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Dear NCCN Cutaneous Melanoma Guideline Panel:

On behalf of Partner Therapeutics, I respectfully request the *NCCN Cutaneous Melanoma* Guideline Committee review the enclosed data that support adding the combination of ipilimumab and sargramostim (glycosylated yeast-derived rhu GM-CSF) to the Guideline as a second-line or subsequent treatment option for metastatic or unresectable melanoma. Today, most patients with metastatic melanoma receive PD-1:PD-L1 blockade therapy in the adjuvant or first line setting. Many of these patients are left with few options when they experience disease progression. Ipilimumab is FDA approved for treatment of melanoma, whereas sargramostim is FDA approved yet not indicated for melanoma. We believe combined ipilimumab/sargramostim is an important, less toxic option for patients that merits Committee consideration.

Specific Request: We request the combination of ipilimumab and sargramostim be listed as an "Other regimens" option for second-line or subsequent therapy on page 1 of section ME-I (Systemic Therapy for Metastatic or Unresectable Disease), based on Version 2.2021 of the Cutaneous Melanoma Guidelines.

Rationale: When melanoma metastasizes to distant sites, 5-year survival is only 29.8% (SEER 18 2011-2017, All Races, Both Sexes by SEER Summary Stage 2000). Hence, death due to advanced melanoma represents a persistent unmet medical need. Treatment options for unresectable or metastatic melanoma have dose-limiting, severe adverse events, particularly immune-related adverse events associated with checkpoint inhibitors, including ipilimumab. Nonetheless, ipilimumab remains important for the treatment of patients with advanced melanoma. Dose benefit and risk relationships have been established for ipilimumab, which is approved at 1 mg/kg, 3 mg/kg and 10 mg/kg doses across several indications. Recent long-term follow-up data from Ascierto *et al.* report that a 10 mg/kg dose of ipilimumab versus 3 mg/kg showed an overall survival of 15.7 months vs 11.5 months (hazard ratio [HR]=0.84; p=0.04) in patients with unresectable metastatic melanoma (Ascierto 2020). Improving the benefit-risk ratio of ipilimumab would represent a significant advance in treatment and address a serious unmet medical need. Preclinical and translational studies demonstrated antitumor activity of GM-CSF in advanced melanoma, with additive or synergistic activity observed when combined with immune checkpoint inhibitors (Van Elsas 1999; Li 2009; Kwek 2016). GM-CSF improves antigen presentation by mature dendritic cells, increasing priming and activation of tumor-infiltrating T lymphocytes in tumor draining lymph nodes and the tumor microenvironment (Tarhini 2021). Clinical data supporting sargramostim usage both to increase survival and ameliorate irAEs are detailed below.

ECOG study 1608 was a prospective, randomized phase II trial that compared overall survival of sargramostim plus ipilimumab versus ipilimumab alone in patients with advanced melanoma (Hodi 2014). In total, 245 patients were randomized 1:1 to ipilimumab 10 mg/kg every 3 weeks for 4 cycles, then every 12 weeks, either with sargramostim 250 mcg/day for 14 days of 21-day cycles, or alone. Primary analysis at a median 13.3 months follow-up is summarized in the following table.

Outcomes	Ipilimumab + Sargramostim (n=123)	Ipilimumab (n=122)	P value
Number of deaths	44	60	-
Median overall survival	17.5 months	12.7 months	0.01
0ne-year survival	68.9%	52.9%	0.01
Mortality hazard ratio	0.64		0.01

No significant differences in other secondary clinical outcomes (progression-free survival, clinical response rates) were observed between treatment arms. It is now well established that ipilimumab can improve overall survival without an associated progression-free survival or response rate benefit. This finding may be due to tumor pseudoprogression, *i.e.* increased lesion size that resembles progressive disease yet is actually treatment related. Pseudoprogression is associated with an influx of inflammatory cells that follows some immune-modulating therapies, including ipilimumab. Additionally, posthoc analyses for changes in CD8+ ICOS T cells found increases as a function of treatment to be higher on the sargramostim arm compared to ipilimumab alone (0.5 vs 0.4; p=0.01); CD4+ ICOS T cells were greater but not signicant (2.55 vs 1.85; p=0.11) (Hodi 2014).

In addition to increased survival, fewer patients in the sargramostim group had grade 3-5 adverse events compared to the ipilimumab alone arm (44.9% vs 58.3%; p=0.04). Reduction of grade 3-5 gastrointestinal (16.1% vs 26.7%; p=0.05) and pulmonary (0% vs 7.5%; p=0.003) toxicities favored the sargramostim combination arm over the ipilimumab alone arm. Correspondingly, colonic perforation occurred in 1.7% of patients on the sargramostim combination arm versus 5.8% on the ipilimumab alone arm. A total of 25 patients on the sargramostim combination arm and 39 patients on the ipilimumab alone arm discontinued treatment due to adverse events. Patients who discontinued treatment early due to adverse events had better overall survival in the sargramostim combination arm compared to the ipilimumab alone arm (p=0.04). Additionally, to rule out an improved survival benefit due to toxicity benefit alone, further analysis was performed after censoring treatment-related lethal adverse events; overall survival benefit was maintained on the sargramostim arm (median OS not reached [95% CI, 14.9 months, not reached]) compared with ipilimumab alone (14.3 months [95% CI, 11.1 months, not reached]) (p=0.03) (Hodi 2014).

E1608 study results have been confirmed in 2 additional trials. Kwek *et al.* conducted a prospective, single-arm phase II trial of ipilimumab with sargramostim in 22 metastatic melanoma patients (Kwek 2016). Patients received ipilimumab 10 mg/kg on day 1 with sargramostim 125 mcg/m^2/day for 14 days in 21-day cycles for 4 cycles, followed by 3 months of sargramostim alone, followed by maintenance therapy of ipilimumab with sargramostim every 3 months for up to 2 years. The primary endpoint of disease control rate at 24 weeks was 41%. Median overall survival was 21.1 months, and grade 3-4 adverse events occurred in 41% of patients. Luke *et al*. retrospectively evaluated 32 metastatic melanoma patients who received ipilimumab 3 mg/kg on day 1 with sargramostim 250 mcg/day for 14 days in 21-day cycles for 4 cycles (Luke 2015). Overall disease control rate at 12 weeks was 50% by RECIST criteria and 44% by immune-related response criteria. Median overall survival was 41 weeks. Overall incidence of immune-related adverse events was 31.3% of which 9.4% were grade 3-4 events, including 7.4% grade 3-4 colitis. While this ipilimumab dose was lower compared to the dose used in E1608, adverse events still plague ipilimumab therapy and support the addition of sargramostim to enhance patient tolerance.

The following articles are included in support of this proposed change.

- Ascierto P, Del Vecchio M, Mackiewicz A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. *J Immunother Cancer*. 2020; 8:e000391. doi: 10.1136/jitc-2019-000391
- Van Elsas A, Hurwitz AA, Allison JP. Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. *J Exp Med.* 1999;190(3):355-366. doi: 10.1084/jem.190.3.355
- Li B, Vanroey M, Wang C, et al. Anti-programmed death-1 synergizes with granulocyte macrophage colony-stimulating factor--secreting tumor cell immunotherapy providing therapeutic benefit to mice with established tumors. *Clin Cancer Res*. 2009;15(5):1623-1634. doi: 10.1158/1078-0432.CCR-08-1825
- Kwek SS, Kahn J, Greaney SK, et al. GM-CSF and ipilimumab therapy in metastatic melanoma: clinical outcomes and immunologic responses. *Oncoimmunology*. 2016;5(4):e1101204. doi: 10.1080/2162402X.2015.1101204
- Tarhini AA, Joshi I, Garner F. Sargramostim (rhu GM-CSF) and immune checkpoint inhibitors: combinatorial therapeutic studies in metastatic melanoma. *Immunotherapy*. 2021. In Press. doi: 10.2217/imt-2021-0119
- Hodi SF, Lee S, McDermott DF, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. *JAMA*. 2014;312(17):1744-1753. doi:10.1001/jama.2014.13943
- Luke JJ, Donahue H, Nishino M, et al. Single institution experience of ipilimumab 3 mg/kg with sargramostim (GM-CSF) in metastatic melanoma. *Cancer Immunol Res*. 2015;3(9):986–991. doi: 10.1158/2326-6066.CIR-15-0066

Combining sargramostim with immune checkpoint inhibitors for advanced melanoma remains of clinical interest. The ongoing ECOG-ACRIN 6141 phase II/III trial is evaluating the combination of ipilimumab, nivolumab, and sargramostim, compared to ipilimumab plus nivolumab alone in unresectable stage III and IV melanoma. The trial recently resumed accrual to the phase III portion after meeting prespecified efficacy and safety thresholds.

We believe this evidence supports adding the ipilimumab/sargramostim combination to the *NCCN Cutaneous Melanoma* Guideline as an option in second line therapy for metastatic or unresectable disease, given its improved toxicity profile and impact on overall survival compared to ipilimumab alone. Please do not hesitate to reach out to me directly at 216-978-8003 or hillard.lazarus@partnertx.com if you have any questions.

Sincerely,

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