Published in final edited form as:

Ann Surg Oncol. 2014 June ; 21(6): 2059–2067. doi:10.1245/s10434-013-3373-z.

The GIST of Targeted Therapy for Malignant Melanoma

Danielle M. Bello, MD, Ronald P. DeMatteo, MD, and Charlotte E. Ariyan, MD, PhD

Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

The high response rates to the tyrosine kinase inhibitor imatinib in KIT-mutated gastrointestinal stromal tumors (GIST) has led to a paradigm shift in cancer treatment. In a parallel fashion, the field of melanoma is shifting with the utilization of targeted therapy to treat BRAF-mutated melanoma. We reviewed published literature in PubMed on GIST and melanoma, with a focus on both past and current clinical trials. The data presented centers on imatinib, vemurafenib, and most recently dabrafenib, targeting KIT and BRAF mutations and their outcomes in GIST and melanoma. The BRAF^{V600E} melanoma mutation, like the KIT exon 11 mutation in GIST, has the highest response to therapy. High response rates with inhibition of KIT in GIST have not been recapitulated in KIT-mutated melanoma. Median time to resistance to targeted agents occurs in ~7 months with BRAF inhibitors and 2 years for imatinib in GIST. In GIST, the development of secondary mutations leads to resistance; however, there have been no similar gatekeeper mutations found in melanoma. Although surgery remains an important component of the treatment of early GIST and melanoma, surgeons will need to continue to define the thresholds and timing for operation in the setting of metastatic disease with improved targeted therapies. Combination treatment strategies may result in more successful clinical outcomes in the management of melanoma in the future.

Chronic myelogenous leukemia was the initial tumor model in which targeted pharmacologic agents were successfully used to treat malignancies with specific genetic mutations. Identification of mutations in *bcr-abl*, a constitutively activated tyrosine kinase, resulted in the use of the tyrosine kinase inhibitor, imatinib, for chronic myelogenous leukemia.^{1–3} This paradigm was then expanded to gastrointestinal stromal tumors (GIST), where an activating mutation of the KIT proto-oncogene was shown to be inhibited by imatinib.² This review will discuss the role of vemurafenib in patients with melanoma, with attention to anticipated issues as learned from the GIST model.

TARGETED THERAPY IN SOLID TUMORS: LESSONS LEARNED FROM THE GIST MODEL

GISTs are mesenchymal tumors of the gastrointestinal tract. Historically treatment involved surgery; however, many patients experienced recurrence, and metastatic disease was

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C. E. Ariyan, MD, PhD ariyanc@mskcc.org.

CONFLICT OF INTEREST The other authors declare no conflict of interest.

DISCLOSURE RPD is a consultant for Novartis.

considered fatal.⁴ Classical chemotherapy for recurrence with doxorubicin resulted in only a 20 % survival at 2 years.⁵ Of those selected patients able to undergo surgical resection for metastatic disease, median survival was 27 months compared to 8 months in those who did not undergo surgery.⁶

GIST is thought to arise as a result of activating mutations in the KIT or the PDGFR α proto-oncogene (Fig. 1).⁷ KIT mutations can occur in up to 85 % of GISTs.⁸ The majority of these mutations are located in exon 11 (70 %) and exon 9 (10 %). The PDGFR α proto-oncogene mutation has been found in ~10 % of GISTs, with the majority of mutations located in exon 18.⁹ The remaining 5–10 % of GISTs, which lack a mutation in the KIT or PDGFR α proto-oncogene, are considered wild-type tumors. Interestingly, a subset of these patients have a V600E BRAF mutation, and BRAF inhibitors have been successfully used in the treatment of GIST harboring this mutation.^{10,11}

Identification of the gain-of-function mutation in KIT led to a study of the use of the tyrosine kinase inhibitor, imatinib, in metastatic GIST.^{12,13} A phase I trial demonstrated a very high response rate, which was confirmed by a phase II and a phase III trial with response rates of 48–67 %.^{5,14–17} These findings created a paradigm shift in the treatment of metastatic GIST, with imatinib as the first line agent. Knowledge of KIT mutation status is important in GIST, as specific mutational sites correlate with response to therapy. Patients with exon 11 mutations usually have an excellent response to therapy, while patients with an exon 9 mutation may be resistant to imatinib. GISTs harboring KIT exon 9 mutations occur with increased frequency in the small bowel and colon and may benefit from dose escalation to obtain a response.^{10,18–20}

Surgery for metastatic GIST now is only done in combination with targeted therapy. The timing of surgical intervention necessitates a balance between obtaining the maximum response to treatment, and avoiding resistance to imatinib, which occurs at a mean of 2 years after initiation of therapy.⁵ For those patients with a good response to imatinib and resectable disease, surgery is a reasonable option and may offer the patient a drug holiday. However, patients with multifocal resistance after imatinib have a poor survival after surgical debulking and should be considered for a second-line tyrosine kinase inhibitor or a clinical trial rather than surgery.²¹ It should be noted that a randomized trial has not been performed comparing surgical resection of residual metastatic GIST after imatinib therapy versus continued medical therapy alone.

As surgery remains an important component in the treatment of primary and metastatic disease, studies investigated how to combine and optimize the use of imatinib with surgical excision in GIST. Retrospective analysis characterized tumors with a high risk of recurrence after surgical resection, which included increasing tumor size and mitotic rate, evidence of tumor rupture, and anatomic location.^{22–25} The first trial gave adjuvant imatinib (ACOSOG Z900 trial) to high risk patients with either tumors ≥ 10 cm, intraperitoneal rupture, or four or more peritoneal implants. Patients were given a year of adjuvant treatment, and long-term follow-up demonstrated a 5-year survival of 83 %, compared to a historical 5-year survival of 40 %.²⁶ Two subsequent prospective randomized trials solidified the benefit of adjuvant imatinib after primary surgical resection. In the ACOSOG Z9001 trial, patients with a GIST

3 cm in size were assigned to adjuvant imatinib versus placebo. The study was stopped because of a significant difference in recurrence free survival (RFS), 20 % of patients recurred in the placebo arm, versus 8 % of patients in the imatinib arm.²⁷ Although no difference was noted in overall survival, it was unclear if the lack of survival benefit was secondary to a short follow-up interval or the ability of imatinib to salvage patients, as those patients who recurred crossed over to imatinib treatment. With more than 6 years of follow-up, OS is still similar between the arms (unpublished data). The value of adjuvant imatinib was confirmed in a randomized phase III study of 12 versus 36 months of treatment after surgical resection in patients with GIST containing any high-risk features. Thirty-six months of adjuvant imatinib improved both RFS and OS when compared to patients only receiving the therapy for 1 year.²⁸ However, the improvement in OS was based on a very small number of events and disease-specific survival was not actually altered. Overall, it appears that adjuvant imatinib is effective in prolonging RFS but is not necessarily curative.

In the management of GIST tumors, several key concepts emerged in the integration of a novel, efficacious targeted therapy. First of all, the timing of surgery was now stratified with the risk of recurrence. Tumors with a relatively favorable pathology continued to be treated with surgery alone. Resectable tumors with high-risk features are now treated with adjuvant imatinib in order to decrease the risk of recurrence. Metastatic tumors are treated with imatinib up front, and usually only selected patients with a favorable response are chosen for further surgical resection. The emergence of resistance after prolonged drug therapy favors the timing of surgery at a point of maximal response in the metastatic setting. In melanoma, similar concepts are emerging in the era of targeted therapy.

TRANSLATION OF TARGETED THERAPY FOR MELANOMA

Metastatic melanoma, has classically been treated with surgery or systemic chemotherapy.²⁹ Up until recently, chemotherapy options included an alkylating agent, such as dacarbazine. The disease-specific survival was uniformly poor with a historical survival of <1 year (Table 1).³⁰ Surgery for metastatic melanoma in carefully selected patients has suggested a durable survival in up to 20 % of patients.^{31,32}

Whether this result represents the selection of patients with a favorable tumor biology or a true benefit of surgery was the investigation of a phase III trial comparing the benefit of surgical versus medical therapy for stage IV metastatic melanoma (NCT01013623), which was closed.

The Emergence of New Therapeutic Targets: Mutations in Melanoma, BRAF and KIT

In 2002, genome-wide screens of melanoma demonstrated mutations resulting in a substitution of glutamic acid for valine at position 600 in the gene BRAF, Val600Glu (designated herein as BRAF^{V600E}).³³ BRAF is part of the RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) signal transduction pathway (Fig. 2a). The BRAF^{V600E} mutation destabilizes the inactive conformation of the BRAF kinase, shifting the equilibrium to the constitutively active state.³⁴ This leads to activation of the MAPK pathway, ERK activation, and cell proliferation (Fig. 2b). Other BRAF mutations include V600 K (5–6 %), V600R (1 %), V600E2 (0.7 %), V600D, and others.^{35–37} Mutations of the tyrosine kinase

KIT, as has been described in GIST, have also been demonstrated in melanoma. ~20 % of patients with mucosal or acral melanoma have a mutation of KIT.^{38,39} Other mutated genes in the MAPK pathway, such as those of NRAS, GNAQ, and GNA11, have also been identified and may also serve as therapeutic targets in the future.

Initial targeting of the RAF pathway with sorafenib yielded disappointing results, perhaps in part as a result of an inability to obtain an optimal dose of drug to inhibit the pathway.¹ However, the next generation RAF inhibitors, Vemurafenib (formerly PLX4032; Roche, Basel, Switzerland), demonstrated high response rates never previously seen in the treatment of metastatic melanoma.⁴⁰ In a phase I dose escalation trial with vemurafenib (PLX4032), a 60 % response rate was obtained in patients with the BRAF mutation receiving at least 240 mg.⁴¹ In a randomized phase III trial, treatment with vemurafenib improved overall survival and progression free survival in comparison to patients treated with dacarbazine. The response rate of vemurafenib was 45 % versus dacarbazine, which was 5 %.⁴²

Another BRAF inhibitor, dabrafenib (GSK21118436; GlaxoSmithKline, Brentford, UK), which may have enhanced selectivity for BRAF^{V600E}, has also demonstrated significant results. In a phase II study (BREAK-2) of 92 patients, the objective response rate was 59 %, with two objective responses in 16 patients with the BRAF V600K mutation.⁴³ The efficacy of dabrafenib was confirmed in a phase III randomized multicenter trial (BREAK-3) comparing dabrafenib with dacarbazine with response rates of 53 and 19 % for dabrafenib and dacarbazine, respectively.⁴⁴

Mutations in KIT are identified in ~20 % of patients with mucosal or acral melanomas (Fig. 3).^{38,39} The majority of KIT mutations (up to 46 %) are located within exon 11. Exon 13, which encodes for the proximal tyrosine kinase domain, is mutated in 19 % of cases.^{45,46} Exon 9, which encodes for the extracellular domain, is mutated in 6 % of cases. Lastly, exons 17 and 18, which encode for the distal tyrosine kinase domain, are mutated in 10 and 19 %, respectively.⁴⁷ Phase II clinical trials have demonstrated a response rate of melanoma harboring KIT mutations to imatinib therapy of ~15 to 20 %.^{47,48} Of note improved response rates were correlated with mutations in exons 11 (L576P) and 13 (K642E).⁴⁷⁻⁵⁰

INTEGRATION OF SURGERY WITH TARGETED THERAPIES

In the management of metastatic disease, new algorithms are developing because of the success of these new drugs. However, the success of surgery alone should not go unrecognized. The survival of carefully selected patients with metastatic disease have 5-year survival rate of up to 42 %. Despite the inherent bias in selecting patients for surgery, it does support the use of surgery as an initial treatment component, particularly in patients with low volume or M1a disease.

Clinical trials are currently examining the role of BRAF inhibitors in the adjuvant setting of patients with stage III disease. In a similar fashion to the GIST trials, these melanoma trials are offered to patients deemed to be high risk. The first study is a phase II trial of patients with resected stage IIIC melanoma with the BRAF V600E or V600K mutation (NCT01682213) where all patients will receive adjuvant BRAF inhibition. A second study randomizes patients with resected stage IIC or III melanoma with BRAF^{V600E}

(NCT01667419) to adjuvant treatment or placebo. Patients with stage IIIA must have at least 1 mm focus of metastatic disease in the lymph node.

An additional question is whether BRAF inhibitors can be used in a neoadjuvant fashion to surgery, as imatinib is used, in marginally resectable disease or in patients with meta-static disease. The response to BRAF inhibitors is within weeks, enabling early detection of drug efficacy and resultant tumor shrinkage. Currently this is being done in individual cases and surgeons will have to define the role of debulking or definitive surgery after BRAF inhibition. An example of neoadjuvant BRAF treatment in the setting of a patient presenting with bulky inguinal and pelvic lymphadenopathy is demonstrated in Fig. 4. The same principle can be applied for patients who have a mixed or partial response to targeted therapy. This theoretically represents a good time for surgical debulking before perpetual resistance.

Therefore, much like GIST tumors, targeted mutations of melanomas have been identified. Effective inhibition of these pathways has resulted in high response rates for BRAF inhibition and is changing the field of melanoma dramatically. Clearly the BRAF^{V600E} mutation, much like the KIT exon 11 mutation in GIST, has the best response to therapy. High response rates with inhibition of KIT in GIST have not been recapitulated in KIT-mutated melanoma, for unclear reasons. Whether alternative dosing can affect the response of the KIT or BRAF^{V600K} mutation remains unclear and is the subject of ongoing clinical trials.

THERAPEUTIC TOXICITY: MANAGING THE CONSEQUENCES

Imatinib Toxicity

Generally, imatinib, an orally administered agent, is well tolerated. Most common adverse events include anemia, edema, nausea, diarrhea, rash and muscle cramps. From clinical trials, it is known that a majority of patients will have one symptom, but most are mild and this only leads to discontinuation of the drug in up to 14 % of patients.³⁶ Care has to be taken with imatinib, as it is a competitive inhibitor of the cytochrome P450 system and may alter concentrations of other drugs, which are metabolized by the CYP450.

Toxicity of RAF Inhibitor Therapy

Vemurafenib is also orally administered and well tolerated, with the most common side effects being arthralgia, fatigue and rash. In a randomized trial, 38 % of patients required dose modification or interruption because of side effects. The cutaneous toxicity can be quite significant and involves a remarkable photosensitivity, with blistering in 12 % of patients. Another unique skin toxicity is the development multiple low-grade squamous lesions in 18 % of patients while receiving therapy.⁴² These lesions include squamous cell carcinoma, and keratoacanthomas, which are low grade and usually require only local therapy. The etiology of these neoplasms remains unclear but may be secondary to paradoxical activation of wild type cells, which lack a BRAF mutation.^{51–55}

MECHANISMS OF RESISTANCE

Primary Resistance

In GIST, primary resistance is associated with mutations in KIT exon 9 or PDGFR α mutations, many of which can be overcome by increasing drug dosage or switching to an alternative tyrosine kinase inhibitor such as sorafenib.⁵⁶ In BRAF^{V600E} melanoma, alterations or deletions of molecules in the MAPK pathway may play a role in primary resistance to RAF inhibition.^{57–60} One such molecule is PTEN.^{57,61} Loss of PTEN, a negative regulator of AKT, has been demonstrated in a subset of BRAF mutant melanoma resulting in AKT activation. When PTEN is lost and BRAF is inhibited, there is an increase in downstream AKT signaling, leading to decreased apoptosis.⁶¹ Additionally, concomitant PTEN and RB1 protein loss results in cell cycle checkpoint dysregulation and intrinsic resistance to BRAF and MEK inhibitors.⁵⁷ Cyclin D and protein kinase D3 (PKD3) may also play a role in primary resistance to BRAF inhibitors. Inhibition of mutant BRAF in cell lines leads to the weakening of MEK/ERK signaling, a reduction in cyclin D1 expression, and cell cycle arrest.⁵⁸ However, a small subset of BRAF-mutant melanoma cell lines harbor cyclin D1 amplifications. Cell lines that possess both amplifications in cyclin D1 and BRAF mutations demonstrate intrinsic resistance to BRAF inhibition.⁶⁰

Secondary Resistance

Secondary, or acquired, resistance suggests tumor progression after an initial response to the drug occurred. Acquired or secondary resistance eventually occurs in most GIST and melanoma patients treated with targeted therapies. The median time to resistance is approximately 7 months with BRAF inhibitors and 2 years for imatinib in GIST.^{5,41,42} In GIST, the development of secondary mutations, especially those in the tyrosine kinase domains encoded by exons 13 and 17 of KIT lead to the development of secondary resistance.^{62–64} However, there have been no similar gatekeeper mutations found in BRAF inhibitor resistant cell lines or biopsies taken from patients who have failed vemurafenib.^{65,66} Multiple mechanisms have been shown to play a role in acquired resistance to BRAF inhibitors such as constitutive signaling of receptor tyrosine kinases (IGF-1R and PDGFR α), increased expression of COT (MAP3K8,TPL-2) in the MAPK cascade, NRAS and MEK1 mutation acquisition and resultant BRAF alterations.^{60,67–71} Recently, work has identified a new mechanism of RAF acquired resistance, with an in-frame deletion of exons 4–8, encoding the RAS-binding domain critical for BRAF activation.⁷² The significance and frequency of these mechanisms of resistance in melanoma remains unknown and are under clinical investigation.^{69,72–76}

FUTURE DIRECTIONS

Combination with Immunotherapy

Recently, significant progress has been made in the fields of both immunotherapy and targeted therapy. Ipilimumab (Yervoy, Bristol-Meyers Squibb), a human monoclonal antibody that targets cytotoxic T-lymphocyte antigen 4 (CTLA-4), has been shown in two phase III randomized control trials to improve overall survival in patients with advanced melanoma.^{77,78} Although responses can be durable and result in a cure, the response rate is

only 10–20 %.^{77–79} Targeted therapies have high response rates but resistance invariably develops, and therefore, investigations are underway to combine immunotherapy and targeted therapies to obtain better long-term outcomes. Preclinical models have suggested that combining immunotherapy with any treatment that enhances cell death can increase antitumor responses. In a GIST model, it has been demonstrated that the tyrosine kinase inhibitor is synergistic with CTLA-4 blockade.⁸⁰ There is currently a phase I clinical trial combining ipilimumab with dasatinib in sarcomas (NCT01643278). It is important to note that the “off target” effects of many targeted therapies are not well known. These studies will have to be carefully undertaken to minimize any potential toxicity. This is highlighted by the recent report of liver toxicity combining ipilimumab and vemurafenib which closed this phase I trial to further patient accrual.⁸¹

Most recently the treatment of melanoma has been advanced by the efficacy of additional immunotherapies. PD-1 blockade is based upon similar principles at CTLA-4 blockade. PD-1 is expressed on activated T cells and “exhausted” T cells. The ligand for PD-1, PL-L1, is expressed on many tumor cells, including many melanomas. Blockade of PD-1 has led to promising results in melanoma. In a phase I study, 42 % of patients responded to PD-1 blockade.⁸² Similar but not as encouraging results were found for PD-L1 blockade with 17 % of patients having a response.⁸³ Combination treatment with CTLA-4 blockade (ipilimumab) and PD-1 blockade (nivolumab) demonstrated a response rate on the order of 50 %.⁸⁴ Whether targeted treatments could be combined with new immunotherapies to improve survival remains under investigation.

CONCLUSION

Many lessons in the treatment of melanoma can be gleaned from the GIST model. The BRAF^{V600E} mutation, much like the KIT exon 11 mutation in GIST, has the best response to therapy. The successful inhibition of KIT in GIST has not been recapitulated in KIT-mutated melanoma, for unclear reasons. Although surgery remains an important component of the treatment of GIST and melanoma, surgeons will need to continue to define the thresholds and timing for operation in the setting of improved neoadjuvant and adjuvant treatments. Combination treatment strategies, accounting for individual pathway alterations, may result in more successful clinical outcomes in the management of melanoma in the future.

Acknowledgments

Supported in part by the National Institutes of Health under Ruth L. Kirschstein National Research Service Award T32 CA009501 (DMB), and RO1 CA102613 (RPD).

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FIG. 1.
Structure of KIT and PDGFRA and distribution of identified mutations in GIST

FIG. 2.

Normal activation of MAPK pathway and pathway response to RAF inhibition. a Normal activation of the wild-type cell RAS–RAF–MEK–ERK pathway promotes cell growth. b Mutations of the MAPK pathway, especially those of oncogenic BRAF^{V600E} in melanoma, result in enhanced signaling in the MAPK pathway and eventual tumor formation and growth. In the presence of a BRAF inhibitor that blocks BRAF, MEK–ERK signaling in BRAF^{V600E} mutant cells is suppressed, causing tumor shrinkage. *RTK* receptor tyrosine kinase (e.g., KIT, FLT2, PDGF, VEGF), *RAS* rat sarcoma, *RAF* rapidly accelerated fibrosarcoma, *MEK* MAPK/ERK kinase, *ERK* extracellular signal–regulated kinase

FIG. 3. Structure of KIT and distribution of identified mutations in melanoma. KIT mutations are found in 2–6 % of all malignant melanoma, mostly in the acral and mucosal subtypes

FIG. 4.

Neoadjuvant vemurafenib. A patient with primary melanoma of the leg presented with bulky superficial and deep inguinal nodes (**a red arrows**). A BRAF^{V600E} mutation was noted, and a metastatic disease assessment was negative. The patient initiated neoadjuvant vemurafenib therapy, with significant reduction in the size of the lymphadenopathy at 12 weeks (**b yellow arrows**), at which time he underwent lymph node dissection. Pathology revealed three positive nodes, and the BRAF^{V600E} mutation was detected in the posttreatment specimen. The patient subsequently developed brain metastasis

TABLE 1

Mutation and survival data of GIST and melanoma

Characteristic	GIST	Melanoma
U.S. incidence	4,000	75,000
Primary localized disease		
Cured by surgery (%)	70	~70 ^a
Median survival metastatic disease		
Historical (months)	<12	<10
Surgery alone (months)	27	12
Current	5 years	16 months
Imatinib		
Response rate (%)	80	20 ^b
Median PFS	20 months	3.5 ^b
Vemurafenib		
Response rate	–	50 %
Median PFS	–	7 months
Primary mutations		
KIT (%)	85	20 ^b
Exon 11 (%)	65	45 ^a
PDGFR α (%)	10	–
BRAF V600E (%)	1	50
Secondary resistance mechanisms	KIT exon 13, 17 mutation	Multiple ^c

GIST gastrointestinal stromal tumor, *PFS* progression-free survival^aVaries depending on tumor histopathologic features (thickness, ulceration, mitoses)^bAcral and mucosal melanoma^cIncludes constitutive signaling of receptor tyrosine kinases (IGF-1R, PDGFR α), increased expression of COT (MAP3K8,TPL-2) in the MAPK cascade, and acquisition of new NRAS or MEK1 mutations