METRO-PD1: A Phase I Feasibility Study Evaluating Anti-PD1 (NIVOLUMAB) In Combination With Metronomic Chemotherapy In Children And Teenagers With Refractory/Relapsing Solid Tumors Or Lymphoma

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RATIONAL

Metronomic chemotherapy (MC) consists in giving low doses of anticancer agents on a daily/weekly basis. MC has been shown to inhibit tumor angiogenesis and to stimulate the immune system through selective depletion in regulatory T cells, modulation of myeloid-derived suppressor cells or maturation of dendritic cells. Recently, **immune checkpoint inhibitors** have yielded a considerable interest in pediatric oncology.

Combining MC to antiPD1 will not only prevent chemotherapy induced immunosuppression, but can also deplete or mature cells from the immune system, and may strengthen the inhibition of the immune blockade obtained with antiPD1.

A multicenter Phase I study was designed to evaluate Anti-PD1 Nivolumab in combination with 3 different metronomic chemotherapy (MC) regimens in children with refractory /relapsing solid tumors or lymphoma.

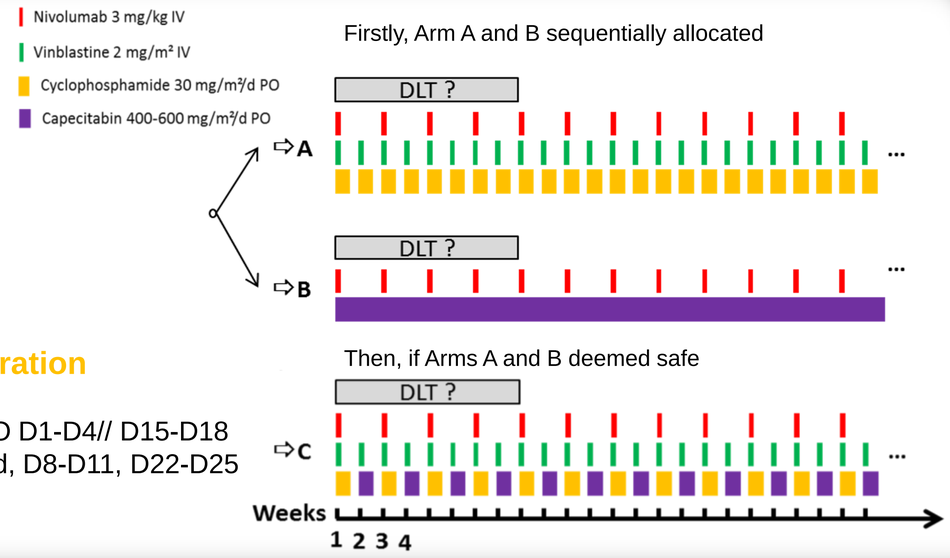
METHODS/OBJECTIVES

Objectives were to identify the MC regimen deemed feasible when given with Nivolumab, to evaluate the safety profile, Overall Survival (OS), and Progression-Free Survival (PFS). Dose-limiting toxicities (DLTs) were evaluated over the first two 28-day cycles. Patients were evaluable if they received > 2 cycles and > 70% of the planned dose. Patients received intravenous (IV) **Nivolumab 3 mg/kg D1 & D15** combined with :

Arm A: Dendritic cell maturation & Treg depletion
Vinblastine 2 mg/m^2 IV weekly
Cyclophosphamide 30mg/m^2/d PO D1-4, D8-11, D15-18, D22-25

Arm B: Myeloid-Derived Suppression Cell depletion
Capecitabine PO 400-600 mg/m^2/d

Arm C: multiple immune restoration
Vinblastine 2 mg/m^2 IV weekly
Cyclophosphamide 30 mg/m^2/d,PO D1-D4// D15-D18
Capecitabine PO 400-600 mg/m^2/d, D8-D11, D22-D25



MAIN INCLUSION CRITERIA

- ✓ Histologically proven progressive/refractory solid malignant tumor
- ✓ Age > 4 to < 18 years (patients > 18 years if initial diagnosis before the age of 18)
- ✓ Evaluable and/or measurable disease defined by adequate standard imaging criteria
- ✓ Adequate hematologic, cardiac, renal and hepatic functions
- ✓ Patients on stable doses of corticosteroids (≤ 0.25 mg/kg prednisolone or equivalent) for at least 7 days prior to receiving study drug
- ✓ Written informed consent
- ✓ Patients can have received prior treatment with antiPD1 or anti-PDL1 if at least SD for 6 months or PR or CR was obtained.
- ✓ Patients with a known partial deficiency of dihydro-pyrimidine-deshydrogenase (DPD) activity are eligible, and must have an uracilemia value ≥16ng/ml and <150ng/ml

Assessment of DLTs during the first two 28-day cycle, defined as :

Hematological toxicity:

Grade 4 neutropenia for more than 7 days

Grade 3 or 4 thrombopenia requiring transfusions for more than 7 days

Febrile neutropenia with or without documented infection

Requirement of platelet transfusion support for more than 5 days

Non-hematological toxicity grade 3 or 4:

Grade ≥ 3 total bilirubin and/or ALT and/or AST (non-transient < 7 days)

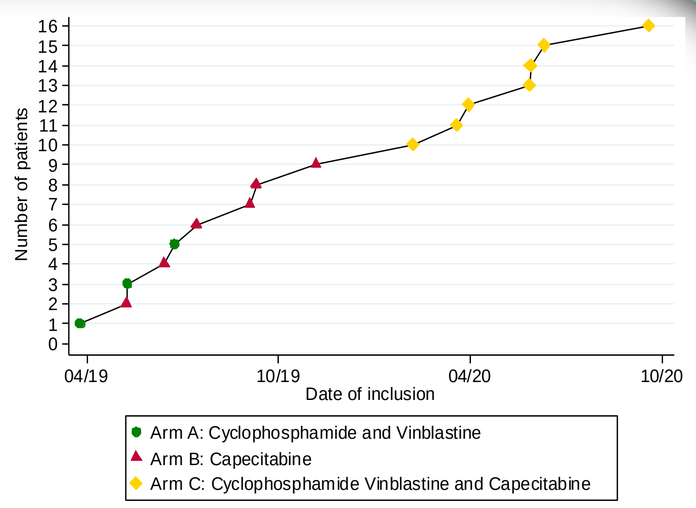
Grade ≥ 3 nausea, vomiting, or diarrhea despite appropriate symptomatic therapy

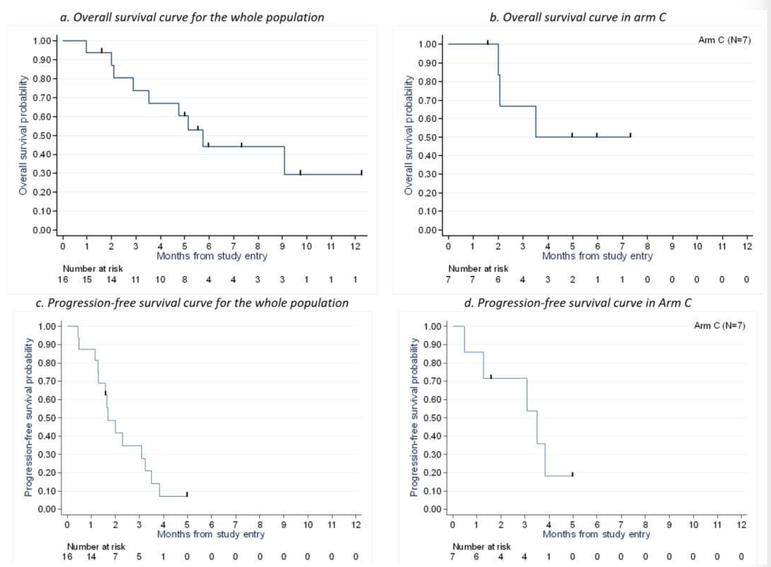
Other grade ≥ 3non-hematological toxicities except for the exclusions noted below

Grade 2 toxicities that are considered not tolerable for the patient

RESULTS

- ✓ 16 patients enrolled between March 2019 and Sept 2020, 3 in arm A, 6 in arm B, and 7 in arm C
- ✓ Median age: 11.5 years (5-19)
- ✓ Previous treatment : 3.5 (1-4) lines of systemic treatment, surgery (87.5%) and/or radiotherapy (69%)
- ✓ Median number of cycles : 2 (1-11), median treatment duration : 56.5 days (28-342).
- ✓ 13 out of 16 patients available for DLT : 3 in arm A, 4 in arm B, 6 in arm C.
- ✓ Overall, treatment was well tolerated, **No DLT was observed during the first two 28-day cycle,**
  - ✓ Grade 3 adverse events (AE) and Serious AE in 43.8% and 12.5% respectively over the first 2 cycles. No grade 4 occurred.
  - ✓ Most frequent < grade 3 clinical toxicity was asthenia.
  - ✓ Most frequent ≥ grade 3 biological toxicities were anemia and lymphopenia.
  - ✓ 12% did not report any AE related to treatment during all duration of treatment.
  - ✓ Toxicities ≥ grade 3 were rare : loss of appetite (2) catheter infection (1), hypoalbuminemia (1), hypokalemia (2), bone pain (1), Intracranial hypertention (1), dyspnea (1), pleural effusion (1)
  - ✓ 5 SAE (1 in A, 3 in B, 2 in C), all during cycle 1-2, all but 1 due to disease progression.
  - ✓ 75% of patients did not present any SAE, no immune related sever toxicities reported.
- ✓ Three-month and 6-month OS rates: 75% (95%CI: 46-90) and 44% (20-66), respectively.
- ✓ Three-month and 6-month PFS rates: 37% (15-60) and 12% (2-33), respectively.
- ✓ Best overall response: stable disease for 6 patients (37.5%), progressive disease for 10 (62.5%).
- ✓ 4 patients alive at the date of last news: 1 in arm B (12.2 months from inclusion) and 3 in arm C with a follow-up of respectively 7, 10 and 14 months.





OS and PFS curves, whole population (a,c) and Arm C (b,d)
(N=16, intention to treat data set)

CONCLUSION

Treatment with Nivolumab in combination with cyclophosphamide, vinblastine and capecitabine (Arm C) is safe. Randomized phase II trial comparing Arm C +/- Nivolumab is ongoing.

THANKS

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