Nivolumab for EB SCC

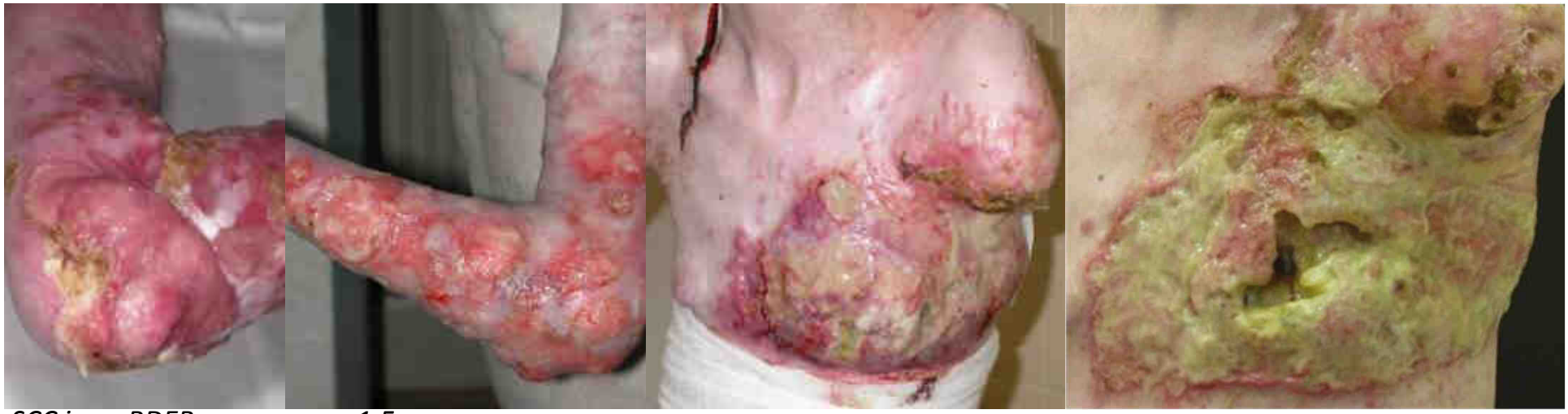
Martin Laimer

Salzburg

Facing the burden…

Fine 2009, Yuen 2011, Mittapalli 2015, Martins 2016, Mellerio 2016

- **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**
  Cranmer 2010, Stratigos 2015, Mellerio 2016, Montaudié 2016

  – **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

Cranmer 2010, Stratigos 2015, Mellerio 2016, Montaudié 2016

- **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

Guthrie 1990, Sadek 1990, Khansur 1991, Cartei 2000, Benasso 2001,Behshad 2011
Wechsler 1970, Schwartz 1981, Lentz 1990, Mallipeddi 2002, Arnold 2009, Kim 2013

Treatment of advanced EB SCC

Stratigos 2015, Mellerio 2016

– **EGFR antagonists** may be useful for palliation

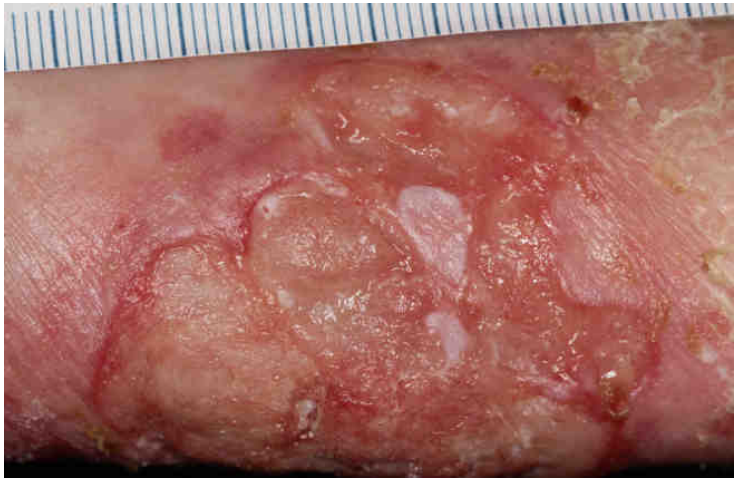
- 2nd line after failure of mono- / poly-CTX and PD
- mAb: cetuximab, panitumumab
- Small molecule kinase inhibitors: erlotinib, gefitinib, dasatinib, rigosertib
- Limited evidence, rash, anaphylaxis

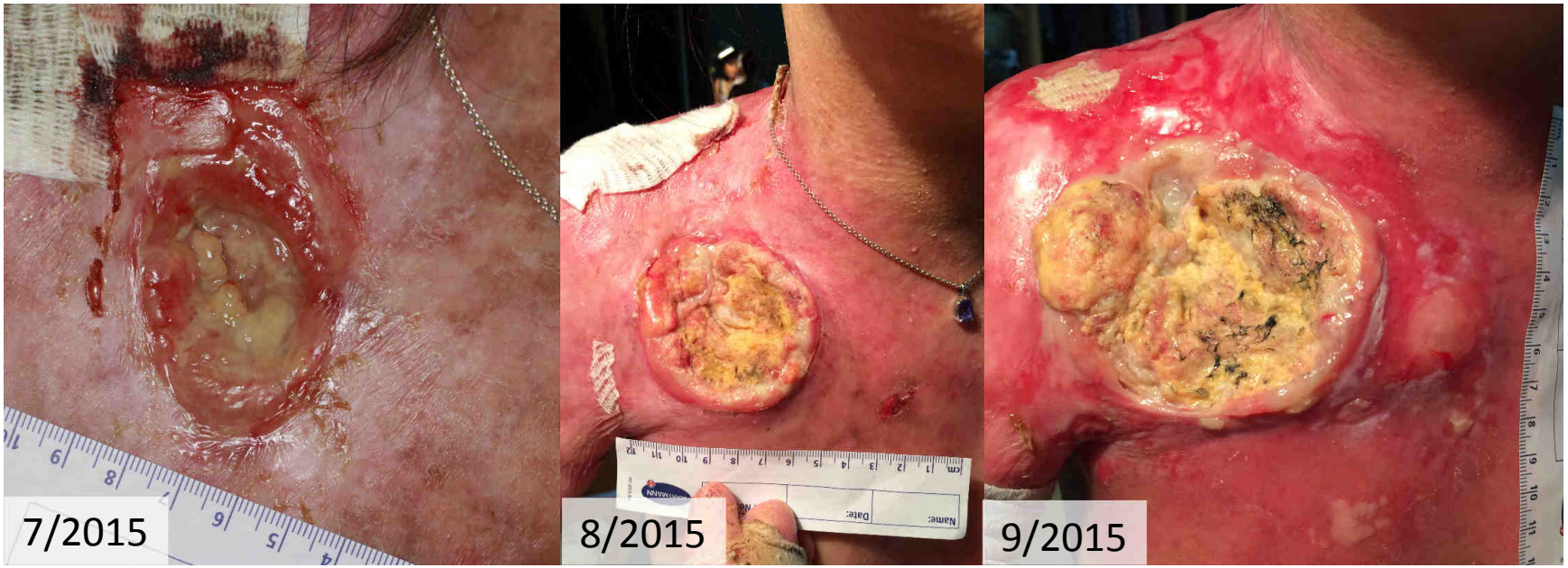
Burtness 2005, Maubec 2005, Maubec 2011, Lewis 2012, Alter 2013
Arnold 2009, Frampton 2010, Sharafinski 2010, Kim 2013, Foote 2014

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**
- **Pembrolizumab 4.2015 – 2.2016**
- **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**

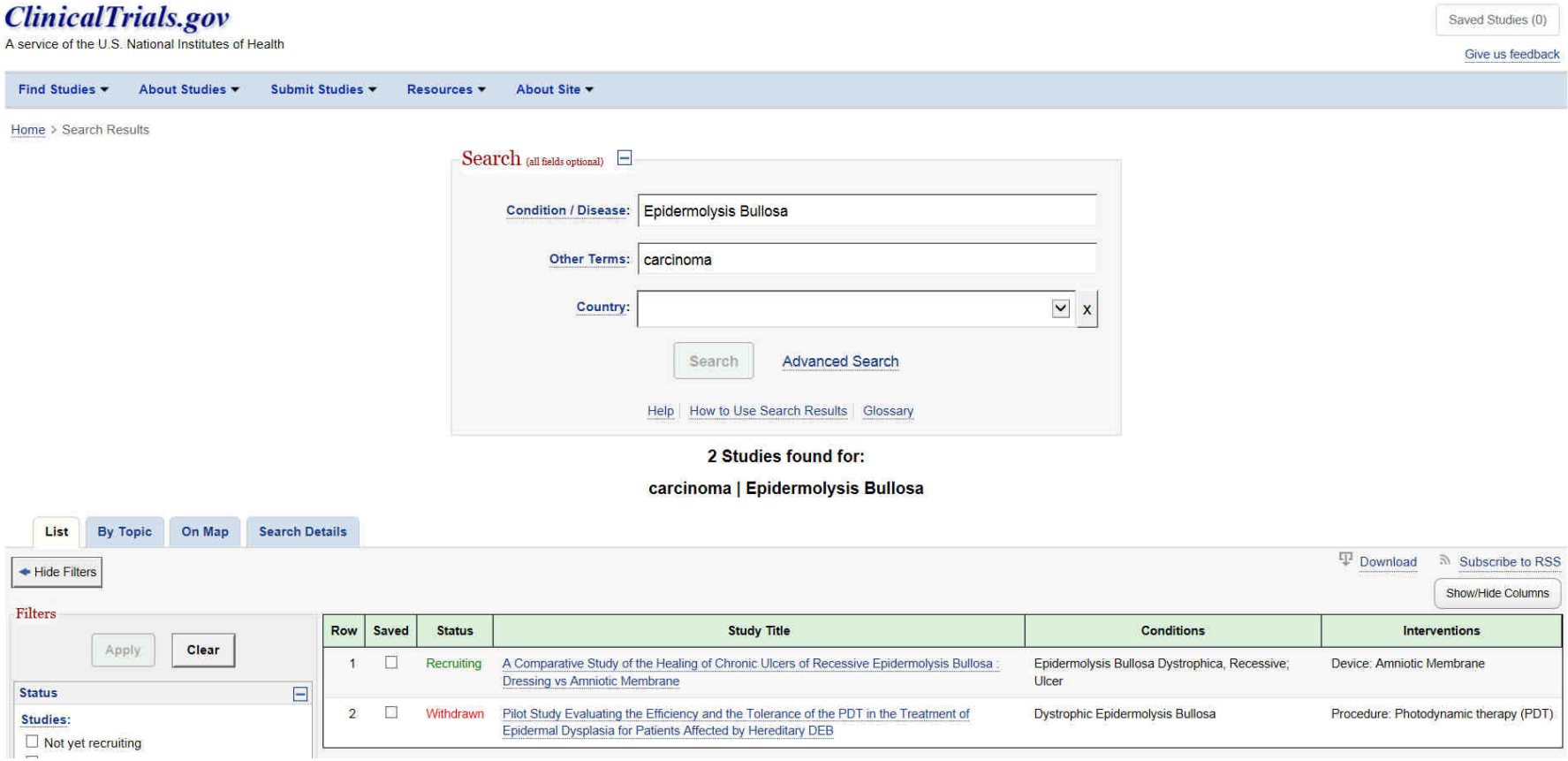




Treatment of advanced EB SCC

Stratigos 2015, Mellerio 2016

- Stage IV patients should go for **clinical trials**

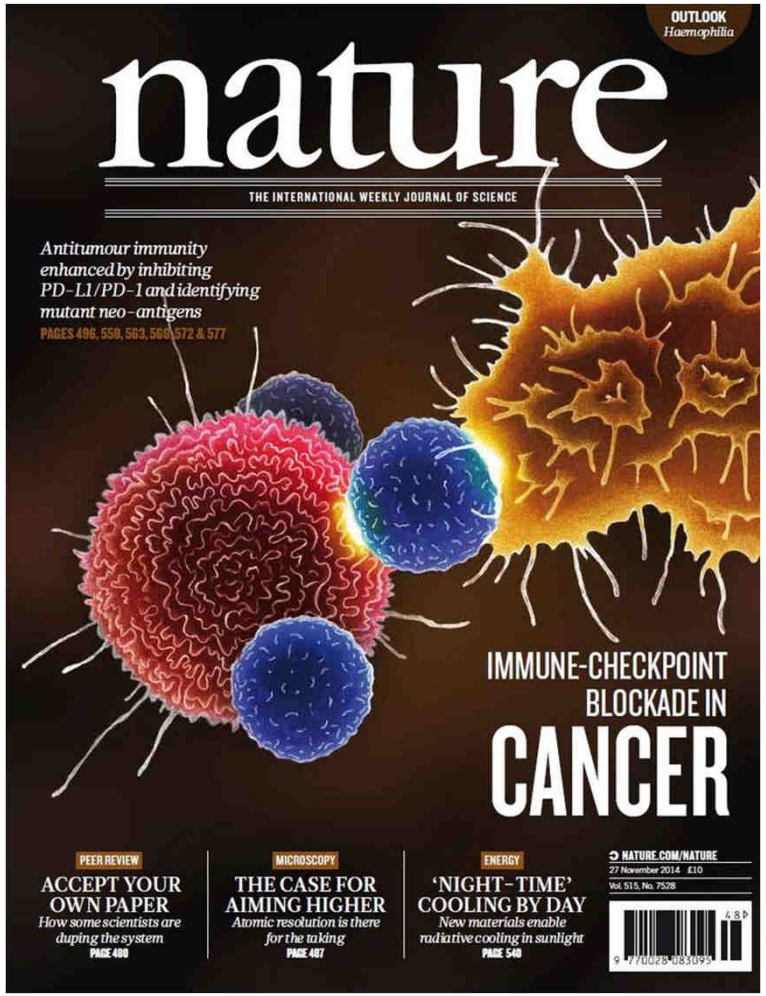


accessed 18-Sep-2017

Hot topic: Cancer immunotherapy

Freeman 2000; Thompson 2005, Zhang 2010, Mu 2011

- 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

Immune surveillance

Wieder 2016

- Tumorantigen (Cancer-Testis) and MHC (I) expression
- $CD8^+$ T-lymphocytes
  - IFNg + TNF → **tumor senescence**
  - FasL → **apoptosis**
  - Lytic granula → **cytolysis**
- NK cells
  - Lytic granula → **cytolysis**
  - FcƐIIIa → **antibody-dependend cellular cytotoxicity**

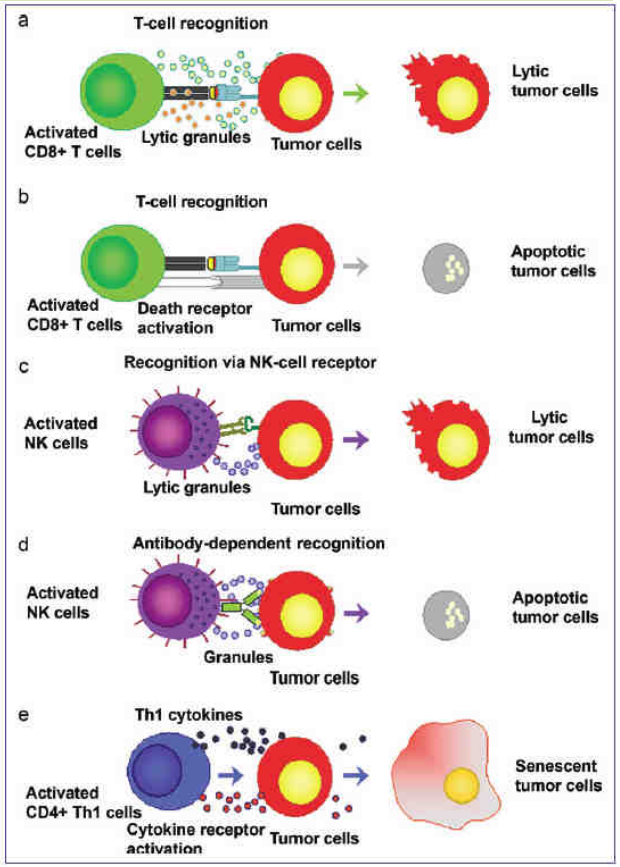
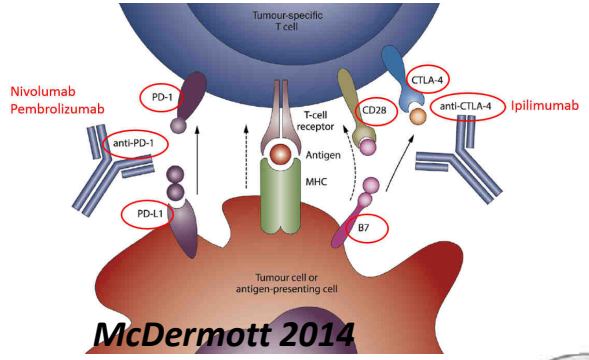


Figure 3 Mechanisms of immunotherapies. The figure depicts established immunotherapy mechanisms: cytolysis by CD8-positive killer cells (a), receptor-mediated induction of programmed cell death or apoptosis (b), MHC-independent NK cell-mediated cytotoxicity (c), NK cell-mediated antibody-dependent cellular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

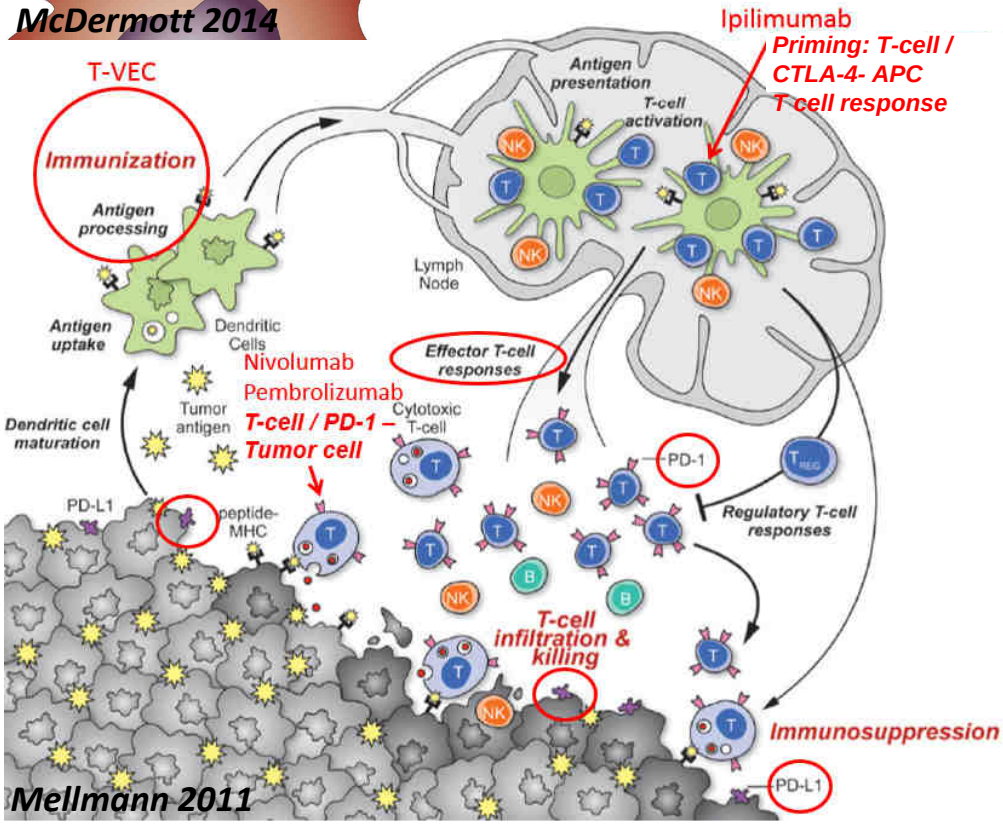
Checkpoint blocking antibodies
in cancer immunotherapy

Thompson 2005, Zhang 2010, Mu 2011

- 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



McDermott 2014



Mellmann 2011

PD-1 / PDL-1 Blockade

CA209-587 NIVOSQUACS IB Version 16, 23 Jun 2017

- Blockage with significant recent promise in treatment of expanding list of malignancies

PD-1 / PDL-1 Blockade

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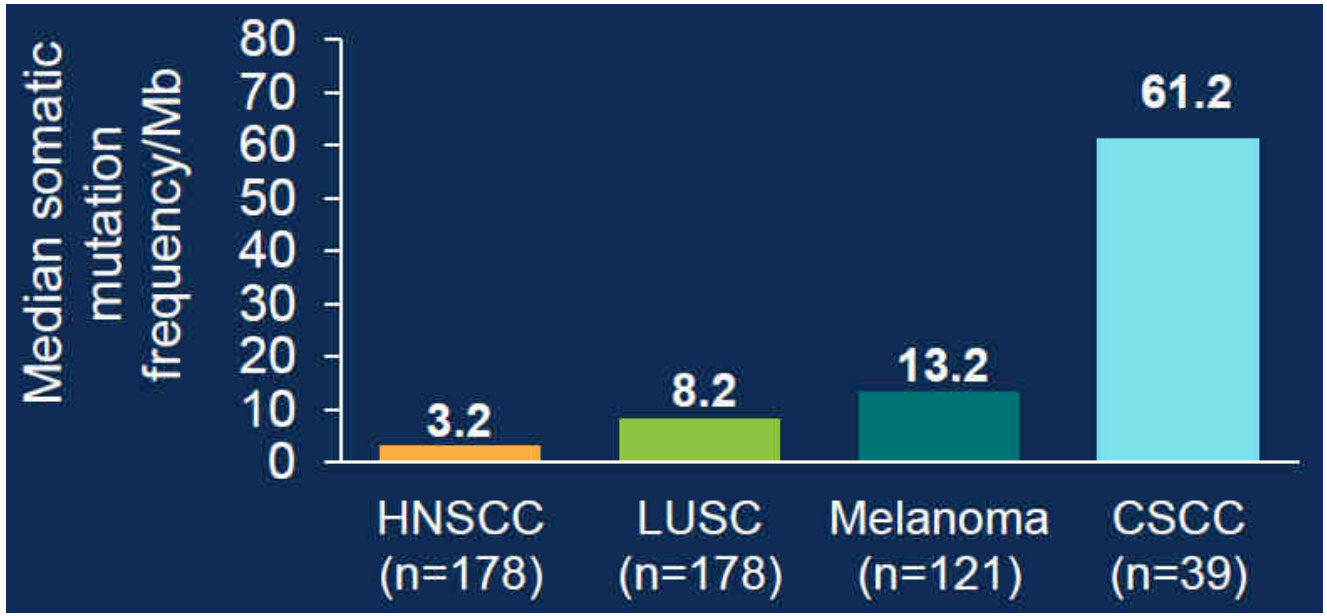
- Approved for
  - unresectable or metastatic **melanoma**
  - previously treated metastatic **NSCLC**
  - previously treated advanced **RCC**
  - previously treated relapsed or refractory **cHL**
  - metastatic **UC**
  - previously treated recurrent or metastatic **SCCHN**
- Investigated for
  - **gastric 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



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Rationale

Walter 2010

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

Rationale

Tyring 1989, Chopra 1990, Euvrard 2003, Martinez 2003, Thompson 2005, Fine 2009, Prudie 2010, Zhang 2010, Mu 2011, Zwald 2011, Tsukada 2012, Karia 2013

- 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

- Anecdotical 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

Degache 2017

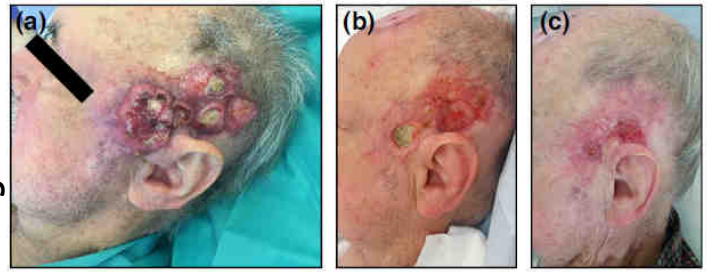
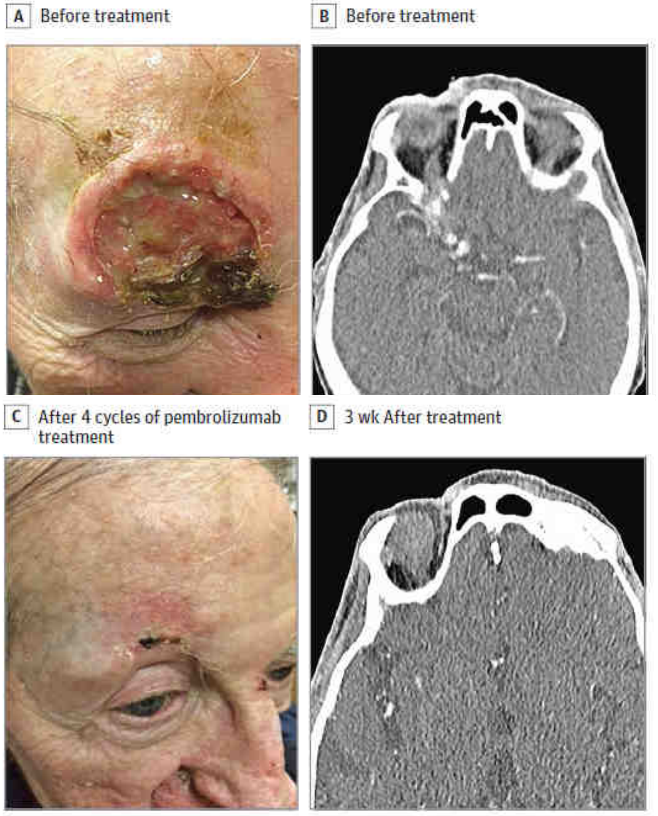


Figure 1 Locally advanced unresectable cutaneous squamous cell carcinoma characterised by a large ulcerated lesion with infiltrated vegetating borders involving the left temporal area (a). After two (b) and six infusions (c) of an anti-PD1 inhibitor, there is significant reduction of the surface of the ulceration and infiltrating of tumour.

Stevenson 2017

Figure 1. Response of Locally Advanced Cutaneous Squamous Cell Carcinoma (cSCC) to Pembrolizumab



A, Pretreatment photograph of the patient's forehead and periorbital area shows locally advanced cSCC with infiltration into the orbital rim. B, A computed tomographic (CT) scan confirmed deep extension of the cSCC with bony infiltration. C, A posttreatment photograph of the same facial areas shows near-complete tumor regression after 4 cycles of pembrolizumab treatment. D, Three-week posttreatment CT scan confirmed regression of soft-tissue extension and bony infiltration and partial tumor resolution.

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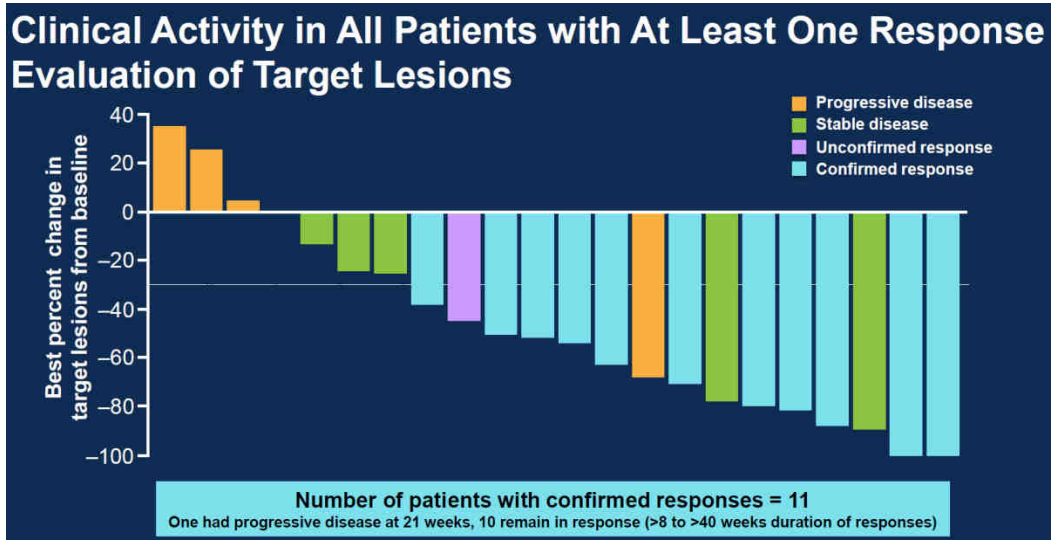
- REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy



Median age 73 a
81% males

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- **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)

Immune checkpoint blockage

- Currently **limited correlatability** of clinical effectiveness (lack of biomarker) with tumor immune microenvironment

  Picard 2017, Stevenson 2017, Chang 2017, Al-Rohil 2016, Borradori 2016, Le 2017

  – 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

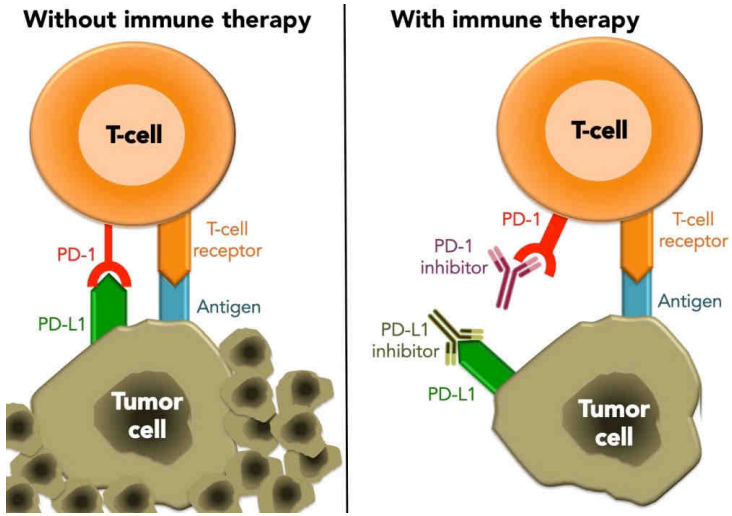
NIVOSQUACS

- 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**

NIVOSQUACS

- 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

NIVOSQUACS

- 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

NIVOSQUACS

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

NIVOSQUACS

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- **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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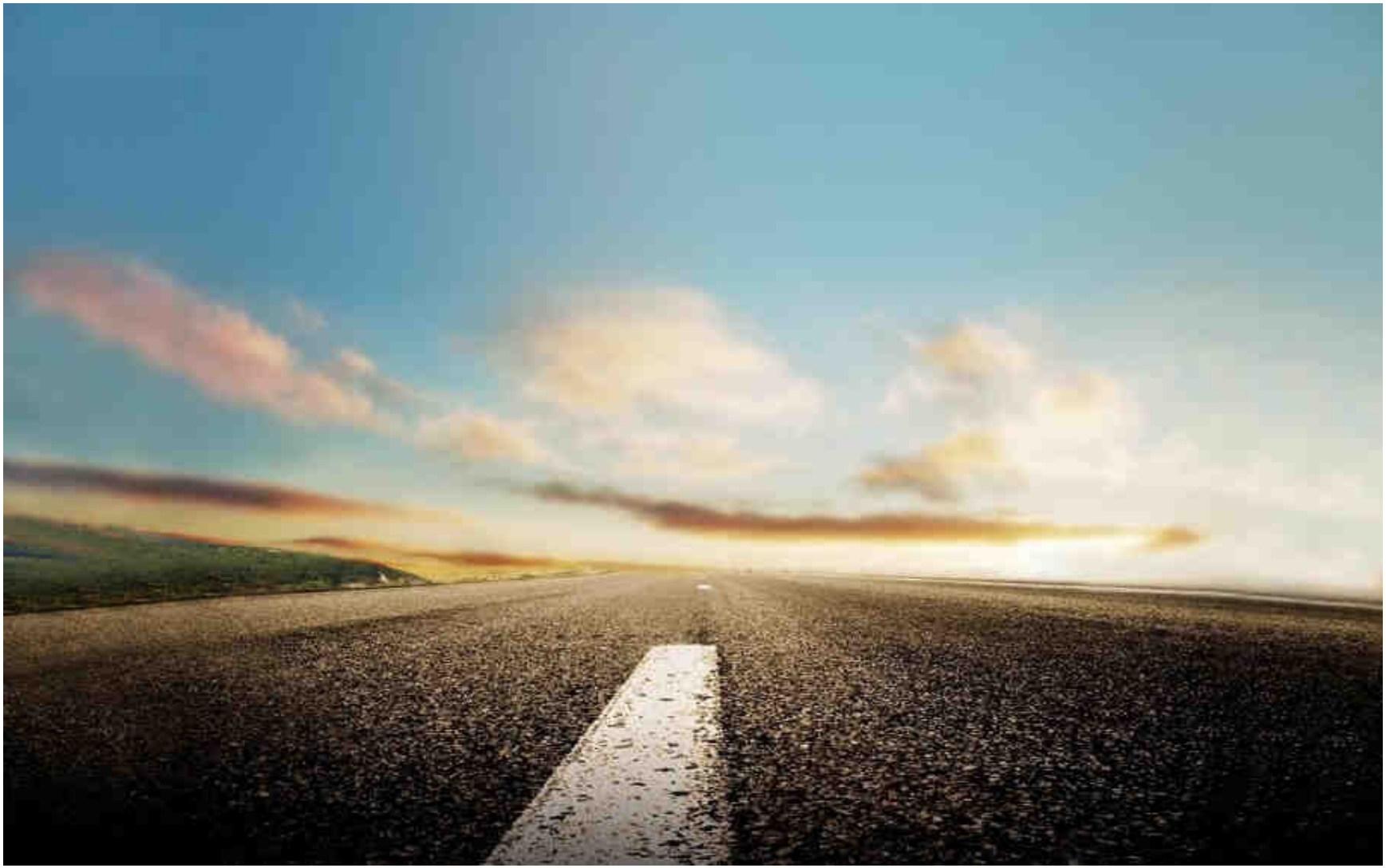
Impressive dynamics in the field

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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