Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma

Objectives and endpoints

The primary objective is to compare progression free survival at 6 months between patients treated with ipilimumab as compared to patients treated with T-cell therapy using tumor-infiltrating lymphocytes (TIL).

Target population

Patients with irresectable or metastatic (stage IIIc or IV) melanoma, who are ≥ 18 and ≤ 75 years of age, who are eligible for treatment with ipilimumab, and who are physically and mentally able to tolerate high-dose interleukin-2 and high-dose cyclophosphamide and fludarabine.
See main inclusion criteria.

Treatment plan

Eligible patients (n = 168) will be randomized between arm A or B. Patients that are randomized in arm A will receive standard therapy with ipilimumab 3 mg/kg, q 3 weeks, maximal 4 times. Patients randomized in arm B will receive TIL therapy consisting of chemotherapy for 7 days (cyclophosphamide 60 mg/kg for 2 days, fludarabine 25 mg/m^2 for 5 days), infusion of autologous TILs followed by high-dose interleukin-2, 600.000 IU/kg/dose every 8 hours for up to 15 doses.

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Main inclusion criteria

- ≥ 18 and ≤ 75 years of age.
- The patient has locally advanced or metastatic cutaneous melanoma.
- The patient has received maximum one line of systemic therapy (except for ipilimumab).
- The patient has a resectable lesion of at least 1 cm^2 ***and*** at least one measurable parameter according to RECIST 1.1.
- The patient has an ECOG performance status of 0 or 1.
- The patient must have adequate organ function and blood samples, e.g.
  - LDH ≤ 2 x ULN
  - Seronegative for HIV, hepatitis, syfillis.

Main exclusion criteria

- Life expectancy less than three months.
- The patient has ocular/mucosal or other non-cutaneous melanoma.
- The patient has more than two CNS metastases, or any lesion that is symptomatic, greater than 1 cm in diameter or show significant surrounding edema on MRI. If CNS metastases have been treated and are stable with no clinical or radiological CNS progression, the patient may be eligible.
- The patient has
  - History of coronary revascularization
  - Documented LVEF < 45%
  - Documented FEV1 ≤ 60%.
- Any active infections, severe autoimmune disease or other major medical illnesses.
- The patient requires systemic steroids for management of immune-related adverse events experienced on another immunotherapy.
- Concurrent treatment with other experimental drugs.