Precision
cancer immunotherapy

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Professor, consultant
Director CCIT
Timeline for Development of Immunotherapy

1891 First cancer "vaccine" demonstrated (Coley bacterial toxin)

1909 Cancer occurs spontaneously: immune system recognizes and protects (Paul Erlich)

Late 1950s Immunosurveillance theory introduced (Thomas Burnet)

1960s Adjuvants (e.g., BCG) shown to eradicate some tumors

1985 Adoptive immunotherapy for patients with cancer

1986 IFNα approved as cancer immunotherapy

1990 BCG approved for bladder cancer

1992 IL-2 approved for RCC

2000

2010 Sipuleucel-T approved as first autologous cellular immunotherapy

2010

2015 T-VEC approved as first oncolytic immunotherapy

2011 Ipilimumab approved for metastatic melanoma

2015 Nivolumab and Pembrolizumab approved for metastatic melanoma, lung cancer & RCC

2017 CD19 CAR-T approved as first genetically modified T cell

Unspecific agents

Precision agents
Tumor microenvironment
Immunostimulatory and – suppressive forces in the tumor micro-environment
Immunotherapy approaches in cancer
Immune check point inhibition

Immune checkpoint inhibition in metastatic melanoma

- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO
Impressive clinical response to ipilimumab + nivolumab
Clinical response rate to PD1/ PDL1 antibody therapy

**Single agent:**
- Melanoma ~35%
- Lung cancer ~30%
- Renal cancer ~25%
- Gastric cancer ~15%
- Bladder cancer ~20%
- Head and Neck cancer ~20%
- Colorectal cancer <10%
- Prostate cancer <10%

**Combination:**
- Melanoma >60%
Check point inhibitor (PD1/PDL1) status

“PDLOMAS” Activity in 2015

PD-1/PD-L1 Blockade

Numbers of trials using common combo strategies:
1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

Michot, EJC 2016
Tang, Annals of Oncol 2017
Personalized immunotherapy
Adoptive T-cell therapy using autologous tumor-infiltrating lymphocytes

1. Tumor removed by surgeon
2. Tumor cut into small fragments
3. Optional cryopreservation
4. > 50x10⁶ TILS
5. Anti-CD3
6. Feeders
7. IL-2
8. IL-2
9. Rapid expansion of TIL (“REP”) (14 days)
10. Fragments or digest put into culture plates
11. Initial TIL expansion (2-4 weeks)
12. TIL infusion
13. 50-200x10⁹ TILS
14. TIL rapidly expanded in static or dynamic conditions
15. Optional cryopreservation
16. 30-45 days for TIL production
Adoptive T-cell Therapy for metastatic melanoma patients – CCIT, Denmark

mOS: 21.8 months

ORR: 42%
Resistance to immunotherapy
Which patients are likely to respond to immunotherapy?
Immuno-Cold versus Hot tumor
PD-L1 expression and efficacy of anti-PD1 (pembrolizumab) in NSCLC

- Tumor foreignness
- Mutational load
- General immune status
- Lymphocyte count
- Absence of inhibitory
  - Tumor metabolism
  - LDH, glucose utilization
- Absence of soluble inhibitors
  - IL-6, CRP
- Absence of checkpoints
  - PD-L1

<table>
<thead>
<tr>
<th>PS</th>
<th>Median (95% CI), mo</th>
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<tbody>
<tr>
<td>≥50%</td>
<td>NR (13.7-NR)</td>
</tr>
<tr>
<td>1-49%</td>
<td>8.8 (6.8-12.4)</td>
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<tr>
<td>&lt;1%</td>
<td>8.8 (5.5-12.0)</td>
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Overall Survival, %

\[ \text{OS was assessed in all patients whose samples were stained within 6 months of cutting.} \]

Analysis cut-off date: August 29, 2014.
Genetic Basis of Response to Immunotherapy

adapted from:
Schumacher and Schreiber, Science 2015
Alexandrov et al., Nature 2013
Correlation between tumor mutational burden and objective response to anti-PD1/PDL1
Combined TMB and Tcell–inflamed signatures are predictive of PFS after anti–PD-1 treatment across multiple tumor types
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Patients (n = 86)</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>18 (21%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>28 (33%)</td>
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<tr>
<td>Stable disease</td>
<td>20 (23%)</td>
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<tr>
<td>Progressive disease</td>
<td>12 (14%)</td>
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<tr>
<td>Not evaluable</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>53%</td>
</tr>
<tr>
<td>95% CI</td>
<td>42% to 64%</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>77%</td>
</tr>
<tr>
<td>95% CI</td>
<td>66% to 85%</td>
</tr>
<tr>
<td>Median progression-free survival time</td>
<td>NR</td>
</tr>
<tr>
<td>95% CI</td>
<td>14.8 months to NR</td>
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<tr>
<td>2-year progression-free survival rate</td>
<td>53%</td>
</tr>
<tr>
<td>95% CI</td>
<td>42% to 68%</td>
</tr>
<tr>
<td>Median overall survival time</td>
<td>NR</td>
</tr>
<tr>
<td>95% CI</td>
<td>NR to NR</td>
</tr>
<tr>
<td>2-year overall survival rate</td>
<td>64%</td>
</tr>
<tr>
<td>95% CI</td>
<td>53% to 78%</td>
</tr>
</tbody>
</table>
Commensal bacteria shape systemic immunity

Adapted from Goldszmid RS & Trinchieri G, Nature Immunology 2012
Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy,1,2,3 Emmanuelle Le Chatelier,4 Lisa Derosa,1,2,3 Connie P. M. Duong,1,2,5 Maryam Tidjani Alou,1,2,3 Romain Daillère,1,2,3 Aurélie Fluckiger,1,2,5 Meriem Messaoudene,1,2 Conrad Rauber Maria P. Roberti,1,2,3 Marine Fidelle,1,3,5 Caroline Flamant,1,2,5 Vichnoi Poirier-Colame,1,2,5 Paule Opolon,6 Christophe Klein,7 Kristina Iribarren,8,9,10,11,12 Laura Mondragón,8,9,10,11,12 Nicolas Jacquetot,1,2,3 Bo Qu,1,2,3 Gladys Ferrere,1,2,3 Céline Clémenson,1,13 Laura Mezquita,1,14 Jordi Remon Masip,1,14 Charles Naltet,15 Solenn Brosseau,15 Courreche Kaderbhai,16 Corentin Richard,16 Hira Rizvi,17 Florence Levenez,4 Nathalie Galleron,4 Benoît Quinquis,4 Nicolas Pons,4 Bernhard Ryffel,18 Véronique Minard-Colin,1,19 Patrick Gonin,1,20 Jean-Charles Soria,1,14 Eric Deutsch,1,13 Yohann Loriot,1,3,14 François Ghiringhelli,16 Gérard Zalcman,15 François Goldwasser,9,21,22 Bernard Escudier,1,14,23 Matthew D. Hellmann,24,25 Alexander Eggermont,1,2,14 Didier Raoult,26 Laurence Albiges,1,3,14 Guido Kroemer,8,9,10,11,12,27,28* Laurence Zitvogel1,2,3,5*

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients

An evolving immunogram

Tumor foreignness
- Mutational load
- Neoantigen load

Tumor sensitivity to immune effectors
- MHC expression
- IFN-γ sensitivity
- Heterozygocity at all MHC loci

Absence of inhibitory tumor metabolism
- LDH, glucose utilization
- IDO1, tumor acidity

Absence of soluble inhibitors
- IL-6 → CRP/ESR
- CD73 → adenosine

General immune status
- Lymphocyte count, LAG3, TIGIT, CD27
- Ki67, PD1+, CD8
- Microbiome
  - Low bacteroides
  - High faecalibacterium prausnitzii

Immune cell infiltration
- Intratumoral T cells
- Shared T cell clones
- B7-H3/CD276 macrophages
- CCL5 attracting T cells
- CCR5 expressing BATF3 DC
- LAG3, TIM3, TIGIT, CTLA4

Absence of checkpoints
- PD-L1

Adapted from Blank Science 2016
Patient specific neo-antigen targeting T-cell therapy

Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

Zacharakis, Nature 2018
Patient specific neo-antigen targeting vaccination therapy

Day 0-14: Tumor & healthy tissue will be collected and sequenced.

Day 14-15: Next generation sequencing data will be analyzed using the Pioneer bioinformatics platform.


Day 30-35: Formulation as "bed-side mixing and vaccination."
Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

An immunogenic personal neoantigen vaccine for patients with melanoma
Precision cancer immunotherapy

- Anti-PD-1/anti-PD-L1
- Bring T cells into tumors
  - + anti-CTLA4 or other checkpoints
  - + immune activating antibodies or cytokines
  - + TLR agonists or oncolytic viruses
  - + immune suppressor cell inhibitors
  - + standard cancer therapies
- Generate T cells
  - Vaccines
  - TCR engineered ACT
  - CAR engineered ACT
  - TIL therapy

Modified from Ribas, Cancer Discovery 2016
Immunotherapy a revolution in cancer care

>3000 immunotherapy agents in development

3,394 agents were identified in six main classes
Personalized immunotherapy of cancer
Today, Tomorrow and The Future

Overall survival for advanced melanoma patients

- Personalized combinations and sequencing
- a-PD-1/mpi
- PD-1 pathway blockade
- ipilimumab

Adapted from Walter J Urba, ASCO 2013