On our way to more effective treatments for cancer

Magnus Jaderberg
Research & Development
Oncos Therapeutics
Helsinki

Cancer has been around a long time

Evidence of osteosarcoma in mummies (1600 B.C.)

1500 B.C. manuscripts describing breast cancer, “no cure only palliative care”

Hippokrates (460-370 B.C.) called it karkinos, imbalance in the 4 body fluids, excess of “black fluid”

Surgery of surface tumors

Religion prevented autopsies to 1000 A.C.

Lymph theory

1840 cancer made up of cells

Trauma theory

Key milestones

1846 general anaesthesia

"The century of the surgeon"

1930 Blood transfusions

1940 Antibiotics

1950 Biology and chemistry

1962 Watson & Crick discover DNA helical structure

1970 Genetic research, mutations, oncogenes, tumor suppressor genes

Diagnosis and prevention

1896 Wilhelm Rontgen discover X-ray
1940s Papanicolaou discovers the Pap-test
1950s Smoking = cancer
1960s Mammography
1970s Carcinogens
Ultrasound
1980s Computed tomography (CT)
Magnetic resonance imaging (MRI)
Positron emission tomography (PET)
Miniature video camera
Endoscopy

Treatment to 2000

"The four pillars"

1) Surgery
2) Radiotherapy (incl. internal radiotherapy)
3) Chemotherapy (WW1 mustard gas induced bone marrow aplasia – alkylating agents)
4) Hormonal treatments (testes removal, tamoxifen)

Development of more effective treatments such as combination therapies and targeted agents are mainly due to improved cell biology, genetics, diagnostic skills and clinical research methodologies

Clinical research in oncology

Not like other TA areas

Experimentation is common – good and bad

Cancer centers/investigators frequently follow their own protocol

Patients are often very ill and may not survive the study

Concomitant diseases are common making efficacy and safety assessments difficult

Diagnostic and invasive procedures make studies very expensive

Biomarkers have not yet made an impact on clinical interpretation or regulatory processes

Clinical research in oncology

Not like other TA areas

Go from animal studies directly to patients (no healthy volunteer phase I)

Cancer patient phase I with dose escalation (3+3), DLT,MTD

Phase II/proof of concept, often single arm, ORR, PFS, 6month PFS

Phase III still with overall survival (OS) as most desired endpoint but PFS is being suggested by FDA/EMA. Logistical/financial challenges of studying OS benefits of cancer with median OS of 5 years – delayed drug development – delayed access to patients!

New kid on the block – immunoncology

1850 Infected tumors sometimes shrank

1910 Viruses can be oncolytic

1975 First synthetic antibody

1997 Retuximab (Mab aB-cell diseases e.g. lymphoma)

1998 Herceptin (Mab aHER2 diseases e.g. breast cancer)

2011 Ipilimumab (Mab aCTLA4 e.g. melanoma)

Cancer versus immune system

* Cancer cells, only when visible, are seen as “danger”
* Cancer cells good at hiding from the immune system
* Like bacteria, change character/antigens
* Create an immune suppressive environment
* Multiple ways of immune system attack:

  Interferon induces CD8+ T-cells

  Dendritic cells can be armed with tumor specific antigens = “educate” T-cells

  Chimeric antigen receptors (CARs) = “arm” T-cells

  T-cells can be engineered to recognize tumor antigens

  General immune stimulation e.g. check point inhibitor

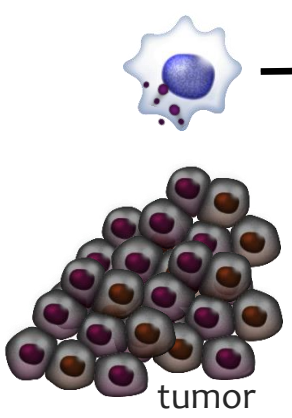
  Oncolytic virus can prime/start an immune response

Cancer immunotherapy

"Recognition of threat"

Innate Immune System

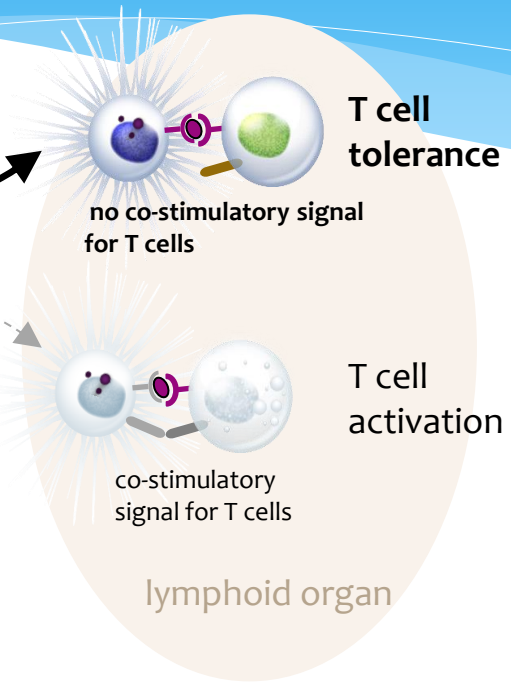
Dendritic cells continuously monitor their environment for a threat



- Cancer cells are mutated "self" tissue and have multiple mechanisms of escaping the immune response

"T cell activation"

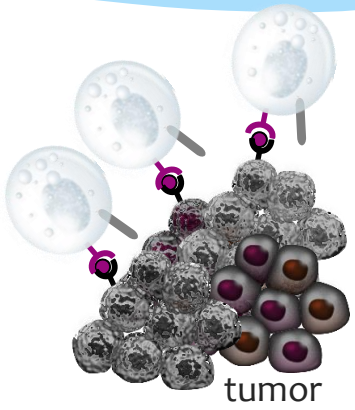
Adaptive Immune System



- In many cancer indications, T cells are not activated against cancer antigens

"Immune attack"

Anti-tumor Immune Response



Example of primer with oncolytic virus

"Recognition of threat"

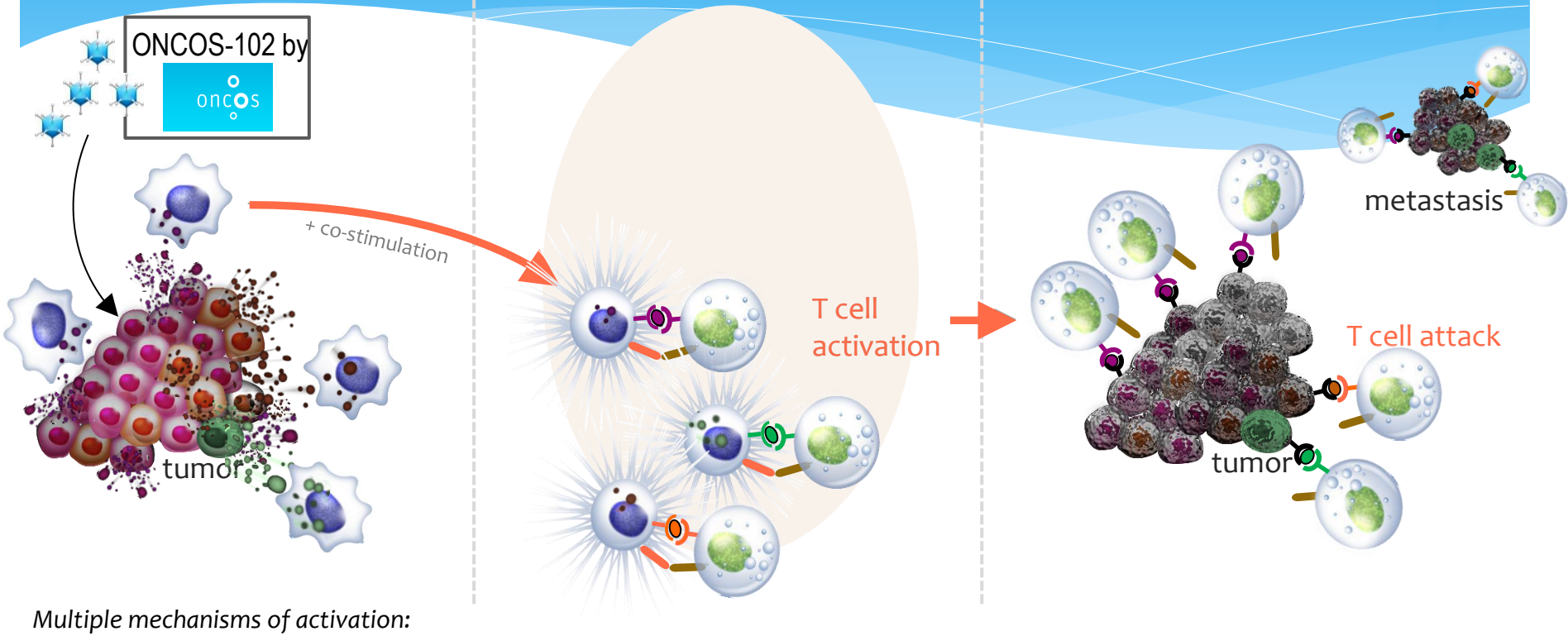
Innate Immune System

"T cell activation"

Adaptive Immune System

"Immune attack"

Anti-tumor Immune Response



Multiple mechanisms of activation:

- TLR stimulation
- Pro-inflammatory cytokines
- Danger signal
- Release of tumor antigens
- Local GMCSF expression

Targeted anti-tumor immune response:

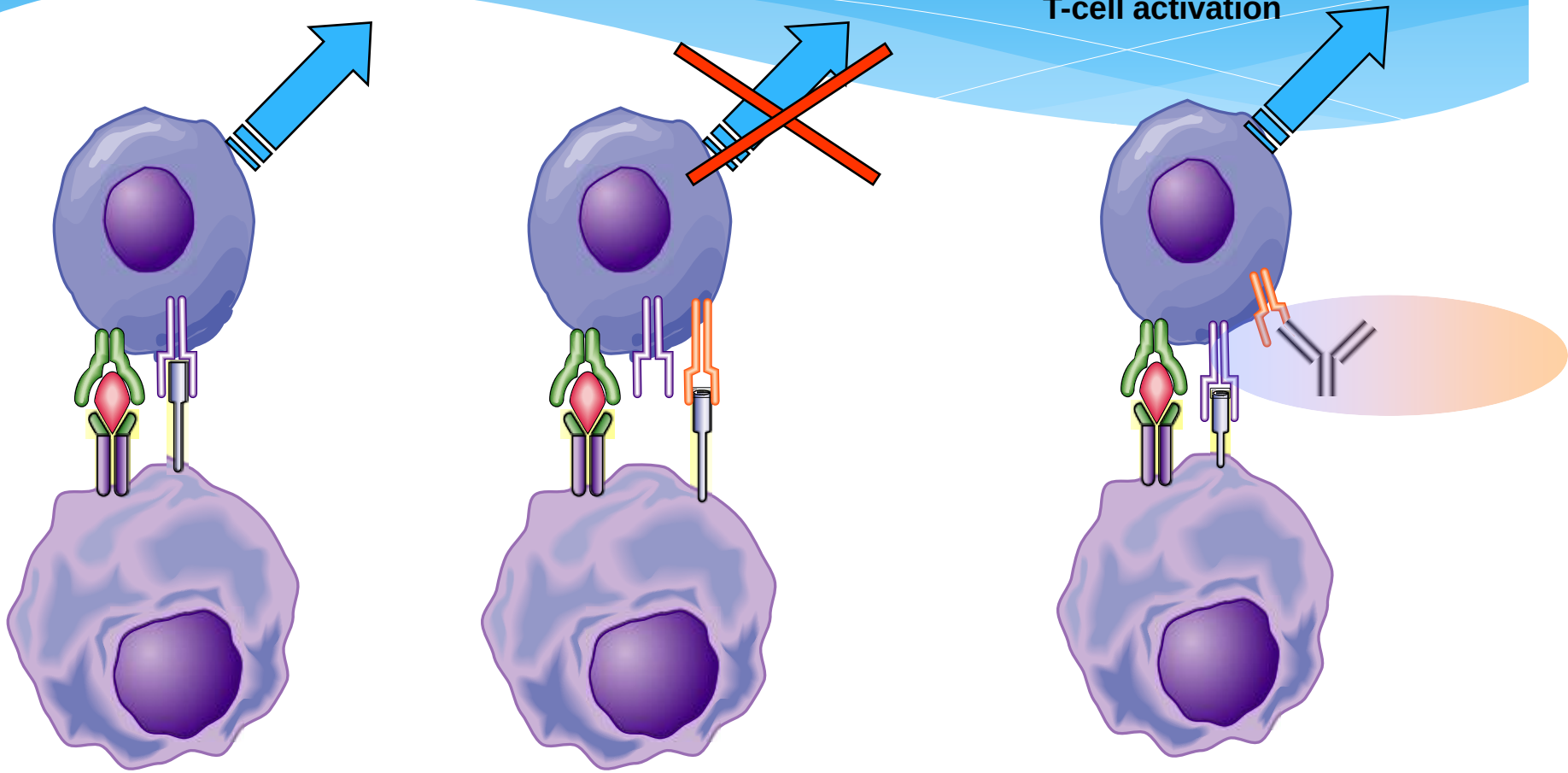
- ONCOS-102 teaches immune system to recognize unique cancer cells of each patient
- "*in situ* vaccination"

Example of general immune stimulation with check point inhibition via CTLA-4

Co-stimulation via CD28:
T-cell activation

CTLA-4 blocks co-stimulation:
No T-cell activation

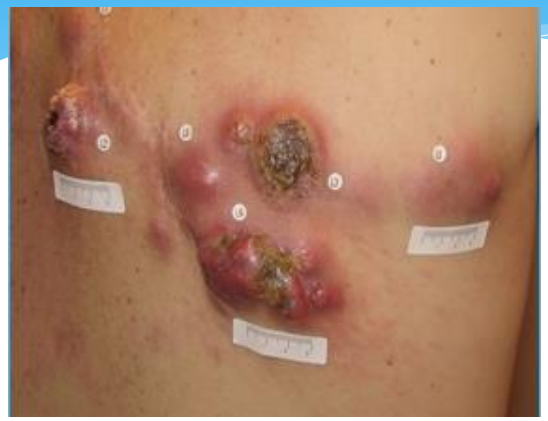
Ipilimumab blocks CTLA-4:
T-cell activation



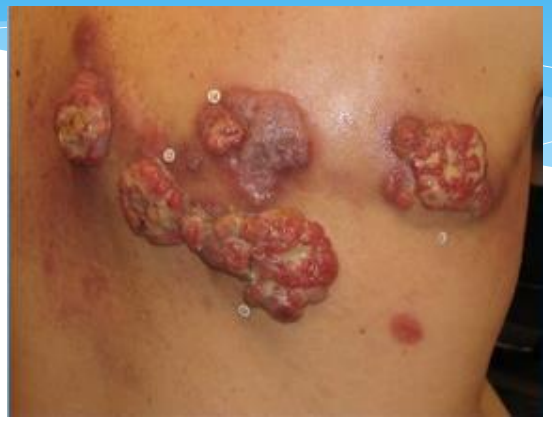
Ipilimumab blocks negative signaling From CTLA4 and thereby stimulates the immune system

Ipilimumab can “cure” malignant melanoma

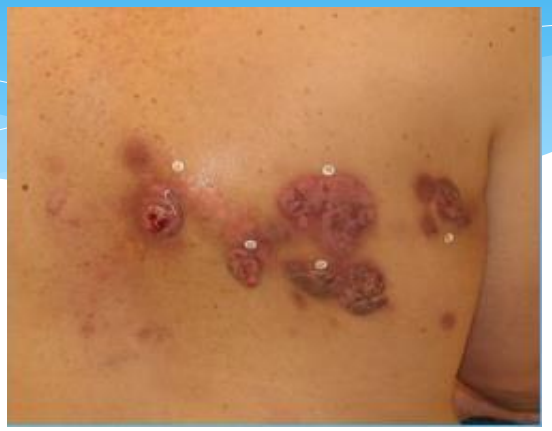
Screening

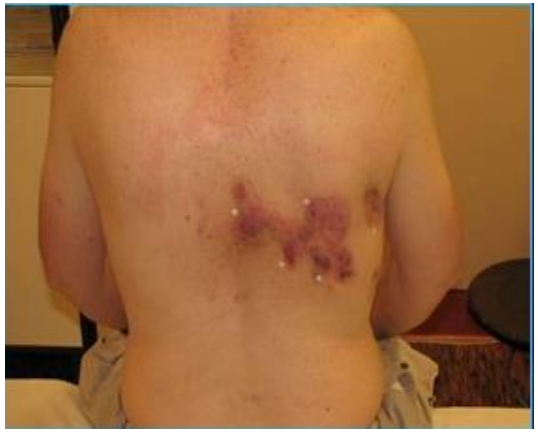


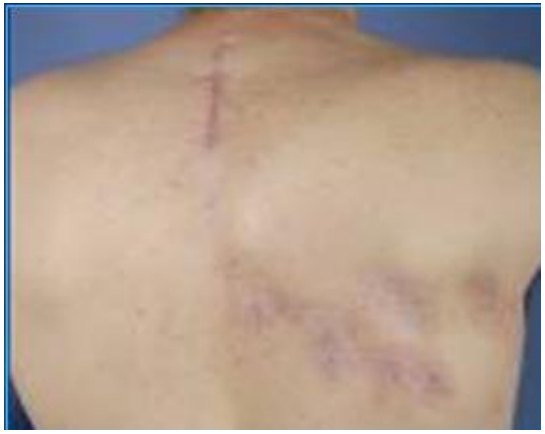
Week 12: swelling & progression

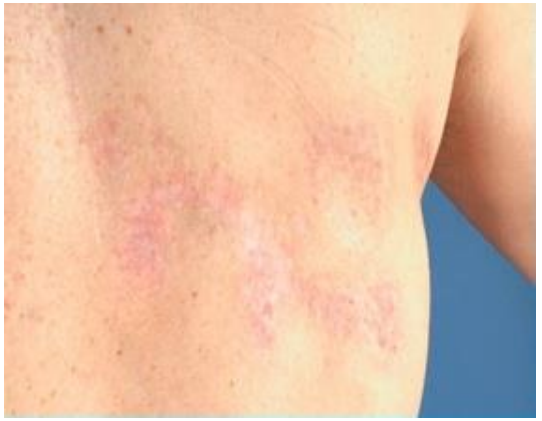


Week 14: improved









Progress of efficacy in malignant melanoma

* Before ipilimumab 7 months median OS
* Ipilimumab 10
* Nivolumab 20
* Pembrolizumab 20
* Ipilimumab+Nivo >30 Estimation based on interim data at ASCO 2014
  but increased level of AEs

Melanoma on the way to be cured !

How do study any new therapies in this indication ?

Endpoint considerations in immune oncology

* Surrogate end points: Immune system is a highly complex (number of active components) and dynamic system (tumor – lymph node – blood) – where do we measure quantity and functionality of cancer specific T-cells?
* How do we assess immune endpoints when we combine immune tx with chemo tx not knowing the immune modulatory properties of chemo?

Combination of immune therapies

Check point blockade plus, for example, an oncolytic virus

Rationale:

Oncolytic virus to prime/start an immune reaction

Check point blockade to boost/"release the brake"

Surrogate endpoints from biopsy of tumor:

Increase of innate immune cells e.g. macrophages

Increase in tumor infiltrating lymphocytes (TILs) ?

Functionality of these TILs – cytotoxic ?

Cancer specific TILs ?

Endpoint considerations

* Longer survival require earlier read out

  Milestone survival = KM survival probability at a pre-specified time point e.g. 2 years in melanoma
* Traditional (RECIST, WHO) criteria to assess response and tumor volume don't work as we often see inflammation related increased tumor volume and patients with stable disease (tumor not grown nor shrunk) can have excellent survival = long term OS benefit is driven not only by patients who achieved objective response
* Initial tumor growth (PD) often turn to PR/CR later – delayed response as it takes time for the immune system to respond. PFS not likely to capture this!
* Lead to immune-related response criteria (irRC)