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Clinical trials in melanoma patients with brain metastases

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Dear Editor

With the approval of inhibitors of CTLA-4, BRAF, MEK, and PD-1 for advanced melanoma, systemic therapy has dramatically improved. Due to the historically poor prognosis for patients with melanoma brain metastases (MBMs), coupled with concerns about blood–brain barrier penetration of larger molecules, the original trials with most of these agents excluded patients with brain involvement. Treatment of MBMs has consisted primarily of local therapy with surgery, whole brain radiation, or stereotactic radiosurgery. Each carries its own set of short- and long-term risks that may affect neurological and neurocognitive functions (Flanigan et al., 2013). Effects of newer systemic therapies on MBMs therefore need assessment.

A substantial proportion of metastatic melanoma patients develop MBMs; the incidence at autopsy is 75% and ~40% develop clinically apparent disease (Flanigan et al., 2011). Among the first trials evaluating BRAF-targeting therapy for untreated MBMs was a trial with sorafenib and temozolomide (Table 1). Patients with asymptomatic MBMs had a median progression-free survival (PFS) of 3.5 months, compared to 4.2 months in patients without, demonstrating feasibility of systemic therapy for untreated MBMs (Amaravadi et al., 2009). The phase I trial of dabrafenib in unresectable BRAF-mutant melanoma included ten patients with small, untreated MBMs; tumor shrinkage was seen with no additional toxicities (Falchook et al., 2012). This led to a phase II trial of dabrafenib in 172 patients with lesions <40 mm diameter. The intracranial response rate (RR) among patients without and with prior surgery or radiation was 39 and 30.8% (Long et al., 2012). A pilot study of 19 patients with previously untreated MBMs using vemurafenib showed 30% shrinkage in MBMs in 37% (Dummer et al., 2014).

Immune therapies also have activity in MBMs. A retrospective study of patients on a phase II trial with ipilimumab identified 12 patients with MBMs at trial entry. Two had a partial response (PR) in the brain, three had stable disease (SD); three of these five were still alive at 4 yr (Weber et al., 2011). A subsequent prospective, multicentered phase II trial studied ipilimumab specifically in patients with MBM (Margolin et al., 2012). Patients with either asymptomatic MBMs or symptomatic MBMs on a stable steroid dose were enrolled. The 12-week cerebral disease control rate was 24% in patients off steroids, 10% in patients on steroids. The difference is likely due to steroid immunosuppression and patient

characteristics. In a phase II study of ipilimumab plus fotemustine, 20 patients had asymptomatic brain metastases, 25% had SD or PR in the brain, and 25% had a CR. Interestingly, patients with MBMs had the same median overall and 3-yr survival as those without (di Giacomo et al., 2012).

These limited studies suggest that both targeted and immune therapies have activity in the brain, and might reduce the need for radiation and surgery for local control. Case series for both targeted and immune therapies have confirmed activity of these drugs in patients with MBM (Gibney et al., 2015; Knisely et al., 2012). These studies have demonstrated that accrual of patients with MBM to trials is feasible and have resulted in additional studies for MBMs with newly approved drugs or drugs in late stages of development (Table 2).

With the increasing population of patients with MBM, revision of clinical research programs to include them in disease-specific systemic therapy trials is required. In recent years, trials tend to include patients with treated, stable brain metastases, and pharmaceutical companies are now supporting MBM-specific trials prior to drug approval. The trials in Table 1 show that brain and extracerebral responses are typically concordant, and studies in other malignancies confirm this, suggesting that drugs cross the impaired blood–brain barrier seen in brain metastases (Bachelot et al., 2013; Costa and Kobayashi, 2012). Additional studies are evaluating systemic therapies together with radiation. Systemic therapy studies use variable inclusion criteria specific to brain metastases. Allowable prior local therapy is inconsistent, as are concurrent steroid use, allowable lesion size, and response criteria (Table 3). Limiting the number and/or size of allowable metastases in immune therapy trials and use of prophylactic anti-epileptics might increase RRs and decrease steroid use. Separate cohorts for patients with leptomeningeal disease are warranted. Image interpretation in MBMs is challenging, and clinical trial end points and response criteria require revision. MBM-related adverse events and neurotoxicity similarly need refinement, including long-term neurotoxicity and effects of local and systemic intervention on adjacent brain parenchyma. Moreover, the interaction between systemic therapies and radiation and resultant neurological toxicities is unknown. These newer clinical trial designs for brain metastasis patients will contribute to a rapidly evolving field while providing hope to patients with MBM.

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Table 1

Completed melanoma brain metastases trials

Author	Therapy	Cohort	# of Patients	Key inclusion criteria	RR (intracranial)	PFS	OS
Amaravadi (2009)	Sorafenib and temozolomide	N/A	53	Asymptomatic, prior radiation allowed, no steroids	15%	3.5 months	8 months
Long (2012)	Dabrafenib	A	89	No prior local therapy	33.7%	14.7 weeks	27.2 weeks
		B	83	1 prior local therapy, steroids allowed	28.9%	16.4 weeks	29.3 weeks
Dummer (2014)	Vemurafenib	N/A	24	1 prior local therapy, steroids allowed	16.1%	3.9 months	5.3 months
Margolin (2012)	Ipilimumab	A	51	Asymptomatic	16%	1.5 months	7 months
		B	21	Requiring steroids	5%	1.2 months	4 months

Table 2

Current clinical trials for patients with melanoma brain metastases involving systemic therapy

ClinicalTrials.gov Identifier	Title	Status	Phase
NCT01721603	A Phase 2 Prospective Trial of Dabrafenib with Stereotactic Radiosurgery in BRAF V600E Melanoma Brain Metastases	Active, not recruiting	Phase II
NCT02115139	GEM Study: Radiation and Yervoy in Patients with Melanoma and Brain Metastases (GRAY-B)	Recruiting	Phase II
NCT01703507	Ipilimumab and Whole-Brain Radiation Therapy or Stereotactic Radiosurgery in Treating Patients with Melanoma with Brain Metastases	Recruiting	Phase I
NCT02085070	MK-3475 in Melanoma and NSCLC Patients with Brain Metastases	Recruiting	Phase II
NCT02097732	Ipilimumab Induction in Patients with Melanoma Brain Metastases Receiving Stereotactic Radiosurgery	Recruiting	Phase II
NCT01950195	SRS (Stereotactic Radiosurgery) Plus Ipilimumab	Recruiting	Phase I
NCT02039947	Study to Evaluate Treatment of Dabrafenib Plus Trametinib in Subjects with BRAF Mutation-Positive Melanoma that has Metastasized to the Brain	Recruiting	Phase II
NCT01378975	A Study of Vemurafenib in Metastatic Melanoma Patients with Brain Metastases	Active, not recruiting	Phase II
NCT02065466	Combo of Abraxane, TMZ, Bevacizumab in Metastatic Melanoma with Brain Metastases	Recruiting	Phase I/II
NCT02230306	Phase II Study of Cobimetinib in Combination with Vemurafenib in Active Melanoma Brain Metastases (CoBRIM-B)	Recruiting	Phase II
NCT01978236	An Open-Label, Multicentre, Corollary Study of Pre-Operative Therapy With Dabrafenib and the Combination of Dabrafenib With Trametinib in Subjects With BRAF Mutation-Positive Metastatic Melanoma to the Brain	Recruiting	Phase II
NCT02320058	A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain Treated with Nivolumab in Combination with Ipilimumab Followed by Nivolumab Monotherapy (CheckMate 204)	Recruiting	Phase II

Table 3

Inclusion criteria and response assessment for patients with melanoma brain metastases (MBMs)—completed studies

Author	Year	Therapy	Phase	Size	Symptoms	Prior therapy	Response assessment
Falchook	2012	Dabrafenib	I	>/3 mm	Asymptomatic from MBMs	No prior resection, SRS, or WBRT	Modified RECIST
Amaravadi	2009	Sorafenib and temozolomide	II		Stable or clinically asymptomatic	Prior radiation allowed if steroids discontinued	RECIST
Long	2012	Dabrafenib	II	5–40 mm	Asymptomatic from MBMs	Cohort A: no prior local therapy Cohort B: progressive disease after local therapy	Modified RECIST 1.1
Dummer	2014	Vemurafenib	Pilot	Measurable disease not required		Prior local therapy required	RECIST 1.1
Margolin	2012	Ipilimumab	II	5–30 mm, and/or 2 measurable lesions >3 mm		Prior irradiation allowed, untreated lesions required.	Modified WHO