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Can immunotherapy be the new weapon in the treatment of gliomas?

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Targeting tumor antigens in gliomas

Target Antigens: EGFRvIII, IDH1R132H, H3.3 K27M

Microenvironment
Post-treatment tissue

Tolerance
Exhaustion

Checkpoint Inhibitors
Rindopepimut: ACT IV Phase 3 Study Design

- **Protocol Title:** An International, Randomized, Double-Blind, Placebo Controlled Study of Rindopepimut/GM-CSF with Standard of Care Maintenance Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma

**BUT:** ACT IV (primary radiochemotherapy with rindopepimut/TMZ maintenance does not indicate any effect on OS (HR: 0.99; 20.4 vs 21.1 months))!

- Combination with standard maintenance temozolomide
  - Interim sample size re-estimation in which the trial may terminate early for futility or predicted success
  - Targeted accrual of 24 months and follow up of 18-24 months
EGFRvIII CAR T cells

3C10.BBz 3C10 scFv CD8α hinge 4-1BB CD3ζ
3C10.28BBz 3C10 scFv CD8α hinge CD28 4-1BB CD3ζ
139.BBz 139 scFv CD8α hinge 4-1BB CD3ζ

PLUS: Evidence for efficacy in a recent NEJM case report (2017)

Johnson, Sci Transl Med 2015
EGFRvIII-vaccine - resistance

BUT: ACT IV provides evidence that this loss of EGFRvIII expression is part of the natural course of disease at recurrence!

26/32 vaccine
0/15 control

Sampson, Neuro-Oncol 2010; Fan, Cancer Cell 2013
Moving up the hierarchy: IDH1 as shared mutated antigen

Suzuki et al., 2015

Capper et al., 2010
Development of an IDH1R132H-specific vaccine for glioma therapy

Peptide Vaccine

Companion Diagnostic

Schumacher, Bunse et al. Nature 2014
WO 2013/102641 A1, PCT/EP2013/050048

Bunse, Schumacher, Sahm et al. JCI 2015
DKFZ, P1203, EPA 14190538.0
NOA-16: IDH1RpepvaccH (NCT-2013-0216)

Screening

- IDH1R132H
- ATRX loss
- Measurable tumor

Cohort 1

XRT: radiotherapy (30 x 2 Gy; Mo-Fr)

aTMZ: adjuvant temozolomide (200 mg/m²; d1-5 of 28-day cycles)

cTMZ: concomitant temozolomide (75 mg/m² daily for 6 weeks)

IDH1R132H vaccine with imiquimod wk 2, 4, 6, 8, 12, 16, 20, 24

MRI + 2-hydroxyglutarate (2HG) magnetic resonance spectroscopy (MRS)

Immune monitoring (IDH1R132H antibody ELISA, EliSpot)

Trial successfully completed – data awaited for the end of 2017.
Randomized F/U trial combining the vaccine and checkpoint inhibition already developed – start end of 2017!
NOA-16 trial: accrual and research

- 1 grade 3 skin toxicity
- 12 mos. PFS rate 92.6% (target 70.7%)
- 5 delayed pseudoprogressions
Challenges in antigen selection

- **Target antigen**
  - Minor antigens
  - CD4 epitopes
  - Low expression
  - Heterogeneous mutations

- **Tumor antigens**
  - Central tolerance
  - Side effects

- **Tumor-associated antigens**
  - Mutated / variant antigens (EGFRvIII, IDH1R132H)
  - Embryonic antigens (WT1, MAGE-1, multi-epitope – ICT-107)

- **Embryonic antigens**
  - No proof of efficacy from controlled clinical trials

- **Mutated / variant antigens**
  - No proof of efficacy from controlled clinical trials
Multicenter, phase I EU trial in patients with newly diagnosed glioblastoma

Accrual started: December 2014 - > 07/2016 Last patient in
NOA-16 & GAPVAC trials: open questions?

- Are tumor-infiltrating IDH1R132H-specific T cells induced by the peptide vaccine?
- If so, what is the phenotype?
- Does it differ from the peripheral phenotype?
- Is the IDH1R132H-specific immune response amplified by checkpoint inhibition?

- HLA restrictions
- Tissue quality
- Complexity – resources
- Complexity – targeting the immune surveillance
- Efficacy of a peptid approach – combination is key!?
Glioblastoma microenvironment - Checkpoints

- Activating receptors
  - CD28
  - OX40
  - GITR
  - CD137
  - CD27
- Inhibitory receptors
  - CTLA-4
  - PD-1
  - TIM-3
  - BTLA
  - VISTA
  - LAG-3

- CTLa-4 Inhibitor
- PD-1/PD-1L Inhibitors

Mellmann, Nature 2011
Checkpoint inhibition – open questions

- Can defined neoantigen-specific immune responses be amplified using a checkpoint inhibition?
- If so, does this translate into a measurable amplification intratumoral immune response?
- Does a hypermutator phenotype predispose towards response to checkpoint inhibition?
- What are mechanisms of immune evasion prohibiting this amplification?
Checkpoint inhibitors in glioma

NEXT STEP: AMPLIFY NEOVAC

Bouffet et al. JCO 2016
The AMPLIFY-NEOVAC trial

- IDH1-mutated glioma
- Recurrence 60% hypermutator
- Radiotherapy > 12 mos alk. chemotherapy
- n=48 1:1:2
- IDH1 vaccine
- IDH1 vaccine + CI
- CI
- Mutanome TCRseq
- Microenvironment
The AMPLIFY-NEOVAC trial

- To demonstrate safety of the peptide vaccine targeting the neoepitope IDH1R132H in combination with checkpoint inhibition in patients with progressive gliomas

- To evaluate the impact of checkpoint inhibition on the peripheral and intratumoral IDH1R132H-specific T cell response in patients with gliomas
The AMPLIFY-NEOVAC trial

- To determine whether a therapy-induced hypermutator phenotype predicts response to checkpoint inhibition in patients with gliomas.

- To identify mechanisms of immune evasion and resistance to the IDH1R132H vaccine and checkpoint inhibition.

- To identify specific peripheral and intratumoral T cell responses and T cell receptors to constitutive neoantigens and spread antigens after IDH1R132H vaccination.
AMPLIFY-NEOVAC Trial Centers

Berlin
Düsseldorf / Essen
Dresden
Frankfurt
Heidelberg
Tübingen
Freiburg
München
Checkpoint-Inhibitors in Gliomas

Checkmate 143

Phase 3, Open-label RCT

BUT: No hint for efficacy in the press release and abstract for WFNO 2017 (Reardon et al.)

Sampson et al, Poster presentation at ASCO 2015 (Abstract 3010)
Intravenous Administration of ParvOryx in Combination with Checkpoint Inhibition versus Lomustine (CCNU) in Patients with Progressive Glioblastoma. **ParvOryx03**

- **Lomustine 110-130 mg/m²**
  - q 42 days

- **ParvOryx 1E09 pfu i.v.**
  - Day 1, 20, 41, 81
  - plus
  - **Atezolizumab 200 mg i.v.**
  - Day 4, than q3w

- **ParvOryx plus Bevacizumab plus Atezolizumab**

- **ParvOryx 1E09 pfu i.v.**
  - Day 1, 20, 41, 81
  - plus
  - **Bevacizumab 15 mg/kg q 3 weeks**
An oral vaccine targeting VEGFR-2

Anti-tumor activity

VEGFR-2 specific CD8+ T-cell kills target cell

MHC class I - mounted VEGFR-2 peptides

Target cell (high churning, VEGFR-2 expressing)

Strong specific T-cell response

CD8+ T-cells destroy the tumor vasculature and other VEGFR-2 expressing cells

Infected apoptotic cells are processed by the immune system
VXM01 phase I pilot study in patients with operable recurrence of a glioblastoma to examine safety, tolerability, immune and biomarker response to the investigational VEGFR-2 DNA vaccine VXM01: Exploratory, open-label, uncontrolled, monocenter, Phase I pilot study.
Two VXM01 Patients Showed Tumor Response… in two different indications

**Glioblastoma**
- 1 VXM01 patient (male, 47 y), candidate for reoperation, was not operated due to tumor shrinkage under VXM01
  - Prior radiochemotherapy
  - VXM01 treatment
    - Initiation plus 3 boostings
    - No other anti-cancer therapy during study
  - Tumor shrinkage continued
  - Partial response

**Pancreatic cancer**
- 1 VXM01 patient (female, 65 y), inoperable at study start became operable under VXM01
  - Tumor safely resected
  - Strong immune and biomarker responder
  - High level of CD8+ T-cells in tumor
Many thanks for your attention!

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