Adoptive T cell transfer
TILs in solid cancer

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DISCLOSURE OF INTEREST

Honoraria for speaker, consultancy or advisory role:
• Roche, Novartis, Merck, MSD, Celgene, Incyte, TILT bio, Pfizer, BMS, AstraZeneca, IO Biotech, Sanofi-Aventis, Ipsen, Pierre Fabre

• Co-founder IO Biotech

My institution have received limited research grants from:
• BMS, Roche, Novartis
Patient case

- 47 y/o man

History

- **2006**: primary melanoma in the face
  - Resection of several local recurrences during the next years
- **2012**: Recurrent disease lung and small intestines
  - **Treatment**: highdose Interleukin-2 + Interferon-α2b: PD
  - **Treatment**: Ipilimumab 3 vs 10 (4 courses): PD
- **2012, October**: tumor-resection and TIL production
- **2013, January**: bowel-obstruction (resection of metastatic lesions in the intestines)

- The weeks before T cell therapy: weight loss, several blood transfusions, pneumonia, diarrhea
Patient case

- **2013, February**: Adoptive T cell therapy
  - Day -7 to -1: chemotherapy
  - Day 0: infusion of $1.31 \times 10^9$ TILs
  - Day 0-2: decrescendo IL-2 - (71 MIU, 60%)

- **Adverse events**
  - Day 2 during IL2:
    - Capillary leak syndrome
    - Hypotension (hemodynamic unstable)
    - Respiratory distress
    - Decreasing diuresis
    - Bowel obstruction

Discharged day 39
Baseline CR according to RECIST after 13 months

8 weeks: PR

CR according to RECIST after 13 months

CR ongoing 5 years after TIL

CR verified with MRI
Tumor Infiltrating Lymphocytes - TILs

T cells frequently infiltrate melanomas

TILs have the potential to recognize multiple targets on tumor cells

Erdag G et al., Cancer Res 2012;72(5):1070-80

Adoptive T-cell therapy using autologous tumor-infiltrating lymphocytes

- Tumor removed by surgeon
- Tumor cut into small fragments
- Optional cryopreservation
- >50,000,000 TILs
- Anti-CD3 Feeders IL-2
- IL-2
- Fragments or digest put into culture plates
- Initial TIL expansion (2-4 weeks)
- TIL rapidly expanded in static or dynamic conditions
- Rapid expansion of TIL ("REP") (14 days)
- 50-200x10^6 TILs
- TIL infusion
- 30-45 days for TIL production

Patient hospitalized

0 - 10 days
TIL in combination with lymfoedepleting chemotherapy

3-step treatment:
Lymfoedepleting chemotherapy
  2 days: cyclophosphamide (60 mg/kg)
  5 days: Fludarabin (25 mg/m²)

Intravenous infusion of in vitro expanded TILs
  Day 7: reinfusion of 20–140x10⁹ TILs

High dose IL-2
  720,000 IU/kg iv every 8. hours until limiting toxicity

Rosenberg et al, PNAS 2004
Temporary bone marrow suppression

HD chemotherapy leads to:

- reduced level of immune suppressive immune cells
- reduced immune competition

Rosenberg Science 2015
Toxicity

• Intensive chemotherapy
  – Bone marrow suppression
  – Electrolyte derangement
  – Nausea, diarrhoea

• T-cells
  – Fever, chills, dyspnoea

• IL-2
  – Fever, capillary leak syndrome, fluid retention, hypotension, electrolyte derangement, nausea
  – Autoimmune manifestations are less frequent

All patients experience temporary grade III-IV events
All patients receive RBC/platelet transfusion and antibiotics
Adoptive T-cell Therapy for metastatic melanoma patients - NCI, USA

Before the era of checkpoint inhibitors

- Response rates
  ~ 50-70%
- > 20%
  long term survivors

20 CR: 3-year survival 100% and 5-year survival 93%
Adoptive T-cell Therapy for metastatic melanoma patients – CCIT, Denmark

Patients previously progressed on HD IL2 and ipilimumab

- 25 patients with progressive treatment-refractory metastatic melanoma

- 3-step treatment: HD chemotherapy, TIL infusion, IL-2
  - Intermediate dose IL-2 (Decrescendo-regimen*)
    - 18 MIU/m² over 6 h, 12 h and 24 h
    - 4.5 MIU/m² over 24 h for 3 days


Clinical Cancer Res 2016

- ORR: 42%
- mOS: 21.8 months

Partial response patients with 100% change have non-target lesions present
Can baseline Patient Characteristics predict response?

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Responders OR, (n = 10)</th>
<th>Non-Responders OR, (n = 14)</th>
<th>P-value OR vs NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>56 (40;68)</td>
<td>51 (25;63)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sex (% male)**</td>
<td>5 (50)</td>
<td>5 (36)</td>
<td>0.68</td>
</tr>
<tr>
<td>Primary tumor origin (% skin)**</td>
<td>8 (80)</td>
<td>10 (71)</td>
<td>1.00</td>
</tr>
<tr>
<td>AJCC Stage (% M1c)**</td>
<td>8 (80)</td>
<td>12 (86)</td>
<td>1.00</td>
</tr>
<tr>
<td>BRAF status (% wt)**</td>
<td>5 (50)</td>
<td>6 (43)</td>
<td>1.00</td>
</tr>
<tr>
<td>HLA-A2 (% HLA-A2)**</td>
<td>2 (20)</td>
<td>7 (50)</td>
<td>0.21</td>
</tr>
<tr>
<td>Tumor burden (cm)*</td>
<td>12.5 (1.9;34.2)</td>
<td>12.9 (5.5;21.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>LDH level (% elevated)**</td>
<td>6 (60)</td>
<td>9 (60)</td>
<td>1.00</td>
</tr>
<tr>
<td>Metastatic sites*</td>
<td>2 (1;6)</td>
<td>4 (1;7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Previous treatments*</td>
<td>2 (1;4)</td>
<td>2 (2;4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Prior response to IL-2**</td>
<td>2 (22.2)</td>
<td>4 (26.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Prior response to Ipilimumab**</td>
<td>1 (12.5)</td>
<td>1 (7.7)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*) Median (range), Mann-Whitney
**) n (%), Fisher’s Exact test

Clinical Cancer Res 2016
Immunology correlates to tumor regression

Infusion products

- Tested against autologous tumor
- Tested against allogeneic tumors

Clin Cancer Res 2016
PD-1+ Polyfunctional T cells persist following TIL therapy

3 functions = triple positive for TNF, IFN-γ and CD107a after coculture with tumor cells
Additional predictive Biomarkers

Figure 2. Tumor mutation and neoantigen load predict response and benefit from ATCT. Mutation (A) and neoantigen (B) load in Responders and Non-responders. Overall survival in patients stratified by mutation (C) and neoantigen (D) load.
Which patients are candidates to TIL therapy?

General criteria
• Age < 70
• > resectable metastatic lesion of sufficient size (> 1 cm³)
• Good clinical performance status of ECOG 0 or 1
• No brain metastases (1-2 smaller, subclinical brain metastases could be allowed)
• Sufficient organ function
• No active systemic infections, coagulation disorders or other active major medical illnesses which exclude HD chemotherapy/Interleukin-2.
• Metastatic melanoma
  — Progressive disease after standard therapy including check point inhibitors?
PD-1 resistance: unmet medical need

Can T cell therapy work in patients progressed on anti-PD1?
T cell responses in patients with melanoma resistant to multiple immunotherapies

Median CD8+ T cell responses: 23%

>80% of patients with detectable response. Median CD8+ T cell responses: 23%

Median in PD-1 naive (Donia et al., Cancer Res 2015)

Annals of Oncology 2018
In vitro tumor-reactivity is associated with clinical tumor regression

A  Best change in target lesion size (%)

<table>
<thead>
<tr>
<th>Time</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6 weeks</td>
<td>5.2%</td>
<td></td>
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<tr>
<td>12 weeks</td>
<td>26.8%</td>
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<td></td>
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<tr>
<td>18 months</td>
<td>46.7%</td>
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<tr>
<td>24 months</td>
<td>0.07%</td>
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B  Change in target lesion size from baseline (%)

- Progression
- Progression with new lesion

C  Patient MM12: Partial response with NED

D  CD8+ PBLs vs autologous tumor cells

- Baseline
- Discharge
- 6 weeks after TIL
- 12 months after TIL

Annals of Oncology 2018
Randomized phase III study comparing TIL based ACT to standard ipilimumab treatment in metastatic melanoma


Patients: 162 patients with metastatic (stage IV) melanoma and a resectable metastasis will be randomized 1:1 between arm A, standard treatment (ipilimumab) and arm B, TIL treatment.

Arm A: standard ipilimumab (3 mg/kg x 1 day i.v., q3w, 4 treatments).

Arm B: non-myeloablative chemotherapy (cyclophosphamide 60 mg/kg/day x 2 days i.v., fludarabine 25 mg/m²/day x 5 days i.v.) followed by intravenous adoptive transfer of at least 5 x 10⁹ TIL followed by high dose interleukin-2 (720.000 IU/kg/dose every 8 hours for up to 15 doses).

Stratification: Patients will be stratified for BRAF V600 mutation, 1⁰ or 2⁰ line treatment, and treatment center.

Primary endpoint:
  - PFS at 6 months

Secondary endpoints:
  - PFS according to irRC. ORR according RECIST 1.1 and irRC. CR rate. Overall survival. safety.
  - a constructive technology assessment (CTA) will be performed to evaluate the impact on patient, organizational and economic consequences.

Status: >50 patients randomized
Phase III TIL treated patient

Infused TIL Tumor reactivity

Clinical response to TIL therapy

Baseline 7/4-15
1. FU 29/5-15
2. FU 6/7-15
3. FU 4/9-15
What about other cancer types?

Metastatic cervical cancer
Selection of HPV TILs
CR in 2 of 9 patients

NCI, JCO 2015

Metastatic ocular melanoma
PR in 6 of 20 patients
2 prolonged responses

NCI, Lancet Oncol 2017
Expanding TIL treatment to other tumor types, CCIT

TIL-based ACT- clinical pilot study in patients with disseminated ovarian cancer.

- Advanced ovarian cancer (high grade serous carcinoma)
- Progressive or recurrent resistant disease after platin-based chemotherapy or later

First ovarian cancer patient treated with TIL based ACT

Before TIL therapy 6 weeks after TIL therapy
Adoptive Cell Therapy with Tumor-Infiltrating Lymphocytes in Patients with Metastatic Ovarian Cancer: A Pilot Study.
Magnus Pedersen, Marie CW Westergaard, Morten Nielsen, Troels Holz Borch, Lars G Poulsen, Helle Hendel, Trine Juhler-Nøttstrup, Özcan Met, Marco Donia, Inge Marie Svane.

In submission

Figure 1: Clinical response

Transient tumor effect, why and what can be done?
PD-1 is expressed on ovarian TILs and is shown to be associated with impairment of tumor antigen-specific CD8 T cells.

- Ovarian Tumor-derived NY-ESO-1–specific CD8+ T cells demonstrated impaired effector function, and enriched co-expression of LAG-3 and PD-1.

- LAG-3 and PD-1 blockade enhanced effector function of NY-ESO-1–specific T cells.

- Expression of PD-1 on the surface of about 60% of TILs from fresh tumor digest from ovarian tumors.

Indicating a potential benefit of adding anti-PD1 to TIL therapy
More frequent Ag specific TIL responses in patients after ipilimumab therapy

TIL reactivity from ipilimumab treated and untreated melanoma patients

Broader repertoire of T cell responses against common tumour antigens were found

Indicating a potential benefit of adding anti-CTLA4 to TIL therapy

Oncotarget 2017
TIL based ACT in combination with check point inhibitors

- Tumor resection
- Tumor cut into small fragments
- >50x10⁶ TILS
- Anti-CD3 Feeders IL-2
- IL-2
- Patient hospitalized
- Fragments or digest put into culture plates
- Initial TIL expansion (2-4 weeks)
- Rapid expansion of TIL ("REP") (14 days)
- Rapid expansion in static or dynamic conditions
- TIL infusion
- ipilimumab
- clophosphamid
- Fludarabin
- Interleukin-2
- Anti-PD1
- 2 weeks
- 0, 1, 2, 3, 4, 5, 6, 7, 14 weeks
TIL based ACT across cancer types in combination with check point inhibitors

• **Patient case**

• 57 years old male.
• Oropharyngis cancer with multiple lung metastasis.

• **History**
• 2012: diagnosed with bilateral tonsillar cancer (T1N0M0; Planocellular, P16+).
  – Bilateral tonsilectom and radiotherapy.
• 2017: multiple lung metastasis.
  – Treatment: progressed on Capecitabine/Paclitaxel and Pembrolizumab.
**TIL based ACT across cancer types in combination with check point inhibitors**

**Patient case**
- Infusion of 110x10e9 T cells.
- IL-2 treatment with 2 MIE every night for 2 weeks.
- Developed high fever and parotiditis during IL-2 treatment.
- Received the last 5 doses of IL-2 and 3 doses of nivolumab after discharge
- Evaluation with CAT-scan 6 weeks after T-cell infusion

6th of February 2018  
(Before admission)

9th of April 2018  
(6 weeks after T-cell infusion)

Unpublished
Conclusions

• T cell therapy using lymphodepleting high-dose chemotherapy and IL-2 is feasible and in general safe to use.

• Toxicity is manageable in a normal department of oncology.
  – Only available at few centres worldwide

• Complete and long-lasting response can be obtained.

• T cell therapy show clinical efficacy also after progressive disease on other immunotherapies

• Selected patients with metastatic melanoma should be offered T cell therapy
  – Many phase I/II data, phase III study ongoing
  – T cell therapy is still an experimental treatment
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