Status of the Cancer Vaccine Field and Development of Novel Immunotherapies

CAPITAL MARKETS DAY

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Drug based therapy in oncology

- First World War and S-Lost
- Lost Derivatives: Cyclophosphamid
- Toxic agents against fast cell growth: Pt, Antimetabolites, many others
- Agents directed against tumor specific cell biochemistry: eg.: Kinase Inhibitors
- Antibodies with and without payload
  - Classical passive antibodies
  - Activating antibodies
  - Checkpoint Inhibitors
- Cancer Vaccines
- Derivatized cells (CAR-T and others)
- “Precision Medicine”

Precision Medicine

- Several definitions around
  - Specific for a certain tumor type
  - Specific for a patient group
  - Specific for a patient

- The more precise things become the better for the patient, or so most people think

Immune Oncology – a few comments to history

- First cancer vaccination approach: late 1970s at Sandoz with a goat antibody used as vaccine against EpCAM
- First Monoclonal Antibody against "Micrometastases in Cancer": Panorex 1995 – 1998
- First Cancer Vaccine ideas targeted against Cancer specific proteins: late 1990ies
- First interaction with regulators on patient specific cancer vaccine development: 2002
  - BfArM, PEI, CDER, CBER

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The main issue of cancer therapies

- Lack in specificity: the target as well as the entire body are being attacked
- Antibodies the first break through, but effective only in combination and only in some cases
- CAR-T cells: Very effective, if they reach the target
  - “Kymriah is an immunocellular therapy containing tisagenlecleucel, autologous Tcells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor(CAR)”

CAR-T Cells: Kymriah

- **Kymriah is indicated for the treatment of:**
  - **Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.**
  - **Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.**

Kymriah

- **Kymriah is intended for autologous use only (see section4.4).**
- **Manufacture and release of Kymriah usually takes about 3-4 weeks**
- ***"Kymriah must be administered in a qualified treatment centre. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Kymriah. A minimum of four doses of tocilizumab (anti IL6R) for use in the event of cytokine release syndrome and emergency equipment must be available prior to infusion***
- ***Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion***
- ***Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after Kymriah infusion…"***

Checkpoint Inhibitors: PD-1 and CTLA-4

- Roughly 100 new molecules under development
- Examples approved are Nivolumab and Pembrolizumab
- “The active substance in Keytruda, pembrolizumab, is a monoclonal antibody, a protein that has been designed to recognise and block a receptor (‘target’) called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system (the body’s natural defences) preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system’s ability to kill the cancer cells”

Yervoy: Ipilimumab, CTLA-4 inhibitor

- **“The active substance in Yervoy, ipilimumab, is a monoclonal antibody. A monoclonal antibody is a type of protein that has been designed to recognise and attach to a specific target in the body.**
- **Yervoy increases the number and the activity of a type of white blood cells called T cells which form part of the immune system and which can kill cancer cells. It acts on T cells by attaching to and blocking the activity of CTLA-4, a protein that controls the activity of T cells.**
- **Yervoy is usually used in combination with another medicine, nivolumab, but can also be used on its own for melanoma”**

Indications

- **Keytruda is a cancer medicine used to treat:**
  - **melanoma, a skin cancer,**
  - **non-small cell lung cancer (NSCLC), a type of lung cancer,**
  - **classical Hodgkin lymphoma, a cancer of the white blood cells,**
  - **urothelial cancer, a cancer of the bladder and urinary tract,**
  - **a cancer affecting the head and neck known as head and neck squamous cell carcinoma (HNSCC),**
  - **renal cell carcinoma (a type of kidney cancer).**
  - **Keytruda is mainly used for cancers that are advanced, have spread to other parts of the body (metastatic) or are not responding to other treatments. In some cancers, it is only given to patients whose tumours produce high levels of a protein known as PD-L1.**
  - **Keytruda is also used to help prevent the cancer from coming back after patients had surgery to remove melanoma (adjuvant therapy).**
  - **Keytruda is used on its own except for NSCLC and renal cell carcinoma where it is used in combination with other cancer medicines.**

Keytruda contains the active substance pembrolizumab

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Cancer Vaccines

- **Initial clinical tests failed**
  - **Given usually on top of standard of care**
    - E.g. RCC treatment with Kinase Inhibitor (Sunitinib) basic therapy
  - **First results were meager**
    - Immune response small
    - No relevant clinical effect
  - **Reasons:**
    - Cancer environment effectively blocked activity
    - Specificity, i.e. immunogenicity against cancer, was not that great

Learnings

- Better understanding of the design needs of a vaccine compound immunogenic against cancer
- Better understanding of the biochemical pathway on how a cancer vaccine needs to be designed to eventually trigger the kill of a cancer cell utilizing the immune system, comparable to killing bacteria invading the body

New approaches

- Improvements in specificity and immunogenicity
  - ISA
  - BioNTech
  - Immatics
  - Vaccibody
- Better understanding of need for combinations to “push the immune system”
  - Checkpoint Inhibitors as best example

Current development challenges

- **Clinical trial peculiarities in patient individual therapies**
  - **Standard: RCT (Randomized controlled Trial) in a single cancer entity, entity defined by location of cancer**
  - **New:**
    - Often single arm trials with “historic” control as randomization and blinding difficult
    - Trial with different cancer locations but commonalities in biochemistry
  - **Regulators accept this usually if one of two scenarios are being present:**
    - No other therapeutic option available: Against (palliative) standard of care
    - Treatment effect large enough to overcome any doubts regarding contribution of investigational “drug”

Manufacture

- Classically a batch is being manufactured for many patients
- In individualized therapies a batch is made for one patient
  - Size
  - Analytics, e.g. sterility
  - Stability
  - Packaging
  - Labelling

Labeling

- Current labelling is describing a compound
- Question: What will be described in patient individualized drugs?
  - The patient?
  - The cancer?
  - The way to get to the drug?

  Data protection legislation in the EU

Necessity to involve regulators early

- Individual development plan for every single new drug
  - CMC
  - Clinical
  - Preclinical
- Discussion of development pathway with the aim to reach agreement globally
- Actors:
  - CBER of FDA
  - EU with PEI in the lead

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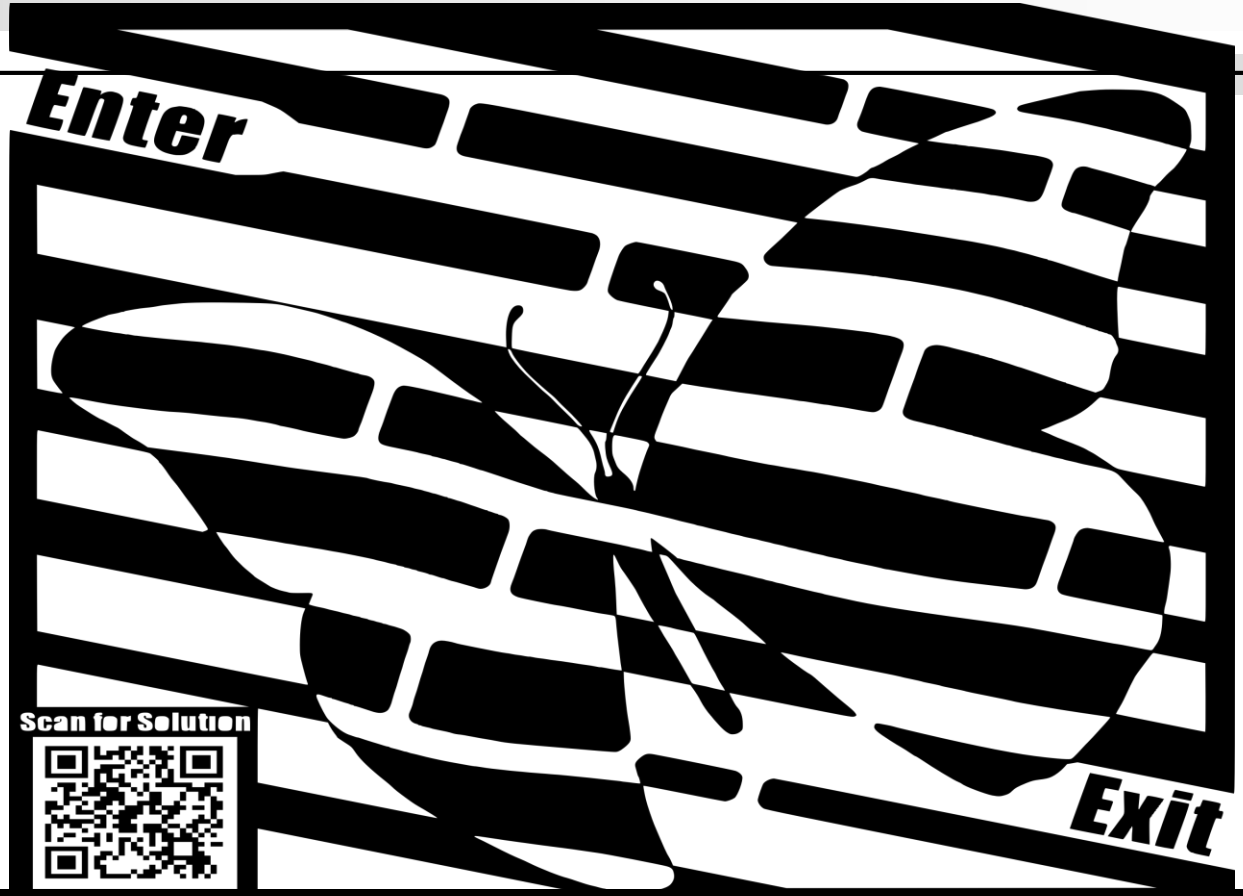

Thank You

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