Behandeling van uitgezaaid melanoom met Tumor Infiltrating Lymphocytes (TIL), ervaringen uit onze fase III studie

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Disclosure

• Onderzoek in samenwerking met:
  – NEON Therapeutics
  – BMS
  – Medimmune

• Niet gerelateerd met deze studie
Melanoma: incidence and immunogenicity

- Responds poorly to chemotherapy
- Immunogenic:
  - Many melanoma antigens known
  - Recognized by T lymphocytes
    - Shared and neo-antigens (high mutational load)
- Number #1 tumor type for immunotherapy

Alexandrov et al. Nature. 2013
Tumor reactivity of T cells is determined solely by the T cell receptor (TCR)

Reasons T cell does not kill cancer cell:

- Improper priming/activation of T cells
- “Correct” T cell receptor not present
- Immune suppressive tumor micro-environment

Majority of immunotherapy aims to restore/increase tumor recognition by T cells
Immunotherapy—T cell versus melanoma

Active immunotherapy
- Peptide vaccine
- DC vaccine
- Genetic vaccine
- IL-2
- IFN
- IL-15
- IL-21

Adoptive cell transfer (ACT) immunotherapy
- TIL therapy

T cell checkpoint blocking and stimulating antibodies
- CTLA4
- PD-1
- CD40
- OX40
- CD137

TCR or CAR genetic engineering

kindly provided by Toni Ribas & Christian Blank
Patient pretreated with lymphodepleting chemotherapy

T cells are isolated from melanoma tumors

Rapid Expansion

Infusion of TIL + high dose IL-2

- 50% response rate in phase I/II trials in multiple centers (US, Israel, DK)
- 10-20% Complete responders
- Worldwide >500 patients treated
TIL production overview

- Single cell suspension from autologous tumor mass
- Outgrowth phase (approx 14 days)
- Rapid Expansion → high cell numbers (14 days)
- Washing and preparing infusion bag
- QP release of ATMP

- Surgery to infusion 4-6 weeks

<table>
<thead>
<tr>
<th>Quality Controls (QC)</th>
<th>Specification</th>
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<tbody>
<tr>
<td>QC(1) Microbiological contamination</td>
<td>negative (day -2 before infusion)</td>
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<tr>
<td>QC(3) Total cell number</td>
<td>&gt;5x10^9 TIL and &lt;2x10^{11}</td>
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<tr>
<td>QC(4) Viability</td>
<td>&gt;70% living cells</td>
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Example Complete Response (CR) first phase I/II trial at NKI

Prior to TIL

Biopsy at 7 weeks showed no viable tumor cells
→ ongoing CR >8 years

Van den Berg et al, in preparation
Clinical prospects of TIL

- >500 patients have received TIL treatment worldwide
- Phase I/II
- Registration and/or reimbursement requires formal proof of efficacy

Phase III multicenter study

- 168 patients planned, started in 2014
- 2\textsuperscript{nd} line metastatic melanoma (after failure aPD-1)

Randomization

\[ \text{TIL} \rightarrow \text{Ipilimumab (a CTLA-4)} \]

- Temporary re-imbursement TIL therapy for this trial in NL
- KWF funding to open additional centers abroad
Inclusion phase III TIL trial

Total inclusion TIL trial NL + DK

Inclusie totaal NL + DK
Gewenste Inclusie

Aantal patienten

Tijd

September 2014
September 2017
September 2020

0
20
40
60
80
100
120
140
160
180

168
74
Lessons learned

• Strong interdisciplinary network within NKI-AVL allows smooth operation
  – Setup during phase I/II

• Fresh T cell product, production in close proximity patient required → Harmonization production process:
  – Important to include centers as early as possible

• Voluntary Harmonization Procedure (VHP) successfully used for submission in different countries

• Patient recruitment challenging:
  – Dipped in 2015-2016 because approval aPD-1 as first line MM
  – Currently increase in inclusion:
    • Progression upon aPD-1
    • More referrals from other melanoma hospitals
  – KWF funding allows to open additional centers
Future of TIL therapy

• After failure of aPD-1, better second line treatment still desired in MM:
  – Current second line: Braf inhibition or aCTLA-4
  – We believe TIL is better than the current alternatives

• Costs:
  – Academic price of a full TIL treatment (clinical + production) ≈ 60.000 euro
  – Commercial price of aCTLA-4 drug product = 80.000 euro
  – Health Technology Assessment included in phase III

• If phase III trial successful, we aim for approval and re-imbursement of TIL therapy
  – Training of clinical and production centers in the Netherlands included in temporary re-imbursement program
  – Sanquin Laboratory Cellular Therapy trained as additional production center for this trial and beyond
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All patients!