Paradigm Shift in Cancer Therapy: Targeting Immune Cells rather than Cancer Cells

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Disclosures

Over the last 5 years:

• **Principal Investigator of Clinical Trials from the following companies:** Roche/Genentech, BMS, Merck (MSD), Pfizer, Lytix pharma, Eisai, Astra Zeneca/Medimmune, Bayer, Celgene, Chugai

• **Member of Clinical Trial Scientific Committee:** NCT02528357 (GSK)

• **Member of Data Safety and Monitoring Board:** NCT02423863 (Oncovir, Inc.)

• **Scientific Advisory Boards:** Merck Serono, eTheRNA, Lytix pharma, Kyowa Kirin Pharma, Bayer, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, GSK, Oncovir, Pfizer, Seattle Genetics, Flexus Bio

• **Teaching/Speaker activities:** Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi

• **Scientific & Medical Consulting:** Roche, Pierre Fabre, Onxeo, EISAI, Bayer, Genticel, Rigontec, Daichii Sankyo, Imaxio, Sanofi, BioNTech
Despite large improvements for leukaemia (9-fold) and myeloma (6-fold) the median survival time still remains low with patients diagnosed in 2007 predicted median survival time at 3 and 2 and half years respectively.
Tumor Targeted Therapies

Specificity

Personalized Predictive
TUMOR TARGETED THERAPIES

Before BRAFi

After 15 weeks of BRAFi

After 23 weeks of BRAFi

Wagle N, et al. JCO. 2011 Aug 1;29(22):3085-96

Paradigm Shift in Cancer Therapy

Historical Paradigm: Targeting Tumor Cells

New Paradigm: Targeting Immune Cells

Tumor Cell

Lymphocyte
Immune Checkpoint Targeted Therapy

Cytokines produced: IFNγ, TNFα and granzyme B

CTLA4-targeted antibody

Antibodies to block co-inhibitory signals

PD1-targeted antibody

T cell

CTLA4

PD1

CD28

B7

TCR

Antigen

MHC

APC
Immune Checkpoint Antibodies

**Antiserie CTLA-4**
- Tremelimumab (AZ)
- Ipilimumab (BMS)

Approved

**Antiserie PD-1**
- Nivolumab (BMS) & Pembrolizumab (MSD)

Approved

**Antiserie PD-L1**
- Durvalumab (AZ/Medimmune)
- Avelumab (Pfizer)
- Atezolizumab (Roche/Genentech)

Approved
Spectrum of Activity of Immunotherapy

- Melanoma (Mel)
- Renal Cell Carcinoma (RCC)
- Non-Small Cell Lung Cancer (NSCLC)
- Bladder Cancer
- Head and Neck Squamous Cell Carcinoma (HNSCC)
- Gastric Cancer
- Hodgkin Lymphoma (Hodgkin)
- Diffuse Large B-Cell Lymphoma (DLBCL)/FL
- Microsatellite Instability (MSI)
- Ovarian Cancer
- Triple-Negative Breast Cancer (TNBC)
- Mesothelioma
- Hepatocellular Carcinoma (HCC)
- Esophageal Cancer
- Small Cell Lung Cancer (SCLC)
- Biliary Tract Cancer
- Anal Cancer
- Merkel Cell Carcinoma (MCC)
- Thymic Carcinoma
- Endometrial Cancer
- Mismatch Repair Deficient (MMRd)
- Glioblastoma Multiforme (GBM)
- Cervical Cancer
- Salivary Gland Cancer
- ER+ Breast Cancer (ER+ BC)
- Thyroid Cancer
- Sarcoma
- Panoblastoma Multiforme B-Cell Lymphoma (PMBCL)
- Primary Central Nervous System Lymphoma (PCNSL)
- NKT Lymphoma

Additional Approvals

EMA Approvals

FDA Additional Approvals
Long Duration of Responses

JCO, April 20, 2015.
Which translates into benefits in OS
Auto-Immune Toxicity

Bompare et al Invest New drugs 2012

Financial Toxicity

Tumor Targeted Therapies: 10% of Patients

Immune Targeted Therapies: 90% of patients

NON SMALL CELL LUNG CANCERS
CHEMOTHERAPIES

CENTRAL PHARMACY
Preparation of Chemotherapies

HOSPITALIZATIONS FOR COMPLICATIONS
Febrile Neutropenia, Transfusions,…

SURGERY
Central Venous Line

HOSPITALIZATION FOR THERAPY
Drug Infusion, Hyperhydration, supportive care (anti-emetic, growth factors,…)

Image Description:
- A patient is sitting in a hospital bed, receiving care from a healthcare provider.
- The diagram illustrates the process of chemotherapy preparation, hospitalization for therapy, and surgical interventions, highlighting the central venous line setup and support for chemotherapies.
IMMUNOTHERAPIES

CENTRAL PHARMACY
Preparation of Chemotherapies
Flat Dose Preparation in advance

SURGERY
Central Venous Line
Peripheral Line *(Sub-Cutaneous?)*

HOSPITALIZATIONS FOR COMPLICATIONS
Febrile Neutropenia, Transfusions, ...
irAEs
Ambulatory Organ Specialist

HOSPITALIZATION FOR THERAPY
Drug Infusion, Hyperhydration, supportive care (anti-emetic, growth factors, ...)

OUTPATIENT CLINIC
30mn IV – No Supportive Care
PD-1/PD-L1 interactions in a Tumor
Factors Influencing αPD(L)1 Efficacy

- PD-L1
- Mutation Load
- Neo Epitopes
- Oncogenic Stress
- Microbiota
- Inflammation
This is just the beginning

AGONISTIC

T-cell stimulation

ANTAGONISTIC

Activating receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3
Immunotherapy Beyond Checkpoints

Oral Immuno Modulators
Oncolytic Virus
CAR T-cells
Bi Spe
Cytokines / Vaccines

T-VEC approval
CTL019
Blinatumomab approval
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