Immune activation and clinical responses following long-term infusion of anti-GD$_2$ antibody ch14.18/CHO in combination with interleukin-2 in high-risk neuroblastoma patients

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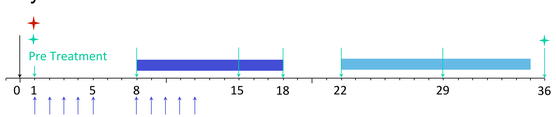
Introduction:

Immunotherapy with bolus infusion of monoclonal anti-GD$_2$ antibody (mAb) ch14.18 in combination with cytokines effectively prolonged survival in high risk neuroblastoma (NB). In a compassionate use program, we piloted a treatment using continuous infusion of ch14.18/CHO in combination with interleukin-2 (IL-2) and 13-cis-RA and report PK, immune activation, clinical response and survival.

Methods and Patients:

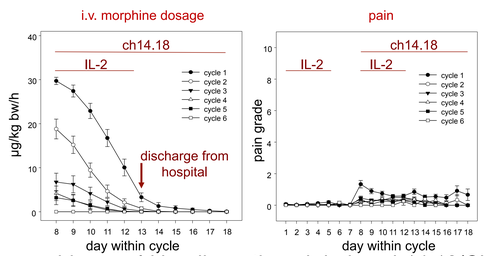
- 53 high risk neuroblastoma patients
- 5-6 cycles
- Clinical response assessments in pts with measurable disease by mIBG, MRI/CT, bone marrow- and catecholamine- analysis before, after 2/3 and after 5/6 cycles.



↑ aldesleukin (rh IL-2); 2 x 5 daily s.c. injections (6 x 10^6 IU/m^2/ day = 60x10^6 IU/m^2/ cycle)
■ ch14.18/CHO (ANP 311); 10 day continuous i.v. infusion (10 mg/m^2/day = 100 mg/m^2/cycle)
■ 13 cis retinoic acid; 14 days p.o. (160 mg/m^2/day (b.i.d.); 2240 mg/m^2/cycle)

↓ pharmacokinetics and effector function (ADCC, CDC, whole blood assay)
+ human anti chimeric response determination
+ Fc receptor polymorphism and KIR/KIR ligand mismatch

Pain toxicity profile assessment:

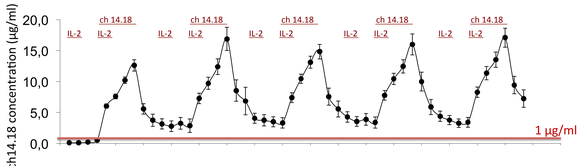


I.v. morphine could be discontinued during ch14.18/CHO. All patients could be transferred to outpatient care.

morphine application	Phase I Bridging Study (SIOPEN, Europe) (8hr infusion; n = 16) (5)	LTI (SIOPEN, Europe) (10 day infusion; n = 53)
starting dose	50 µg/kg bw/h	30 µg/kg bw/h
additional application	63%	15%
dose increase	50%	15%

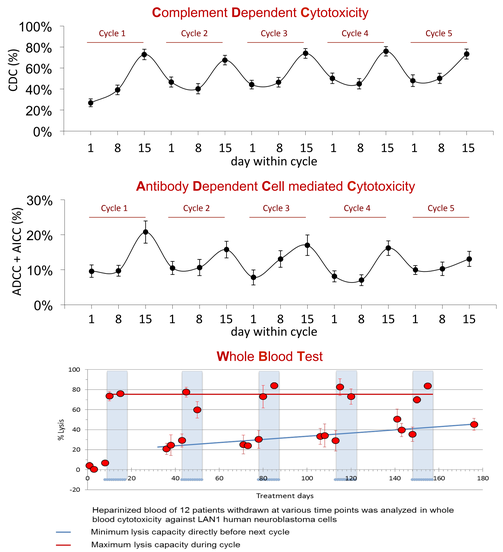
Morphine usage is reduced with LTI compared to 8hr infusion.

Serum level of ch14.18/CHO (1) over cycles



All Patients developed effective serum levels of > 1 µg/ml ch14.18 persisting throughout the entire treatment period of 6 months.

Effector function of ch14.18/CHO:

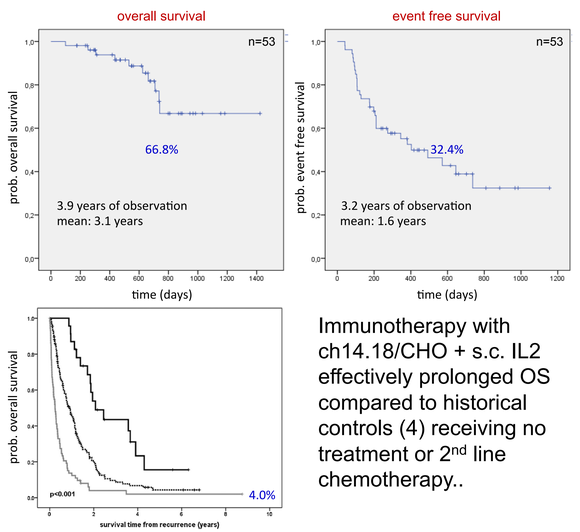


CDC, ADCC and WBT against neuroblastoma cells (LAN-1) indicate persistent anti-neuroblastoma activity for 6 months.

Response rates:

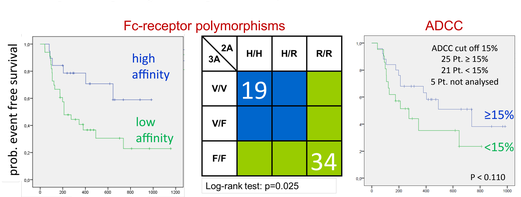
15 of 36 responded (SIOPEN score) (3) = 41.7%
7 of 22 responded (RECIST 1.1): = 31.8%.
6 of 21 responded: = 28.6%.
INRG Criteria (2): 12 of 40 patients showed a response
= 30.0% response rate (5 PR, 7 CR).

Survival analysis:



Immunotherapy with ch14.18/CHO + s.c. IL2 effectively prolonged OS compared to historical controls (4) receiving no treatment or 2nd line chemotherapy..

Fc-receptor polymorphism, ADCC and survival:



High affinity Fc receptor polymorphisms and higher levels of ADCC reaction in vitro are associated with improved EFS supporting **A**ntibody **D**ependent **C**ell mediated **C**ytotoxicity as the primary mechanism of action.

References:

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Summary:

- Application of ch14.18/CHO as long term infusion dramatically improved the pain toxicity profile of this anti-GD$_2$ treatment.
- At the same time, effective Ab levels and anti-neuroblastoma activity (ADCC and CDC) were achieved for the entire treatment.
- Importantly, this translated into remarkable response rates and improved survival in high risk NB patients.

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