Future of IO: Combination

Sung-Bae Kim, MD, PhD
Professor, Dept of Oncology
Asan Medical Center
Seoul, Korea
Disclosure Information

Has received research funding from Novartis, Sanofi-Aventis, Kyowa-Kirin Inc, and DongKook Pharm Co. and has participated as a consultant in advisory boards for Novartis, AstraZeneca, Lilly, Enzychem, Dae Hwa Pharmaceutical Co. Ltd, ISU Abxis, and Daiichi-Sankyo.
Immune Check Point Inhibitors Have Paved the Way to Treat Cancer

Timeline of FDA Approvals of Checkpoint Inhibitors

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>MEL</td>
<td>2L+ MEL</td>
<td>2L+ MEL</td>
<td>2L+ MEL</td>
<td>2L+ SCCHN</td>
<td>2L+ dMMR/MSI-H</td>
<td>Adj MEL</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>2L+ MEL</td>
<td>2L+ NSCLC</td>
<td>2L+ NSCLC</td>
<td>2L+ NSCLC</td>
<td>2L+ UC, 2L+ MSHH/ dMMR solid tumors, 2L+ gastric/ESG (PD-L1+)</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(PD-L1+), 1L MEL</td>
<td>(PD-L1+)</td>
<td>(PD-L1+)</td>
<td>(PD-L1+)</td>
<td>2L+ UC, 2L+ MSHH/ dMMR solid tumors, 2L+ gastric/ESG (PD-L1+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Adj MEL</td>
<td></td>
<td>2L+ UC, 2L+ NSCLC</td>
<td>2L+ UC, 2L+ NSCLC</td>
<td>2L+ UC, 2L+ NSCLC</td>
<td>2L+ UC, 2L+ NSCLC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Anti-CTLA-4
- Anti-PD-1/PD-L1
- Anti-PD-1/PD-L1 + anti-CTLA-4
- Anti-PD-1/PD-L1 + chemotherapy + anti-angiogenic

Unmet Medical Needs for Immune Check Point inhibitors

- Broad activity but only subset patients benefit (usually ~20%)
- Substantial portion of patients who responded develop resistance
- Atypical immune response, immune-related adverse events
- No reliable biomarker to predict efficacy

![Graph showing ORR rates for different cancer types]

ORR: approximate objective response rate

[Legend: FDA approved agent available]
Current Combined Approach

Co-stimulatory mAbs targeting:
- CD137
- OX40
- CD40
- GITR

Conventional agents inducing immunogenic cell death:
- Chemotherapy
- Radiotherapy
- Anti-angiogenics
- Targeted therapies

Other checkpoint inhibitory molecules:
- CTLA4
- LAG3
- TIM3
- BTLA
- TIGIT

Cancer vaccines considering individual neoantigens

Functional modification of immunosuppressive enzymes such as:
- IDO1
- iNOS

T<sub>reg</sub> cell targeting or inhibition

Adoptive cell therapy

Myeloid cell modulation

Personalized combinations guided by biomarkers

PD1 or PDL1 blockade

Nature Reviews Cancer 2015
IO Combination Checklist

• Single agent efficacy
• Biology –driven rationale
• No overlapping toxicities
• Biomarker-based patient selection

• Today, a solid scientific rational & strong activity signals are required for new combinations to be tested
Key words for Combination Strategy

• Efficacy
  - Additive effects
  - Synergistic effects
• Toxicity/safety
• Cost/effectiveness
• IO-IO
• Conventional agent-IO
How to combine
T-Cell Responses Are Regulated by Multiple Ligand-Receptor Interactions With APCs or Tumor Cells


Inhibitory-CTLA-4, PD-1, LAG-3, TIM-3, VISTA(V-domain Ig in suppressor of T-cell activation)
Stimulatory-CD40, OX40, 4-1BB, GITR(glucocorticoid-induced TNF receptor), ICOS (inducible T-cell co-stimulator)
PD-L2–mediated inhibition of T cells

Stromal PD-L1 modulation of T cells

Tumor-associated fibroblast

CD8+ cytotoxic T lymphocyte

CD4+ T helper type 2 (Th2)

M2 macrophage

Treg cell

Dendritic cell

IFN-γ–mediated upregulation of tumor PD-L1

PD-L1/PD-1–mediated inhibition of tumor cell killing

Priming and activation of T cells

i-cell polarization

Immune cell modulation of T cells

TGF-β

IL-4/13

Peptide

PD-1

PD-L1

PD-L2

T-cell receptor

MHC-1

CD28

Shp-2

B7.1

Antitumor Immunity is a Dynamic Process

Cancer–immunity cycle

1. Release of tumor-specific antigens
2. Capture and presentation of cancer antigens by APCs (dendritic cells)
3. Priming and activation of T-cells against cancer-specific antigen
4. Transport of activated T-cells to site of the tumor via bloodstream
5. Infiltration of the tumor microenvironment by T-cells
6. Recognition of cancer cells by T-cells
7. Destruction of tumor cells by activated T-cells

Immune response to cancer

Cancer–immunity cycle

**Priming and activation**
- CD28/B7.1
- CD137/CD137L
- OX40/OX40L
- CD27/CD70
- HVEM
- GITR
- IL-2
- IL-12

**Cancer Ag presentation**
- TNF-a
- IL-1
- IFN-a
- CD40L/CD40
- CDN
- ATP
- HMGB1
- TLR

**Release of tumor-specific antigens**
- Stimulatory factors
- Inhibitors

**Infiltration of T cells into Tumors**
- LFA1/CAM1
- Selectins
- VEGF
- Endothelin B receptor

**Recognition of cancer cells by T-cells**
- T cell receptor
- Reduced pMHC on cancer cells

**Killing of cancer cells**
- IFN-r
- PD-L1/PD-1
- LAG-3
- PD-L1/B7.1
- Arginase
- IDO
- MICA/MICB
- TGF-b
- B7-H4
- BTLA
- TIM-3
- VISTA

**Trafficking of T cells to tumors**
- CX3CL1
- CXCL9
- CXCL10
- CCL5

Combinational Trial of Cancer Immunotherapy

- More than 900 + clinical trials are ongoing
- Mostly empiric

Adapted from Vanessa Luxey of CRI; by Gergely Janny, Chen and Mallinak, Nature 2017
Novel approaches
DNA repair

Role of PARP and BRCA
Mechanisms of DNA Repair:
Homologous Recombination (HR) is a critical DNA repair pathway

- DNA damage - single-stranded (SSBs), double-stranded breaks (DSBs)
- HR - a homologous DNA template to repair DSBs
- HR relies on a large complex of proteins including BRCA1 and BRCA2, PALB2, ATM
- Genetic lesions including germline and somatic mutations in genes (e.g. BRCA) result in deficiency of homologous recombination repair pathway termed - HRD

HR = homologous recombination. BER base excision repair

HRD can be therapeutically exploited by PARP inhibitors: Tumour Selective Synthetic Synthetic Lethality

- By inhibiting PARP1, PARP inhibitors block the repair of SSBs, which if left unrepaired, are converted to DSBs during replication.

- In the setting of HRD e.g. due to a BRCA mutation, DSBs cannot be accurately or efficiently repaired and the PARPi ultimately results in cell death.

Adapted from Guha N. Nat Biotechnol 2011; 29:373-4
Tumour Types for IO PARP Combinations?

• On basis of proposed MOA, tumours most likely to benefit are those most sensitive to PARP inhibition
  • High prevalence of defects in DNA Damage Repair (DDR) genes (e.g. BRCA 1/2, ATM)
  • High prevalence of genomic scarring as defined by HRD score

Prevalence of HRD Among All Tumour Types

Heeke AL, et al. ASCO 2017
### PARP inhibitors in combination with IO Ph 1-2

<table>
<thead>
<tr>
<th>Combination</th>
<th>Tumour Types</th>
<th>N</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib+ pembrolizumab</td>
<td>mCRPC</td>
<td>N=180</td>
<td>NCT02861573</td>
</tr>
<tr>
<td></td>
<td>2 other cohorts in study</td>
<td>Total</td>
<td>KEYNOTE 365</td>
</tr>
<tr>
<td>Olaparib+/- durvalumab</td>
<td>TNBC</td>
<td>N=60</td>
<td>NCT03167619</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DORA</td>
</tr>
<tr>
<td>Olaparib + durvalumab</td>
<td>Muscle Invasive Bladder Cancer (MIBC)</td>
<td>N=110</td>
<td>NCT02546661</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BISCAY</td>
</tr>
<tr>
<td>Olaparib+ durvalumab</td>
<td>NSCLC (post PD-1/L1) 2L+</td>
<td>N=200</td>
<td>NCT03334617</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AZ</td>
</tr>
<tr>
<td>Rucaparib + Atezolizumab</td>
<td>Ovarian Endometrioid</td>
<td>N=48</td>
<td>NCT03101280</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Roche</td>
</tr>
</tbody>
</table>
Checkpoint activation

4.1BB (CD137) and OX40
Stimulation of OX40 and 4.1BB (CD137) can help activate T cells and might inhibit exhaustion.

OX40 and 4.1BB belong to the TNFR superfamily.

**Activation of 4.1BB**
- Stimulation of various immune cells including T & NK cells
- Generation of immunologic memory
- Might ameliorate autoimmunity

**Activation of OX40**
- T cell stimulation
- Inhibition of T regs
- Generation of T memory

**Inhibition of PD-1**

---

**Diagram Notes**

- IL-2
- CD8+
- CTLA-4
- CD28
- TCR
- PD-1
- 4.1BB
- OX40
An anti-tumor immune-response can be initiated or modified in many ways.

Cancer–immunity cycle

1. Release of tumor-specific antigens
2. Capture and presentation of cancer antigens by APCs (dendritic cells)
3. Priming and activation of T-cells against cancer-specific antigens
4. Transport of activated T-cells to site of the tumor via bloodstream
5. Infiltration of the tumor microenvironment by T-cells
6. Recognition of cancer cells by T-cells
7. Destruction of tumor cells by activated T-cells

Promising first efficacy results with 4.1BB activation + checkpoint inhibition

Responses seen in difficult to treat tumors

Tolcher, ASCO 2016. abstract 3002
Examples of combination for clinical practice

1. Nivolumab + ipilimumab in melanoma

2. Pembrolizumab + Chemotherapy for NSCLC

3. Durvalumab + Radiochemotherapy stage III NSCLC

4. VEGFR antagonists + PD(-L)1 in RCC

5. Atezolizumab+Abraxane in TNBC

6. BRAF inh + MEK inh + PD-1 blocking agents for BRAF mutated melanoma.

7. Failure of IDO inhibitor (epacadostat) + pembrolizumab in melanoma.
Targeting VEGF in Cancer Immunity

Due to the multiple effects of VEGF on the tumor immune microenvironment, targeting VEGF enhances the anti-cancer immune response.

A. Promotion of DC maturation

- VEGF impairs DC maturation, resulting in reduced T-cell priming.

B. Normalisation of tumour vasculature

- VEGF promotes the formation of dysregulated tumour neovasculature, which hinders T-cell tumour infiltration and triggers T-cell death.

C. Reprogramming of the tumour microenvironment from immune-suppressive to immune-permissive

- VEGF stimulates expansion of myeloid-derived suppressor cells (MDSCs), resulting in an immunosuppressive tumour microenvironment and dampened anti-cancer immune response.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Regimen</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>IO + IO</td>
<td>Nivolumab + ipilimumab</td>
<td>1st line metastatic melanoma (approved, 2017) 1st line metastatic RCC (US approved, 2018)</td>
</tr>
<tr>
<td>IO + aVEGF</td>
<td>Atezolizumab + Bevacizumab Avelumab + Axitinib</td>
<td>1st line metastatic RCC (P3 positive, 2018) 1st line metastatic RCC (P3 positive, 2018)</td>
</tr>
<tr>
<td>IO + CTx</td>
<td>Pembolizumab + chemotherapy Atezolizumab+Nab-paclitaxel</td>
<td>1st line NSCLC (approved, 2018) 1st line TNBC (approved, 2019)</td>
</tr>
</tbody>
</table>
Safety Considerations

- Immune-mediated tissue injuries are wide-ranging and variable in presentation and time of onset.

- Substantial incremental toxicity can result from combinations, depending on both the patient population, dose and schedule.

- The causality attribution of adverse events may be problematic in case of novel combination.

- Given the unique immune related adverse events associated with immunotherapeutic combinations, increased awareness, early diagnosis and intervention is crucial, especially combination approach.
Potential Predictive Biomarkers and Technology

- PD L1 expression
- Tumor Mutational burden
- Neoantigen load
- MSI
- INF gamma gene sig
- T cell receptor repertoire
- Cytokine analysis
- HLA status
- Microbiome

- WES
- Multiplex Fluorescence IHC imaging
- RNA sequencing
- FACS analysis
- Single cell RNA sequencing
IO Combination in Malignant Melanoma

- The combination of nivolumab (1mg/kg q 3wks) and ipilimumab (3mg/kg x 4) is approved in US and EU for malignant melanoma
- 53% of Grade 3/4 TRAEs (27% for ipilimumab, 16.3% for nivolumab)

Larkin et al AACR 2017
Precision Immunotherapy: Role of Genomics TMB as Predictive Biomarker (CheckMate227)

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB

<table>
<thead>
<tr>
<th>TMB ≥10 mut/Mb and &lt;1% Tumor PD-L1 Expression</th>
<th>TMB &lt;10 mut/Mb and &lt;1% Tumor PD-L1 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>No. at risk</td>
</tr>
<tr>
<td>Nivo + chemo (n = 43)</td>
<td>Nivo + chemo (n = 54)</td>
</tr>
<tr>
<td>Nivo + ipi (n = 38)</td>
<td>Nivo + ipi (n = 52)</td>
</tr>
<tr>
<td>Chemo (n = 48)</td>
<td>Chemo (n = 59)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>Median PFS, mo</td>
</tr>
<tr>
<td>Nivo + chemo</td>
<td>Nivo + chemo</td>
</tr>
<tr>
<td>Nivo + ipi</td>
<td>Nivo + ipi</td>
</tr>
<tr>
<td>Chemo</td>
<td>Chemo</td>
</tr>
<tr>
<td>HR (vs chemo)</td>
<td>HR (vs chemo)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>0.56</td>
<td>0.87</td>
</tr>
<tr>
<td>(0.35, 0.91)</td>
<td>(0.57, 1.33)</td>
</tr>
<tr>
<td>0.48</td>
<td>1.17</td>
</tr>
<tr>
<td>(0.27, 0.85)</td>
<td>(0.76, 1.81)</td>
</tr>
</tbody>
</table>
Response to single agent anti-PD-L1/PD-1

Objective Response Rate (%)

- **Atezolizumab** (n = 115)
  - 1L: 26%
  - 2L+: 6.5%

- **Pembrolizumab** (n = 222)
  - 1L: 23%
  - 2L+: 4.7%

*Keynote-086, Cohort B*

*Keynote-086, Cohort A*

PFS & Duration of Response to anti-PD-L1/anti-PD1

Atezolizumab single agent in mTNBC ≥1L, PDL1+/-

<table>
<thead>
<tr>
<th>Time from start of Tx (mths)</th>
<th>Median PFS</th>
<th>Median DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.4</td>
<td>21.1</td>
</tr>
</tbody>
</table>

Overall Survival

- 1y OS: 100%
- 2y OS: 100%
- 3y OS: 100%

- 1-y OS: 51%
- 1-y OS: 33%

Schmid P, et al. AACR 2017
Atezolizumab (anti-PD-L1) plus chemotherapy in TNBC

**IMpassion130 study design**

- Metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC
  - Prior (neo)adjuvant chemo allowed if TFI ≥ 12 months
- ECOG PS 0-1

**Stratification factors:**
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥1%] vs negative [<1%])

**Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations**

Schmid P, et al. ESMO 2018 (LBA1); Schmid P, et al NEJM 2018
PD-L1 expression in metastatic TBNC

Using SP142 assay with cut-off >1% PD-L1 on tumour-infiltrating immune cells, had PDL1-positive tumors

~40% of patients

H&E staining

PD-L1 immune cells >1%

PD-L1 IC+ 41%

PD-L1 TC+ 9%

34% 7% 2%

PD-L1 measured by Ventana SP142 PD-L1 IHC assay
H&E, haematoxylin and eosin; IHC, immunohistochemistry
Emens LA, et al. IMpassion130 biomarkers.
SABCS 2018 (program #GS1-04)
Progression-free survival: PD-L1 predicts benefit with atezolizumab

<table>
<thead>
<tr>
<th>Population</th>
<th>PFS HR (95% CI)</th>
<th>Interaction Test (treatment × PD-L1 IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 IC+</td>
<td>0.62 (0.49, 0.78)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PD-L1 IC–</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.5152</td>
</tr>
<tr>
<td>ITT</td>
<td>0.80 (0.69-0.92)</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

*Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04); Schmid P, et al. ESMO 2018 (LBA1); Schmid P, et al NEJM 2018*
Overall survival: 2\textsuperscript{nd} Interim Analysis

Stratified HR: 0.86
(95\% CI: 0.72, 1.02)
Log-rank p = 0.0777

24-Month OS Rate (95\% CI)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>(n = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A + nab-P</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>(37, 47)</td>
</tr>
<tr>
<td>P + nab-P</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>(34, 44)</td>
</tr>
</tbody>
</table>

Clinical cutoff date: Jan 2, 2019. Median PFS (95\% CI) are indicated on the plot. Median FU (ITT): 18.0 mo.

Schmid P, et al ASCO 2019
Overall survival: PD-L1 status predicts benefit with atezolizumab

<table>
<thead>
<tr>
<th>Population</th>
<th>Median OS, mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A + nab-P (PD-L1+ n = 185)</td>
<td>25.0</td>
<td>18.0</td>
</tr>
<tr>
<td>P + nab-P (PD-L1+ n = 184)</td>
<td>19.7</td>
<td>19.6</td>
</tr>
</tbody>
</table>

*Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months.
Strategies for Immunotherapy in TNBC

Early Breast Cancer

Chemotherapy backbone: Nab-Paclitaxel, Paclitaxel or Gem/Cabo.
DFI > 6 months

Metastatic Breast Cancer

1st line MBC

≥2nd line MBC

Positive for PDL1: FDA approval 03/2019

IMpassion130, Keynote 355, IMpassion131/132

Keynote 119 negative
Neoadjuvant Chemo + anti-PDL1/anti-PD1 in TNBC

**KEYNOTE-173 phase 1/2 trial**

**Chemotherapy + anti-PD1**
- Pathological CR = ypT0 ypN0
- Paclitaxel Q1W x12 ± carboplatin Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4 + pembrolizumab Q3W x4
- Cohort A (no platinum): 60%
- Cohort B (platinum): 80%

**I-SPY 2 trial**

**Chemotherapy +/- anti-PD1**
- Pathological CR = ypT0/is ypN0
- Paclitaxel Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4
- Control (no immunotherapy): 20%
- Immunotherapy (no platinum): 60%

AC, doxorubicin + cyclophosphamide; CR, complete response; PD, programmed death; PD-L1, programmed death-ligand 1; Q1W, every week; Q3W, every 3 weeks; ypT0/Tis ypN0, no invasive residual in breast or nodes - noninvasive breast residuals allowed; ypT0 ypN0, no invasive or noninvasive residual in breast or nodes

Strategies for Immunotherapy in TNBC

Early Breast Cancer

- Neoadjuvant Trial
  - Single agent WOO part
  - Combination neoadjuvant part

- Adjuvant Trial post neoadjuvant treatment

Metastatic Breast Cancer

- 1st line MBC
- ≥2nd line MBC

Keynote 522, IMpassion031

A-Brave

Adapted from Schmid
Neoadjuvant Chemo + anti-PD1 in early TNBC

KEYNOTE-522 trial

Primary Endpoints:
1. Path CR = ypT0/Tis ypN0
2. EFS

Stage II/III TNBC
N = 1174

weekly Paclitaxel x 12 + Carboplatin + Pembrolizumab
weekly Paclitaxel x 12 + Carboplatin + Placebo
AC x 4 + Pembrolizumab
AC x 4 + Placebo
Adjuvant Pembrolizumab x 9
Adjuvant Placebo x 9

pCR (ypT0/Tis; ypN0): 64.8% with pembrolizumab vs 51.2% with placebo (P = .00055) improved EFS with addition of pembrolizumab (HR: 0.63)

*Prespecified P value boundary of .000051 not reached at this analysis (the first interim analysis of EFS).

Schmid. ESMO 2019. Abstr LBA8_PR.
What is the TNBC Landscape going to look like?
Personalised immunotherapy

- Pre-existing tumours: “inflamed” or “hot” tumours
  - PD-L1/checkpoints
  - CD8 T cells/IFNγ
  - Mutational load
- Excluded infiltrate
- Immune checkpoint inhibitors +/- chemotherapy
- Bring T cells into tumours
  - Priming & activation (e.g. CTLA-4, CD73)
  - Influence infiltration? (e.g. VEGF, AKT)
- Generate T cells
  - Priming, activation & infiltration
  - Neoantigen expression? (e.g. epigenetic modulation)
  - Adoptive Cell Therapy? Vaccination

Adapted from Schmid
How can we test the increasing number of combinations?

Preoperative platform for immunotherapy combinations (ECLIPSE)

Endpoints:
- 2-fold Increase in GzmB+ CD8+ T cell levels
- Immune phenotyping, CD8, PD-L1 & MHC-I, IFNγ gene signature expression, FM1

- Complements MBC trial
- Provide rapid BM-driven assessment/prioritisation
- Assess dynamic changes
- Facilitate patient selection for future enrichment

Other platform trials:
- BEGONIA 1st line TNBC (AKT, MEK, Sting, CD73)
- MORPHEUS 2nd line TNBC (AKT, LIV1-ADC)

Patients with operable, untreated, stage I-III ER+, HER2-negative breast cancer

Anti-PD-L1 (Control arm)
- Anti-PD-L1 + MEKi
- Atezolizumab + AKTi
- Atezolizumab + MEKi + anti-VEGF

Tumour samples

Definitive Surgery or Neoadjuvant Chemotherapy

Adjuvant therapy according to local guidelines

Short-term preoperative treatment (3 weeks)

Preoperative platform for immunotherapy combinations (ECLIPSE)
Future of immuno-oncology

• Precision immunotherapy
  Tumor-related and peripheral blood biomarker; PD-L1 staining, mutational load, T cell tumor infiltrate
  Newer immunotherapies and combinations will be tested in immune basket trials
  Peripheral blood and microbiome analyses will reveal the likelihood of developing severe irAEs
  The use of circulating tumor DNA assays will allow an assessment of early treatment failure and facilitate a switch to alternative immunotherapies

• Adoptive cell therapy
• Neoantigens-rapidly sequenced, incorporated into adoptive cell transfer or vaccine
• Epigenetic treatment- EZH2 (histone methylase) in function of Treg/control of FoxP3
• Novel Antibodies and cytokine
• Adjuvant immunotherapy
Sources of hope: The future of immunotherapy is bright, and the opportunities for new, curative treatments are manifold.

1. New immunosuppressive druggable targets
   LAG-3, NKG2A, TIM-3, TIGIT, Adenosine pathway, MDSC, Treg depleters.

2. Agonist stimulating agents
   T-cell engagers, IL-2PEG, IL-15-Fc, GITR, CD137, CD40

3. Local and tumor-targeted immunotherapies
   Virotherapy, TLR agonists, STING agonists, IL-12

4. Biotechnology
   Bispecifics, probodies

5. Adoptive T-cell therapy

6. Neoantigen-based vaccines
Take home message: IO combination

• Solid scientific rational & strong activity signals are required for new combinations to be tested.

• Building on the base of potent check point inhibitors, new combinations of immunotherapies will improve outcomes for patients and overcome innate and acquired resistance to immune treatment.

• Investigating cancer immunology by “reverse translating” to the lab from clinical studies is needed.