SUPPLEMENTARY METHODS

INCLUSION CRITERIA

- Histologically confirmed unresectable AJCC stage IIIc or stage IV melanoma
- Patients must have metastatic melanoma with a resectable metastatic lesion(s) of sufficient size (≥ 2-3 cm in total) and must be willing to undergo such a resection for experimental purposes. Resected metastases during stage IV disease that were removed at much earlier time points, but were used to grow clinical grade TIL up to Rapid Expansion Protocol may be used as well with informed consent of the patient.
- Patients should have received maximum one line of systemic therapy (except for ipilimumab) for unresectable or metastatic melanoma.[Note that prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized.]
- Patients must be ≥ 18 years and ≤ 75 years of age and must have measurable disease by CT or MRI per RECIST 1.1 criteria (in addition to the resected lesion).
- Patients must have a clinical performance status of ECOG 0 or 1 (Appendix B) [40].
- Patients of both genders must be willing to practice a highly effective method of birth control during treatment and for four months after receiving the preparative regimen.
- Patients must be able to understand and sign the Informed Consent document.
- Laboratory Parameters (**Note**: patients may undergo resection with lab values outside of the parameters listed below if it is anticipated that the resection will correct the abnormality).
    - Hematology:
        - Absolute neutrophil count greater than 1.5 x 10^9/L without support of filgrastim.
        - Platelet count greater than 100 x 10^9/L.
        - Hemoglobin greater than 5 mmol/L, or 80 g/L.
    - Chemistry
        - Serum ALAT/ASAT less than 3 times the upper limit of normal, unless patients have liver metastases (< 5 times ULN).
        - Serum creatinine clearance 50 ml/min or higher.

        - Total bilirubin less than or equal to 20 micromol/L, except in patients with Gilbert's Syndrome who must have a total bilirubin less than 50 micromol/L.
        - LDH ≤ 2x ULN
- Serology:
    - Seronegative for HIV antibody. (The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who are HIV seropositive can have decreased immune-competence and thus be less responsive to the experimental treatment and more susceptible to its toxicities.)
    - Seronegative for hepatitis B antigen, and hepatitis C antibody. Seronegative for syphilis.
    - HSV, EBV, and CMV (positivity for HSV, EBV, or CMV is not an exclusion criterion for participation, but prophylactic medication can be started when deemed necessary prior to chemotherapy treatment in the case patients randomize for the TIL treatment arm).

EXCLUSION CRITERIA

- Life expectancy of less than three months.
- Patients with metastatic ocular/ mucosal or other non-cutaneous melanoma.
- Adjuvant treatment with ipilimumab within 6 months prior to randomization.
- Requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressive drugs within the last 3 weeks prior to randomization.
- Patients who have more than two CNS metastases.
- Patients who have any CNS lesion that is symptomatic, greater than 1 cm in diameter or show significant surrounding edema on MRI scan will not be eligible until they have been treated and demonstrated no clinical or radiologic CNS progression for at least 2 months.
- The following patients will be excluded because of inability to receive high dose interleukin-2 (also see Appendix C):
    - History of coronary revascularization
    - Documented LVEF of less than 45% in patients with:
        - Clinically significant atrial and/or ventricular arrhythmias including but not limited to: atrial fibrillation, ventricular tachycardia, 2° or 3° heart block

    - Documented FEV1 less than or equal to 60% predicted for patients with:
        - A prolonged history of cigarette smoking (greater than 20 pack/year within the past 2 years)
        - Symptoms of respiratory distress
- All patients' toxicities due to prior non-systemic treatment must have recovered to a grade 1 or less. Patients may have undergone minor surgical procedures or focal palliative radiotherapy (to non-target lesions) within the past 4 weeks, as long as all toxicities have recovered to grade 1 or less.
- Women who are pregnant or breastfeeding, because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant.
- Any active systemic infections, coagulation disorders or other active major medical illnesses.
- Any autoimmune disease: patients with a documented history of inflammatory bowel disease, including ulcerative colitis and Crohn's disease are excluded from this study as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, autoimmune thyroiditis (e.g. Hashimoto's disease), autoimmune hepatitis, systemic progressive sclerosis (scleroderma), Systemic Lupus Erythematosus, autoimmune vasculitis (e.g., Wegener's Granulomatosis). Subjects with motor neuropathy considered of autoimmune origin (e.g., Guillain-Barré Syndrome) are excluded from this study. Patients with vitiligo are eligible to enter the study.