Nivolumab for EB SCC

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Salzburg
Facing the burden...


- **EB SCC leading cause** of death in RDEB
  - CR 78.7% / 55 a (sg RDEB)
- Sites of chronic wounding, inflammation, tissue remodeling, scarring
- Multiple, early, aggressive, non-responsive

*SCC in gs RDEB: course over 1.5 yrs*
...and further challenges

• Treatment of advanced (EB) SCC
  
  
  – No widely accepted standard of care
    • Mostly small (uncontrolled) case series or isolated observational studies
  
  – Limited evidence on overall clinical effectiveness
    • Variable response rate (up to 72%; publication bias), rapid recurrence
Treatment of advanced EB SCC

• Reserved wording...
  – Conventional cyotoxic chemotherapy may be of some benefit in a mostly palliative setting
    • (Combinatory) cisplatin, carboplatin, taxol, carboplatin, fluorouracil, doxorubicin, methotrexate, paclitaxel, etopside
    • Toxicity / poor tolerability (liver, kidney, bone marrow, GI), risks may outweigh benefits
Treatment of advanced EB SCC
Stratigos 2015, Mellerio 2016

– **EGFR antagonists** may be useful for **palliation**
  - 2\textsuperscript{nd} line after failure of mono- / poly-CTX and PD
  - mAb: cetuximab, panitumumab
  - Small molecule kinase inhibitors: erlotinib, gefitinib, dasatinib, rigosertib
  - Limited evidence, rash, anaphylaxis

Unmet patients’ needs

sg RDEB, 33 yrs

- SCC right lower arm 11.2012
- Meta right lower arm 10.14
- Meta right axillary LN, right lower arm OA 9.2014
- Meta right clavicle, infiltration M. pectoralis et deltoideus 7.2015
- Electochemotherapy bleomycin; methotrexate
- Cetuximab 6.2013 - 7.2015
- Operability 10.2015
- Progressive disease (right upper arm, regional LNs) 3.2016
- Panitumumab (EGFR+, KRAS wt) 4.2016
- Talimogen laherparepvec (T-VEC) + pembrolizumab 7.2016
- Demise 12.2016
Treatment of advanced EB SCC

Stratigos 2015, Mellerio 2016

- Stage IV patients should go for **clinical trials**
Hot topic: Cancer immunotherapy


• Current attempts to break apparent immune tolerance to tumor cells and antigens by modulating regulatory checkpoints of the immune system
Cancer immunotherapy
Thompson 2005, Zhang 2010, Mu 2011

• Tumor emergence and progression depend upon acquisition of traits that allow cancer cells to evade immune surveillance and effective immune response
• Tumorantigen (Cancer-Testis) and MHC (I) expression

• CD8\(^+\) T-lymphocytes
  – IFNg + TNF $\rightarrow$ tumor senescence
  – FasL $\rightarrow$ apoptosis
  – Lytic granula $\rightarrow$ cytolysis

• NK cells
  – Lytic granula $\rightarrow$ cytolysis
  – Fc\(\varepsilon\)IIIa $\rightarrow$ antibody-dependend cellular cytotoxicity

Figure 3. Mechanisms of immunotherapies. The figure depicts established immunotherapy mechanisms: cytolysis by CD8-positive killer cells (a), receptor-mediated induction of programmed cell death or apoptosis (b), MHC-independent NK cell-mediated cytotoxicity (c), NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) (d), and the newly described mechanism of Th1 cytokine-induced permanent growth arrest or cellular senescence (e).
CTLA-4 and PD-1 are non-redundant negative regulators

- CTLA-4 attenuates early activation of naïve and memory T cells
- PD-1 primarily involved in modulating T cell effector activity in peripheral tissues via interaction with its ligands PD-L1 and PD-L2
• Blockage with significant recent promise in treatment of expanding list of malignancies
• Approved for
  – unresectable or metastatic melanoma
  – previously treated metastatic NSCLC
  – previously treated advanced RCC
  – previously treated relapsed or refractory cHL
  – metastatic UC
  – previously treated recurrent or metastatic SCCHN

• Investigated for
  – gastric cancer, hepatocellular carcinoma, colorectal cancer, glioblastoma, Merkel cell carcinoma, SCLC, esophageal cancers
  – sepsis
Checkpoint blocking antibodies in cSCC
Rationale
Alexandrov 2013, Pickering 2014

• **Higher mutation burden** than any tumor type in The Cancer Genome Atlas (TCGA)

• Mutation load is a potential mediator of tumor immunogenicity

![Graph showing mutation frequency across different tumor types.]

Papadopoulos 2017
Rationale

Walter 2010

• Expression of tumor associated cancer-testis (CT-) and major histocompatibility complex (MHC) class I antigens, evidence of CD8\(^+\) tumor infiltrating lymphocytes
Rationale


• **Immunosuppression** is a well-described risk factor for cSCC
  – Solid organ **transplant patients**
  – Along with malnutrition, anemia and chronic infections in **severe EB forms**
Rationale

• PD-L1 expression has been associated with high risk (metastatic) disease *Slater 2016*

• Blockage in animal studies delayed development of squamous cell carcinoma *Belai 2014, Ritprajak 2015*
Rationale

- Anecdotal beneficial evidence in patients with locally advanced / metastatic SCCHN and cSCC

*Powell 2015, Seiwert 2015; Chang 2016, Winkler 2016, Degache 2017, Papadopoulous 2017, Stevenson 2017*
• REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy

Median age 73 ± 81% males
Preliminary results of first prospective study in advanced cSCC

First line therapy

ORR 46.2% (median follow up 7 months)

- 12/26 patients including 2 complete, 9 partial, 1 unconfirmed partial responses

- DCR 69.2%
  - 18/26 patients, including 12 ORR and 6 stable diseases

No apparent association between objective response and level of PD-L1 expression (81% of tumors positive)

Well tolerated in predominantly older population

Phase 2 study with REGN2810 in patients with unresectable locally advanced and metastatic CSCC ongoing (NCT02760498)
• Currently **limited correlatability** of clinical effectiveness (lack of biomarker) with tumor **immune microenvironment**


— modified by prior and concurrent treatment strategies (radio-, oncolytic virus therapy), tumor load, (immunogenic/cancerogen-specific) mutational tumor profile, clonal/sub-clonal neoantigens, (tumor subtype-specific/predictive) PD-1 (ligand) expression, mismatch repair deficiency, inflammatory state in EB?
NIVOSQUACS

• Phase II Study of Nivolumab in Patients with Previously-Treated Locally Advanced / Metastatic Squamous Cell Carcinoma of the Skin

Short title: NIVOSQUACS

Clinical Protocol BMS CA209-587

EudraCT No. 2016-002811-16
NIVOSQUAACS

- Nivolumab
  - anti-PD-1 monoclonal antibody
  - approved for treatment of advanced melanoma, non-small-cell lung cancer, advanced renal carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, SCC of head and neck
Programmed death receptor-1 (PD-1)

- CD28 family member of T-cell **costimulatory receptors**, expressed on activated T cells, B cells, myeloid cells

- PD-1 blockage **impairs** its specific ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), which have been shown to **down-regulate T-cell activation** upon binding to PD-1

*Topalian 2012; Pedoeem 2014*
NIVOSQUACS

• Investigator initiated, prospective, multicenter, phase II trial
  – Wels, Klagenfurt, Salzburg, St. Pölten, Innsbruck
• Shared IP, operational costs / CRO and patient insurance provided/funded by BMS
Primary objective: ORR to nivolumab

PPK-approved 240 mg flat dose every two weeks for up to two years after initial dosing or until PD or absence of investigator-assessed clinical benefit

Tumor assessment (CT/MRI) at 12-week interval
NIVOSQUACS

Selected inclusion criteria:
• Men and women, 18 years of age and older on day of signing written informed consent
• Histologically or cytologically documented locally-advanced and/or metastatic squamous cell carcinoma of the skin (stage III/IV AJCC 2010) that is incurable and has failed prior systemic therapy
• Archival tumor tissue available for evaluation of PD-L1 expression
• Measurable disease based on Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
• Life expectancy of at least 12 weeks
• Eastern Cooperative Oncology Group (ECOG) Performance status of 0-2
• Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration
Selected exclusion criteria

- **Prior therapy** with CTLA-4 or PD-1 antibodies
- A condition requiring systemic treatment with either **corticosteroids** (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Known **additional malignancy** that is progressing or requires active treatment
- An active, known or suspected **autoimmune disease**. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment
- History of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Positive test for **hepatitis** B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection
• Adverse Events Nivolumab

*Safety data of 16,900 subjects*

- Fatigue (17%)
- Diarrhea (11%)
- Pneumonitis, colitis, hepatitis, nephritis
- Hypothyroidism, Hypopituitarism
- Rash
- Abnormal blood investigations
Contact

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Impressive dynamics in the field

Promising prospects for real life failures

• New (combined) therapy algorithms ahead
  – (Sequential) combination PD-1 and CTLA-4 inhibitors *Long 2017*
  – Combination PD-1/histone deacetylase (HDAC)-inhibitors *Johnson 2017*
    • Entinostat suppresses myeloid suppressor cells
  – Adjuvant cancer immuotherapy for high risk SCC patients *Weber 2017*
Prospects
Thanks for being with us.

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