PRINCIPLES OR MEDICAL THERAPY FOR CANCER

Targeted therapies

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CONFLICT OF INTEREST DISCLOSURE

Dr Christoph Oing

Personal financial interests

Institutional financial interests
- None

Non-financial interests / Leadership role medical societies non-remunerated
- Chairman “Junge DGHO” of the German Society of Hematology and Oncology (DGHO)
- ESMO YOC member

Other
- Travel and conference attendance: IPSEN (2017)
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Agenda

- HISTORY
- SMALL MOLECULES (NIBS)
- ANTIBodies (MABS)
- CELL THERAPY
CANCER TREATMENT

Taking aim...

- Targets DNA/RNA/Proteins
- Not tumour cell specific
- Hits replicating cells only
- Collateral damage / dose limiting toxicity
- Narrow therapeutic range
- Duration weeks - months

Chemotherapy

- Target specific
- Tumour specific
- Less toxic
- Better tolerable
- ’One size fits all‘ dosing
- Duration months – years
- Costly

Targeted therapy
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Cancer complexity

Hanahan & Weinberg, Cell 2011
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Identified drivers and potential targets

Garraway LA et al. JCO 2013
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Molecular therapy options

1. Growth factors and receptor tyrosine kinases
   EGFR, Her2, VEGF/R, c-kit

2. Extracellular matrix & angiogenesis
   VEGF/R, Integrins, hypoxia

3. Signal transduction pathways
   Ras, Raf, MAPK, MEK, ERK, AKT, PI3K

4. Cellular survival pathways
   Cycline-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2, PARP

5. Proteasome
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Drivers vary between entities

Garraway LA et al. JCO 2013
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Tumour heterogeneity

Marusyk A et al. Nat Rev Cancer 2012
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Major obstacles

- Driver identification (low frequencies)
- Intratumoural heterogeneity
- Escape pathways
- Biomarker abundance / assay reliability
- Lack of target specificity and shared target structures
- Toxicity due to "off target / tumour" effects
- Cost-effectiveness and accessability
- Lack of high-level evidence (Phase II early breakthrough)
SMALL MOLECULES
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Breakthrough: Imatinib in CML

- Philadelphia chromosome + CML, chronic phase
- Different options now available
  - Imatinib
  - Dasatinib
  - Nilotinib

\[\text{Saglio et al., NEJM 2010}\]
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Targeting BRAF V600E in stage IV melanoma

- ~50% of melanomas harbour BRAF\textsubscript{mut} (90% V660E)
- Chemotherapy with limited activity

**BRAFi mono**
- RR 50-60%
- DFS 7-9 mos
- OS 13-18 mos

**Comined BRAF/MEKi**
- RR 69-75%
- DFS 11-15 mos
- OS 25 mos
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EGFR TKI inhibitors in NSCLC

Pao W et al. Nat Rev Cancer 2010
## TARGETED THERAPY

### Specificity of TKIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>VEGFR1</th>
<th>VEGFR 2</th>
<th>VEGFR 3</th>
<th>PDGFR</th>
<th>FGFR1/3</th>
<th>EGFR</th>
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MONOCLONAL ANTIBODIES
# TARGETED THERAPY

Antibody structure & nomenclature

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<th>Source</th>
<th>Ending</th>
<th>Example</th>
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<tr>
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<td>Bevacizumab</td>
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<tr>
<td>Fully humanised</td>
<td>-umab</td>
<td>Panitumumab</td>
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</table>
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Rituximab in DLBCL

- Targets CD20 on all B-cells
- First breakthrough with antibody treatment
- Approved for DLBCL, FL, CLL
- Adopted for WHO Essential Medicines List 2015

Salles et al., Adv Ther 2017
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Targeting Her2+ breast cancer

- Metastatic breast cancer, 1st line
- Doce/Trastuzumab vs. Doce/Trastuzumab/Pertuzumab
- OS 56.5 vs. 40.8 months
- Duration of response + 7.7 months

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Targeting PDGFRα in soft tissue sarcomas

Anti-PDGFRα-mab Olaratumab in Soft tissue sarcomas

- Phase III ANNOUNCE trial negative
- Reasons yet unclear
- Not all successful phase II studies translate into positive phase III results
- Early access costly and potentially NOT beneficial

→ Accelerated FDA approval
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Antibody-drug conjugates

- Highly cytotoxic
- Stable in circulation
- Tumour tissue specific

Sharma et al., Nat Rev Drug Discov 2006
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Brentuximab-vedotin in Hodgkin’s lymphoma

- Standard of care for r/r Hodgkin’s lymphoma
- Combinations with chemotherapy also highly effective in the salvage setting
- Currently tested in 1st-line treatment BrECADD (HD21)
- Limited activity in CD30+ r/r testicular cancers

Younes et al., J Clin Oncol 2012
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Modern immunotherapy approaches

**Immune checkpoint blockade**
- Enhanced priming *(CTLA-4i)*
- Rejuvenation of exhausted T-cells *(PD-1/PD-L1i)*

**Adoptive cell transfer**
- TIL expansion
- TCR redirection
- CAR-T cell engineering

Knochelmann et al., Front Immunol 2018
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Tumour immunity

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

CTLA-4i
CAR-T
PD-1i/ PD-L1i

Chen & Mellman, Cell 2013
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PD-1/PD-L1 checkpoint blockade

CTLA-4i
- Ipilimumab
- Tremelimumab

PD-1i
- Nivolumab
- Pembrolizumab
- Avelumab

PD-L1i
- Atezolizumab
- Durvalumab
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Surrogate PD-L1 expression

But also PD-L1 negative tumours respond to PD-1-blockade!
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Predictors of response – MMR deficiency

FDA approval for all MSI high / MMR solid tumours granted in 2016

Le et al., NEJM 2015
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Predictors of response – TMB

Higher TMB $\rightarrow$ Neoantigen load $\uparrow$ $\rightarrow$ Immunogenicity $\uparrow$ $\rightarrow$ IO responses $\uparrow$
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Immune-related side effects

- Timing of onset varies remarkably (even after end of treatment)
- Fatal events possible (pneumonitis / hepatitis / colitis / myocarditis / etc.)

**Neurologic**
- Unilateral or bilateral muscle weakness
- Sensoric disorders
- Paraesthesia

**Pulmonary**
- Pneumonitis

**Hepatic**
- Elevated liver enzyme values (AST, ALT, total bilirubin)

**Gastrointestinal**
- Diarrhoea
- Abdominal pain
- Bloody stools
- Perforation
- Peritonism
- Ileus

**Endocrine**
- Fatigue
- Headache
- Psychic disorders
- Abdominal pain
- Changed bowel movement habits
- Hypotension
- Thyroiditis
- Hypophysitis

**Renal**
- Glomerulonephritis
- Creatinine elevation

**Dermatologic**
- Pruritus
- Rash

**Other**
- Uveitis, Iritis, Conjunctivitis
- Amylase / Lipase elevation
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Side effect management

Depending on CTCAE severity and kind of side effect

- Immunosuppression
- Treatment delay or cessation
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Enhance IO activity via combinations

- Higher activity $\rightarrow$ ORR 58% vs. 44% vs. 19%
- Also higher CTCAE grade III-IV toxicity

Wolchok et al., NEJM 2017
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Reality of Immunotherapy 2019

- Activity in ~20 tumour entities
- Response rates for monotherapy typically 10% - 30%
- Cost: anti-PD-1 ~ € 150k p/a
  anti-CTLA-4 ~ € 120k p/a
- Duration of treatment – unknown (up to 2 years and more)
- Duration of response – unknown (ongoing responses >7 years)
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Open questions in immunotherapy

- Hyperprogression
- Treatment duration
- Cost-effectiveness
- Optimal biomarkers for response prediction (PD-L1 expression, MSI, TMB, …)
- Combination therapy partners
- Turn immunologically cold tumours hot
CELL THERAPY
TARGETED THERAPY
Modern immunotherapy approaches

Adoptive cell transfer
- TIL expansion
- TCR redirection
- CAR-T cell engineering

Immune checkpoint blockade
- Enhanced priming (CTLA-4)
- Rejuvenation of exhausted T-cells (PD-1/PD-L1)

Knochelmann et al., Front Immunol 2018
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Chimeric antigen receptor (CAR)

1. Gen
2. Gen
3. Gen

https://www.slideshare.net/spa718/4-keiya-ozawa
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CAR-T therapy cycle

3-4 hrs

Remove blood from patient to get T cells

30 mins

CAR T cells bind to cancer cells and kill them

3-4 weeks

Make CAR T cells in the lab

Insert gene for CAR

Enrichment & activation

Lentiviral transduction

Expansion of CAR-expressing T-cells

Grow millions of CAR T cells

Isolation of cell product

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CAR-Ts against CD19+ lymphomas

https://www.slideshare.net/spa718/4-keiya-ozawa
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EMA-approved CAR-T therapies

Tisagenlecleucel (Kymria®)
Anti-CD-19 construct
B-cell acute lymphoblastic leukemia (ALL)
r/r diffuse large B-cell lymphoma
$ 475,000

Axicabtagene ciloleucel (Yescarta®)
Anti-CD-19 construct
r/r B-cell non-Hodgkin lymphoma
$ 373,000

Maude et al., NEJM 2018

ELIANA
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Immunotherapy obstacles

- How to best select?
- How to improve activity?
- How to afford?
- How to access?
- At what price?
- How much is a cure worth?
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Reality of targeted treatment approaches

Clinical characteristics
- r/r solid cancer
- Targeted biopsy
- 11 molecular targeting agents

741 screened

293 enrolled

195 randomly assigned

99 treated

96 physician’s choice

Pathway alterations
- Hormone receptor (N=40)
- PI3K/AKT/mTOR (N=46)
- RAF/MEK (N=13)

LeTourneau et al., Lancet Oncol 2015