the MTD determined to be sorafenib 200 mg b.i.d. and bortezomib 1 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle [1]. Although these two agents had been tested in combination previously, we designed our study to maximize exposure to sorafenib by treating patients with weekly bortezomib, a regimen that had shown effectiveness in patients with myeloma with a favorable toxicity profile, compared with days 1, 4, 8, and 11 of a 21-day cycle [1–3]. In this phase I dose-escalation study, we identified sorafenib 400 mg b.i.d. with weekly bortezomib 1.0 mg/m^2 for 3 of 4 weeks as the MTD. Although a dose-escalation cohort was planned, given the lack of clinical activity at or above the MTD (no responses, 1 of 8 with stable disease at 24 weeks) and the increasing therapeutic options for patients with metastatic melanoma, the study was closed after determination of the MTD.

The standard of care for melanoma has changed dramatically over the past 5 years when this study was conceived, given the emergence of effective BRAF-targeted therapy and immune checkpoint inhibitors, leading to approval of 6 agents (BRAF inhibitors vemurafenib and dabrafenib, the MEK inhibitor trametinib, the anti-CTLA4 antibody ipilimumab, and the anti-PD1 antibodies pembrolizumab and nivolumab) by the U.S. Food and Drug Administration since 2011 [4–11]. Still, the majority of patients diagnosed with metastatic melanoma will die of their disease, and novel therapies and combination regimens are needed. Dual targeting of growth factor pathways and apoptosis is an approach that is building momentum, and four phase I clinical trials (NCT02110355, NCT01989585, NCT01897116, NCT02097225) based on compelling preclinical data have been opened recently. Our study serves as an early example of this type of approach. It is hoped that more potent and specific growth factor inhibitors—such as selective BRAF and/or MEK inhibitors for *BRAF*-mutant melanoma or pan-RAF, MEK, or ERK inhibitors for *BRAF* wild-type melanoma in combination with agents that target specific cell-survival mechanisms (BCL-2 family, inhibitor of apoptosis proteins, HDM2, heat shock protein 90, autophagy)—will be an effective therapeutic strategy.

Trial Information

Disease	Melanoma
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	More than 2 prior regimens
Type of study - 1	Phase I
Type of study - 2	Other
Primary Endpoint	Maximum Tolerated Dose
Secondary Endpoint	Efficacy
Investigator's Analysis	Drug Tolerable, Efficacy Indeterminate

Drug Information

Drug 1 **Generic/Working name**	Sorafenib
Trade name	Nexivar
Company name	Bayer-Onyx
Drug type	Small molecule
Drug class	Angiogenesis - VEGF
Dose	Milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	Twice Daily

Drug 2	
Generic/Working name	Bortezomib
Trade name	Velcade
Company name	Millennium Pharmaceuticals
Drug type	Small molecule
Drug class	Proteasome
Dose	Milligrams (mg) per square meter (m^2)
Route	IV
Schedule of Administration	Weekly, 3 weeks on, 1 week off

Dose Escalation Table

Dose Level	Dose of Drug: Sorafenib	Dose of Drug: Bortezomib	Number Enrolled	Number Evaluable for Toxicity
−1	200 mg b.i.d.	1.0 mg/m^2 IV days 1, 8, and 15	3	3
1	400 mg b.i.d.	1.0 mg/m^2 IV days 1, 8, and 15	5	5
2	400 mg b.i.d.	1.3 mg/m^2 IV days 1, 8, and 15	3	3

Patient Characteristics

Number of patients, male	7
Number of patients, female	4
Stage	Stage IV
Age	Median (range): 66 (33–74) years
Number of prior systemic therapies	Median (range): Not Collected
Performance Status	ECOG • 0 — • 1 — • 2 — 0 • 3 — 0 • Unknown — 0
Other	Not Collected
Cancer Types or Histologic Subtypes	• Melanoma 11

Primary Assessment Method

Control Arm: Melanoma

Number of patients enrolled	11
Number of patients evaluable for toxicity	11
Number of patients evaluated for efficacy	10
Evaluation method	Other
Response assessment CR	0
Response assessment PR	0
Response assessment SD	$n = 3$ 27
Response assessment PD	$n = 7$ 64
Response assessment OTHER	$n = 1$ 9

Control Arm: Melanoma

Number of patients enrolled	11
Number of patients evaluable for toxicity	11
Number of patients evaluated for efficacy	10
Evaluation method	Other
Response assessment CR	0
Response assessment PR	0
Response assessment SD	$n = 3$ 27
Response assessment PD	$n = 7$ 64
Response assessment OTHER	$n = 1$ 9

Adverse Events

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Musculoskeletal/Soft Tissue - Pain in extremity	63.64%	27.27%	9.09%	0%	0%	0%	36%
Fatigue (asthenia, lethargy, malaise)	63.64%	27.27%	9.09%	0%	0%	0%	36%
Anorexia	72.73%	27.27%	0%	0%	0%	0%	27%
Cough	81.82%	18.18%	0%	0%	0%	0%	18%
Infection - Tooth infection	90.91%	9.09%	0%	0%	0%	0%	9%
Nausea	63.64%	36.36%	0%	0%	0%	0%	36%
Gastrointestinal - Stomach Pain	72.73%	27.27%	0%	0%	0%	0%	27%
Gastrointestinal - Gastrointestinal pain	90.91%	9.09%	0%	0%	0%	0%	9%
Gastrointestinal - Abdominal pain	81.82%	9.09%	9.09%	0%	0%	0%	18%
Constipation	72.73%	27.27%	0%	0%	0%	0%	27%
Vomiting	72.73%	27.27%	0%	0%	0%	0%	27%
Neurology - Headache	72.73%	18.18%	9.09%	0%	0%	0%	27%
Hypertension	81.82%	0%	9.09%	9.09%	0%	0%	18%
Neurology - Bilateral arm tremor	90.91%	9.09%	0%	0%	0%	0%	9%
Diarrhea	81.82%	9.09%	9.09%	0%	0%	0%	18%
Rash: hand-foot skin reaction	81.82%	9.09%	0%	9.09%	0%	0%	18%
Constitutional Symptoms - Chest Pain	90.91%	9.09%	0%	0%	0%	0%	9%
Neuropathy: motor	90.91%	9.09%	0%	0%	0%	0%	9%
Pruritus/itching	72.73%	27.27%	0%	0%	0%	0%	27%
Phosphate, serum-low (hypophosphatemia)	90.91%	0%	9.09%	0%	0%	0%	9%
Cognitive disturbance	90.91%	0%	9.09%	0%	0%	0%	9%
Heartburn/dyspepsia	90.91%	0%	9.09%	0%	0%	0%	9%
Weight loss	90.91%	9.09%	0%	0%	0%	0%	9%
Urinary frequency/urgency	90.91%	0%	9.09%	0%	0%	0%	9%
Renal/Genitourinary - Hematuria	90.91%	9.09%	0%	0%	0%	0%	9%
ALT, SGPT (serum glutamic pyruvic transaminase)	90.91%	9.09%	0%	0%	0%	0%	9%
Rigors/chills	90.91%	9.09%	0%	0%	0%	0%	9%
Dermatology/Skin - Rash: Maculopapular	90.91%	0%	0%	9.09%	0%	0%	9%
Lymphopenia	90.91%	0%	0%	0%	9.09%	0%	9%
Pain - Back pain	90.91%	9.09%	0%	0%	0%	0%	9%
Taste alteration (dysgeusia)	90.91%	9.09%	0%	0%	0%	0%	9%

Potassium, serum-low (hypokalemia)	90.91%	9.09%	0%	0%	0%	0%	9%
Lipase	81.82%	0%	9.09%	9.09%	0%	0%	18%
Amylase	81.82%	18.18%	0%	0%	0%	0%	18%
Mucositis/stomatitis (functional/symptomatic)	81.82%	18.18%	0%	0%	0%	0%	18%
Cough	90.91%	9.09%	0%	0%	0%	0%	9%
Dry skin	90.91%	9.09%	0%	0%	0%	0%	9%
Secondary Malignancy - possibly related to cancer treatment (Specify, __)	90.91%	0%	0%	9.09%	0%	0%	9%
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	90.91%	9.09%	0%	0%	0%	0%	9%
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	90.91%	9.09%	0%	0%	0%	0%	9%
Tremor	90.91%	9.09%	0%	0%	0%	0%	9%
Musculoskeletal/Soft Tissue - Arthralgia	90.91%	9.09%	0%	0%	0%	0%	9%
Dyspnea (shortness of breath)	90.91%	9.09%	0%	0%	0%	0%	9%
Hemorrhage/Bleeding - Epistaxis	90.91%	9.09%	0%	0%	0%	0%	9%

*No Change from Baseline/No Adverse Event

Dose Limiting Toxicities

Dose Level	Dose of Drug: Sorafenib	Dose of Drug: Bortezomib	Number Enrolled	Number Evaluable for Toxicity	Number with a Dose Limiting Toxicity	Dose Limiting Toxicity Information
−1	200 mg b.i.d.	1.0 mg/m^2 IV days 1, 8, and 15	3	3	0	
1	400 mg b.i.d.	1.0 mg/m^2 IV days 1, 8, and 15	5	5	0	
2	400 mg b.i.d.	1.3 mg/m^2 IV days 1, 8, and 15	3	3	2	

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Drug Tolerable, Efficacy Indeterminate

Discussion

The standard of care for metastatic melanoma has changed dramatically from 6 years ago when this study was conceived. With the emergence of effective BRAF-targeted therapy in patients with *BRAF*-mutant melanoma and immune checkpoint inhibitors for patients with metastatic melanoma agnostic of molecular subtyping, five agents have received approval (BRAF inhibitors vemurafenib and dabrafenib, the MEK inhibitor trametinib, the anti-CTLA4 antibody ipilimumab, and the anti-PD1 antibody pembrolizumab) by the U.S. Food and Drug Administration since 2011 [4–11]. Still, the majority of patients diagnosed with metastatic melanoma will die of their disease, and novel therapies and combination regimens are needed. Dual targeting of growth factor pathways and apoptosis is an approach that is building momentum, and four phase I clinical trials (NCT02110355, NCT01989585, NCT01897116, NCT02097225) based on compelling preclinical data have been opened recently.

Our study serves as an early example of this type of approach. In preclinical testing, we and others identified that bortezomib enhanced sorafenib-mediated toxicity in a variety of cell lines [12, 13]. Given these data, a dose-escalation trial of sorafenib and bortezomib was opened and identified sorafenib 200 mg orally twice daily with bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle as the recommended phase II dose [1]. Given the lack of effective therapies for melanoma at the time, our preclinical data, and the fact that sorafenib 400 mg b.i.d. was being evaluated in combination with chemotherapy at the time in patients with previously untreated melanoma, we designed a melanoma-specific phase I trial to identify a maximally tolerated dose (MTD) of bortezomib in combination with sorafenib 400 mg orally b.i.d. Because weekly bortezomib had been shown to be reasonably effective with a favorable toxicity profile compared with days 1, 4, 8, and 11 of a 21-day cycle, we elected to use escalating doses of weekly bortezomib [2, 3].

In this phase I dose-escalation study, we identified sorafenib 400 mg b.i.d. with weekly bortezomib 1.0 mg/m^2 for 3 of 4 weeks as the MTD. Specifically, 11 patients were enrolled at three dose levels (Table 1), and dose-limiting toxicities (fatigue and rash) were seen in 2 of 3 patients at the highest dose level (sorafenib 400 mg b.i.d. and bortezomib 1.3 mg/m^2 on days 1, 8, and 15) (Table 2). Five patients were enrolled to sorafenib 400 b.i.d. and bortezomib 1.0 mg/m^2 weekly, and none had DLTs; this dose level was defined as the MTD. Of 10 evaluable patients, no responses were seen; however, 2 of 11 patients (18%) remained progression free for longer than 6 months. Furthermore, no unexpected toxicities arose because all documented adverse effects had been seen previously with sorafenib and/or bortezomib.

Although a dose-expansion cohort was planned, given the lack of clinical activity at or above the MTD (no responses, 1 of 8 patents with stable disease at 24 weeks) and the increasing therapeutic options for patients with metastatic melanoma, the study was closed after determination of the MTD. Still, this protocol represents the type of trials that are critical in the targeted therapy era: a plausibly effective combination of novel agents targeting different nodes of cancer signaling. It is hoped that more potent and specific growth factor inhibitors—such as selective BRAF and/or MEK inhibitors for *BRAF*-mutant melanoma or pan-RAF, MEK, or ERK inhibitors for *BRAF* wild-type melanoma, in combination with agents that target specific cell survival mechanisms (BCL-2 family, inhibitor of apoptosis proteins, HDM2, heat shock protein 90, autophagy)—will prove to be a more effective therapeutic strategy.

References

1. Kumar SK, Jett J, Marks R et al. Phase 1 study of sorafenib in combination with bortezomib in patients with advanced malignancies. Invest New Drugs 2013;31:1201–1206.
2. Hainsworth JD, Spigel DR, Barton J et al. Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma: A phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer 2008;113:765–771.
3. Suvannasankha A, Smith GG, Juliar BE et al. Weekly bortezomib/methylprednisolone is effective and well tolerated in relapsed multiple myeloma. Clin Lymphoma Myeloma 2006;7:131–134.
4. Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364:2507–2516.
5. Flaherty KT, Infante JR, Daud A et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367: 1694–1703.
6. Flaherty KT, Puzanov I, Kim KB et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 2010;363:809–819.
7. Flaherty KT, Robert C, Hersey P et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107–114.
8. Hauschild A, Grob JJ, Demidov LV et al. Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–365.
9. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363: 711–723.
10. Robert C, Ribas A, Wolchok JD et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109–1117.
11. Robert C, Thomas L, Bondarenko I et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364: 2517–2526.
12. Yu C, Friday BB, Lai JP et al. Cytotoxic synergy between the multikinase inhibitor sorafenib and the proteasome inhibitor bortezomib in vitro: Induction of apoptosis through Akt and c-Jun NH2-terminal kinase pathways. Mol Cancer Ther 2006;5:2378–2387.
13. Sullivan RJ, Panka D, Cohen MB et al. In vitro synergy of the combination of sorafenib and ABT-737 in melanoma cell lines [abstract 5501]. Presented at: American Association for Cancer Research annual meeting; April 18–22, 2009; Denver, CO.

Tables

Table 1. Adverse effects of sorafenib plus bortezomib

Adverse event	All grades, *n* (%)	Grades 3 and 4, *n* (%)
Fatigue	6 (55)	1 (9)
Anorexia	3 (27)	0
Weight loss	3 (27)	0
Mucositis	3 (27)	0
Sore throat	2 (18)	0
Chills	2 (18)	0
Hypertension	3 (27)	1 (9)
Arthralgia	2 (18)	0
Peripheral neuropathy	2 (18)	0
Nausea	7 (64)	0
Vomiting	3 (27)	0
Abdominal pain	4 (36)	1 (9)
Constipation	4 (36)	0
Diarrhea	2 (18)	0
Pancreatitis	2 (18)	0
AST elevation	2 (18)	0
Rash, maculopapular	3 (27)	1 (9)
Pruritis	4 (36)	0
Palmar-plantar erythrodysesthesia	3 (27)	1 (9)
Dry skin	2 (18)	0

Toxicities seen in >10% of patients are listed, categorized by all grades and by grades 3 and 4 according to the Common Terminology Criteria for Adverse Events version 4.0.

Table 2. Clinical efficacy of the combination of sorafenib plus bortezomib

Outcome	Number
Best response	
Partial response	0
Complete response	0
Stable disease	3
Progressive disease	7
Not evaluable for response	1
Median number of cycles	4
6-month progression-free survival	2

Click here to access other published clinical trials.