Rational combinations of immunotherapy with other agents

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Disclosures

• Advisory Board: BMS, Roche, MSD, Pfizer, Astellas, Ipsen

• Research funding: Pfizer, Astellas
Immunotherapy locomotive
New Immunotherapy studies in Cancer

ClinicalTrials.gov accessed 8Nov 2018
Mechanism of Immunosuppression in Cancer
High mutational load and immunotherapy

Environmental trigger: Eg tobacco, chemicals
DNA repair mutations: MMR, BRCA*

Cancer initiation

Increased mutational burden

More neoantigens

Can measure with Tumor Mutational Burden

IF cancer activates Checkpoint proteins (eg PDL-1)

Mr T-cell

Checkpoint Inhibitor

Mutation rate in various cancers

Hypermutated cancers responds to immunotherapy
Tumor mutational burden and immunotherapy

• Melanoma - increased survival for high TMB (WES) with ipilimumab or tremelimumumab

• NSCLC - improved OR and PFS in high TMB (WES) from pembrolizumab and nivolumab

• NSCLC – improved ORR, PFS, and OS in high TMB (NGS) from atezolizumab and other checkpoint inhibitors

• TMB does not correlate with PDL-1 staining

DNA-repair mutations and Immunotherapy

- Colon cancer with MMR deficiency – 60% response to Pembrolizumab

- Urothelial cancer with deleterious DDR – 80% response to PD-1 inhibitors

- Small series reports of 67% response to nivolumab for BRCA-associated ovarian cancer

Le et al NEJM 2015; Teo et al Clin Oncol 36; February 28, 2018; Matsuo et al Gynecol Oncol Rep 2018 Jun 20;25:98
Hypermutation vs Single driver mutation
High mutational load and immunotherapy?

Environmental trigger
- Eg tobacco, chemicals

DNA repair mutations
- MMR, BRCA2

Cancer initiation

Increased mutational burden

More neoantigens

IF cancer activates
Checkpoint proteins
- Eg PDL-1

Mr T-cell

Checkpoint Inhibitor
Driver mutation and immunotherapy?

Single driver mutation

 EG BRAF, EGFR, Her-2, VHL, K-ras

- Less mutational burden
- Less inflammation
- Less neo-antigens
- PDL-1 may not be upregulated

Cancer initiation and growth

TMB lower?  
Immunotherapy less effective?
TMB lower in tumors with driver mutations

- BRAF/NRAS–mutant melanoma have LOWER mutation rate compared to BRAF/NRAS wild-type (27 vs. 5.6 mutations per Mb)

- BRAF mutant NSCLC has high level of PD-L1 expression, low/intermediate TMB

- Lung cancer
  - TMB high – cigarette smoking
  - TMB low = ALK, EGFR, ERBB2, ROS, RET, and MET mutations

TMB in Melanoma and NSCLC varies with Driver mutation

IO less effective in EGFR mutant NSCLC 2nd-line

• CheckMate 057 - no survival benefit from nivolumab vs docetaxel in patients with EGFR mutation

• KEYNOTE010 - No survival advantage of pembrolizumab vs docetaxel in EGFR-mutant NSCLC (HR: 0.88, 95% CI: 0.45–1.70) compared with EGFR wild-type patients (HR: 0.66, 95% CI: 0.55–0.80)

• OAK - Atezolizumab vs docetaxel - no benefit in patients with EGFR gene mutation (HR: 1.24)
Urothelial cancer and FGF

• ~25% have FGF-3 driver mutation

• FGFR inhibitors have ~40% response

• Phase 2 Erdafitinib trial
  • Only 5% had responded to previous IO

Siefker-Radtke et al. ACO 2018 J Clin Oncol 36, (abstr 4503)
IO vs targeted therapy in BRAF-mutated Metastatic Melanoma

No study
ccRCC does not have high mutational burden

VEGF is Immunosuppressive

- VEGF impairs differentiation and maturation of Dendritic cells
- VEGF suppresses Effector T Cells number and function
- VEGF increases T-Regs
- VEGF increases Myeloid-derived suppressor cells

Yang et al. Front. Immunol., 03 May 2018
VHL, HIF and PDL-1

- ccRCC cell lines with VHL mutations have higher levels of PD-L1
- PD-L1 decreases after pVHL reconstitution and HIFα silencing
- Suggests that PD-L1 is a HIF2α target
PDL-1 expression in RCC is not due to hyper-mutation but VHL activation

Hodgkin’s lymphoma and PDL-1

- Chromosome 9p24.1 translocation in Classical HD
- 97% have alterations in PD-L1/PD-L2
  - Polysomy, copy gain, amplification
- Very high response to PD-1 blockade

Roemer et al. JCO Apr 2016
Rationale for combination therapy

- Tumors that are ‘immunotherapy sensitive’ – combine IO + IO
  - High TMB
  - Mismatch repair defect
  - Homologous recombination defect

- Tumors that are immunotherapy sensitive AND Driver mutation
  - IO + targeted therapy

- Tumors that are immune ‘cold’ – consider IO + non-immune agent
  - Driver mutation – combine with specific inhibitor
  - No driver mutations identified - combine with chemotherapy (if chemotherapy sensitive)
  - Combine with other ‘neoAntigen- releasing’ therapy – PARP, XRT, hormone therapy
Tumors that are ‘immunotherapy sensitive’

- High TMB
  - Melanoma
  - Lung
  - Urothelial
  - Head& Neck

- Mismatch repair defect

- Homologous recombination defect

Combine IO + IO
IO + IO combinations may be additive

• Not greater than additive benefit

• Two agents work independently
Nivo vs Ipi vs Ipi/Nivo in Metastatic Melanoma

Combo overcomes negative affect of driver mutation

BRAF mutant

BRAF Wild type

Hodi et al. Lancet Oncol Oct 2018
CM 227: Ipi/ nivo in NSCLC with high TMB

First-line metastatic
No EGFR or ALK
ECOG 0,1

Stratification
N= 1189
PDL-1 > 1%
Ipi/ Nivo
Chemo
Nivo

N= 550
PDL-1 < 1%
Ipi/ Nivo
Chemo
Nivo + chemo

N= 2877
Co-PrimaryEndpoints
PFS of TMB Populations
OS of PD-L1 Populations
Ipi/ Nivo vs Chemo

Foundation
Helman et al. NEJM Sep 2018
CM 227: lpi/ nivo in NSCLC PFS with high TMB

- Similar for >1 and <1% PDL-1 status
- Low TMB pts had better PFS with chemo
CheckMate 214: Fist line clear cell RCC

**Patients**
- Treatment-naïve advanced or metastatic clear-cell RCC
- Measurable disease
- KPS ≥70%
- Tumor tissue available for PD-L1 testing

**Randomize 1:1**

**Stratified by**
- IMDC prognostic score (favorable vs intermediate vs poor risk)
- Region (US vs Canada/Europe vs rest of world)

**Treatment**

**Arm A**
- 3 mg/kg nivolumab IV + 1 mg/kg ipilimumab Q3W for four doses, then 3 mg/kg nivolumab Q2W

**Arm B**
- 50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

R. Motzer at NEJM 2018
Checkmate 214: Co-primary endpoints

Progression free-survival - Intermediate/ Poor risk group

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>425</td>
<td>304</td>
<td>233</td>
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<td>304</td>
<td>233</td>
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<td>46</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Median PFS (95% CI), months
- NIVO + IPI: 11.6 (8.7–15.5)
- SUN: 8.4 (7.0–10.8)
- HR (99.1% CI): 0.82 (0.64–1.05)
- \( P = 0.0331 \)

Overall survival – All patients

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>425</td>
<td>399</td>
<td>372</td>
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<td>241</td>
<td>119</td>
<td>44</td>
</tr>
<tr>
<td>119</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>44</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS (95% CI), months
- NIVO + IPI: NR (28.2–NE)
- SUN: 26.0 (22.1–NE)
- HR (99.8% CI): 0.63 (0.44–0.89)
- \( P < 0.0001 \)
### ORR and PFS: IMDC favorable risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 125</td>
<td>N = 124</td>
</tr>
<tr>
<td>Confirmed ORR,(^b) % (95% CI)</td>
<td>29 (21–38)</td>
<td>52 (43–61)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.0002)</td>
<td></td>
</tr>
<tr>
<td>PFS,(^c) median (95% CI), months</td>
<td>15.3 (9.7–20.3)</td>
<td>25.1 (20.9–NE)</td>
</tr>
<tr>
<td></td>
<td>HR (99.1% CI) 2.18 (1.29–3.68)</td>
<td>(P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

\(^a\)11% of patients in both arms had tumor PD-L1 expression ≥1%

\(^b\)IRRC-assessed by RECIST v1.1

\(^c\)IRRC-assessed

Presented by B.Escudier at ESMO 2017

Sunitinib better!
Combination IO + IO in Urothelial

Tremelimumab + durvalumab

Sep 2016

Aug 2017
First-line metastatic urothelial studies: IO + IO

Recruitment completed

- Danube
- Durvalumab
- Durvalumab + Tremelimumab
- Platin/ gemcitabine
Rationale for IDO1 Inhibitor + Anti–PD-1

Anti–PD-1 treatment upregulates IDO1 expression\textsuperscript{3,4}

Depletion inhibits T-cells activity

IDO1 enzyme

\begin{align*}
\text{tryptophan} & \xrightarrow{\text{IDO1 enzyme}} \text{kynurenine} \\
\text{kynurenine} & \text{immunosuppressive}
\end{align*}

Increase in immune cell tumor infiltration and an decrease in regulatory T cells\textsuperscript{1,2}

Anti–PD-1 resistance overcome

Keytruda-Epacadostat Combo Fails Primary Goal in Phase 3 Trial for Melanoma, Companies Announce

• All Merck Epicadostat studies stopped

• BMS continues phase 2
Adenosine (ADO)

ATP $\xrightarrow{CD39} \text{AMP} \xrightarrow{CD73} \text{Adenosine} \rightarrow \text{Inosine}$

Receptors on immune cells
- **Pro-Inflammatory**
- **Anti-inflammatory**

Phase 1/2 studies – all in combo with PD1

- OX-40
- GITR
- LAG3
- IDO-1
- Adenosine
Tumors with Driver mutation in Immune-sensitive cancer

- BRAF-mutated Melanoma
- EGFR, ALK mutant NSCLC
- FGF-3 mutated Urothelial cancer
- VHL inactivated Clear-cell RCC

Combine IO + targeted therapy
Targeted therapies + Immunotherapy

• **Targeted therapies augment tumor antigen presentation** to T cells
  - Transtuzumab and cetuximab
  - Vemurafinib - increases tumour antigens

• **Targeted therapies may enhance T cell response and differentiation**
  - mTOR inhibition may stimulate T cells
  - mTOR inhibitors + IO gives greater intratumoral CD8+ T and dendritic cells
  - PI3K/ AKT inhibitors - increases CTLs and NK cells mediated lysis of tumour cells, decreases tumor-promoting inflammation
  - Transtuzumab - primes cytotoxic T lymphocytes, boosts secretion of IFNγ

• **Targeted therapies may sensitize tumor cells to immune-mediated destruction**
  - Bortezomib decreases MHC class I expression = tumor cells more susceptible to NK cells
  - Vemurafinib - decreased secretion of immune-suppressive cytokines

• **Targeted therapies may dampen tumor-induced immunosuppression**
  - Sunitinib diminished expression of CTLA4, PD1, and PDL-1
  - Sunitinib - decreases myeloid-derived suppressor cell and T-reg
  - VEGF-A inhibition - maturation of DCs and inhibition of myeloid derived suppressor cells
  - Imatinib - Blocks IDO, decreases Tregs
  - MAP kinase inhibition induced expression of immunomodulatory molecules in melanoma

Combinations may be synergistic (or additive)

- Greater than additive benefit

- One drug does something that potentiates the action of the other
  - Release of neoantigens
  - More inflammation
  - More tumour mutations
EGFR and PD-1 in NSCLC  

Increased toxicity

• Erlotinib + Nivolumab
  • 19% of grade 3 toxicities

• Osimertinib + Durvalumab
  • high incidence of interstitial lung disease (38%)

• Gefitinib + Durvalumab
  • demonstrated encouraging activity
  • higher incidence of grade 3/4 liver toxicity (40–70%)

• Erlotinib + Atezolizumab
  • Grade 3–4 adverse events in 39%
Targeted therapy + ipilimumab in melanoma

• dabrafenib +/- trametinib + ipilimumab, increased colitis with perforation of the colon (trial abandoned)

• vemurafenib +ipilimumab – hepatotoxicity at weeks 2 to 5 (trial abandoned)

Increased toxicity
KEYNOTE-022 BRAF-mutant Met Melanoma

Patients
- Histologically confirmed unresectable or metastatic stage IV BRAF\textsuperscript{V600E/K}-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors\textsuperscript{a}
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

N = 60
- Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

N = 60
- Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

R (1:1) N = 120

- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

\textsuperscript{a}Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
Progression-Free Survival

### Events, Median, HR, and P Value

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n</th>
<th>Median, mo (95% CI)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>31</td>
<td>16.0 (8.6-21.5)</td>
<td>0.66 (0.40-1.07)</td>
<td>0.04287</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>41</td>
<td>10.3 (7.0-15.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **PFS %**
  - Pembro + D + T: 59%
  - Placebo + D + T: 45%

- **PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, P ≤ 0.025)**

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- **Based on Kaplan-Meier estimate of PFS, per investigator assessment.**
- **Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.**
- **One-sided P value based on stratified log-rank test.**

## Summary of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Pembro + D + T n (%)</th>
<th>Placebo + D + T n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any-grade AE</strong></td>
<td>59 (98)</td>
<td>58 (97)</td>
</tr>
<tr>
<td><strong>Grade 3-4</strong></td>
<td>40 (67)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Led to death(^a)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>25 (42)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Led to discontinuation of all 3 study drugs</td>
<td>15 (25)</td>
<td>9 (15)</td>
</tr>
<tr>
<td><strong>Treatment-related AE</strong></td>
<td>57 (95)</td>
<td>56 (93)</td>
</tr>
<tr>
<td><strong>Grade 3-4</strong></td>
<td>34 (57)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Led to death</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Led to discontinuation of ≥1 study drug</td>
<td>24 (40)</td>
<td>12 (20)</td>
</tr>
</tbody>
</table>

\(^a\)One patient died due to treatment-related pneumonitis and one died of unknown cause. Data cutoff: Feb 15, 2018.

**Treatment-related toxicity doubled**

Median follow-up: 9.6 months (range, 2.7-23.4 months)
Anti-PD1 + targeted therapy in Melanoma and NSCLC

- No increase in efficacy
- Increased toxicity
Key eligibility criteria:
- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:
- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)
N = 886

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

Motzer et al. ESMO 2018
Targeted therapy + IO in RCC: Javelin 101

PFS per IRC in PDL-1 POS population

**Median PFS (95% CI), months**
- Avelumab + axitinib: 13.8 (11.1, NE)
- Sunitinib: 7.2 (5.7, 9.7)
- Stratified HR, 0.61 (95% CI: 0.475, 0.790)
  
  \[P < .0001\]

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PFS per IRC in the overall population

**Median PFS (95% CI), months**
- Avelumab + axitinib: 13.8 (11.1, NE)
- Sunitinib: 8.4 (6.9, 11.1)
- Stratified HR, 0.69 (95% CI: 0.563, 0.840)
  
  \[P = .0001\]

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Motzer et al. ESMO 2018
Merck’s KEYTRUDA® (pembrolizumab) in Combination with Pfizer’s Inlyta® (axitinib) Significantly Improved Overall Survival (OS) and Progression-free Survival (PFS) as First-Line Therapy for Advanced or Metastatic Renal Cell Carcinoma

OCTOBER 18, 2018

KEYTRUDA is First Anti-PD-1 Therapy in Combination to Improve Both OS and PFS in Advanced or Metastatic RCC, the Most Common Type of Kidney Cancer

Pivotal Phase 3 KEYNOTE-426 Trial Met Both Primary Endpoints; Data to be Filed with Global Regulatory Authorities

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that the pivotal Phase 3 KEYNOTE-426 trial evaluating KEYTRUDA® (pembrolizumab) monotherapy and PD-L1 inhibitor in combination with Inlyta® (axitinib) revealed significant improvements in overall survival (OS) and progression-free survival (PFS) over axitinib alone in patients with advanced or metastatic renal cell carcinoma.
**Key Eligibility:**
- Treatment-naive advanced or metastatic RCC
- Clear cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

**Stratification:**
- MSKCC risk score
- Liver metastases
- PD-L1 IC IHC status ($< 1\%$ vs $\geq 1\%)^a$

**Coprimary endpoints**
- PFS by INV-assessment in PD-L1+
- OS in ITT

**Other key endpoints**
- PFS in ITT
- OS in PD-L1+
- ORR

**N = 915**

**Atezolizumab 1200 mg IV q3w**  
+ **Bevacizumab 15 mg/kg IV q3w**

**Sunitinib 50 mg PO QD**  
(4 wk on, 2 wk off)

**Escudier et al ESMO 2017**
IMmotion151 – First line clear-cell RCC

**Progression-Free Survival in PD-L1+**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mo (95% CI)</th>
<th>HR 0.74 (95% CI: 0.57, 0.96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>11.2 (8.9, 15.0)</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>7.7 (6.8, 9.7)</td>
<td></td>
</tr>
<tr>
<td><em>P = 0.02</em></td>
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</tbody>
</table>

**Progression-Free Survival in All patients**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mo (95% CI)</th>
<th>HR 0.83 (95% CI: 0.70–0.97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>11.2 (8.6–13.3)</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>8.4 (7.5–9.7)</td>
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</tr>
</tbody>
</table>

Escudier et al ESMO 2017
Chemo-sensitive tumors which are also immune-sensitive

• Lung cancer
• Urothelial
• Head & Neck

Combine IO + chemotherapy
Chemotherapy + immunotherapy in IO-sensitive cancers

- Anti-PD1/ PDL1 is effective as monotherapy
- Chemotherapy is effective
  - A few combination trials for safety
  - Minimal efficacy trials
  - Extrapolate for all IO, chemo combos

Straight to Phase 3
Chemo +/- anti-PD1, L1

Liu et al Eur J Cancer, Sep 2018
Phase 2 Atezo + Chemo in NSCLC

- Chemo and Atezo toxicity no different than mono-regimen
- No difference in chemo regimen

Liu et al Eur J Cancer, Sep 2018
IMpower 150: Atezolizumab + chemo as 1L for NSCLC

EGFR or ALK genetic alterations included

Socinski et al NEJM June 2018
IMpower133: 1L Atezolizumab + Chemotherapy in Extensive Small-Cell Lung Cancer

Rash, hypothyroidism
Febrile neutropenia
Other EA

Same as single regimen
TMB not predictive

Horn et al, NEJM Sept 2018
First-line metastatic urothelial studies

**Danube**
- Durvalumab
- Durvalumab + Tremelimumab
- Platin/ gemcitabine

**ImVigor 130**
- Atezolizumab (PDL1 POS pts only)
- Atezolizumab + Platin/ gemcitabine
- Platin/ gemcitabine

**Keynote 361**
- Pembrolizumab
  - (PDL1 POS pts only)
  - Platin/ gemcitabine

**Checkmate 901**
- Ipilimumab + nivolumab
- Nivolumab + Platin/ gemcitabine
- Platin/ gemcitabine
First-line metastatic Head & Neck cancer

Keynote 048
- Pembrolizumab + Platin + 5FU
- Platin/5FU + Cetuximab

Checkmate 561
- Ipilimumab + nivolumab
- Platin/5FU + Cetuximab
Tumors that are immune-insensitive

• Breast cancer

• Prostate cancer

• Bowel cancer

Combine IO + with neoantigen-releasing therapy
‘Neo-antigen- releasing’ therapy

- Radiotherapy
- Chemotherapy
- Hormone therapy in CRPC
- PARPi in DDR deficient cancer
- CAR-T
- T-cell agonists (OX-40, GITR, IL-2)
- Vaccines
Enzalutamide + Pembrolizumab in CRPC

- 10 patients progressing on ENZA; No prior chemotherapy
- 3/10 had response + 3/10 had SD
  - PSA falling from 46, 71, and 2,503 ng/ml to ≤ 0.1 ng/ml
  - Soft tissue response in 2
- 2 biopsied
  - CD3+ CD8+ T cell and CD163+ macrophage infiltrates; PD-L1 expression
  - 1 had microsatellite instability (MSI)
- WHY?
  - Circulating Dendritic cells, PDL-1 POS in Enza resistant patients (Bishop, Oncotarget 2015)
  - No related to AR resistance
- Multiple Phase 1b and 3 trials underway
Summary — Immune Sensitive tumours

1. Anti PD-1 + CTLA4 combination are effective
   - Melanoma (overcomes negative effective of BRAF mutation)
   - NSCLC with high TMB
   - mRCC
   - Urothelial Cancer?

2. Other IO + IO – Await study results

3. IO + targeted therapy
   - Toxic in Melanoma
   - Toxic in NSCLC
   - Effective in RCC
Summary – Immune Sensitive tumours

4. IO + chemotherapy
   • Effective in NSCLC (overcomes negative effective of EGFR or ALK mutation)
     • Effective in SCLC
     • Urothelial cancer?
     • Head & Neck?
Summary – Immune Insensitive tumours

Multiple Phase 1/2 studies underway
PD-1 + something
Rationale

1. Empiric combinations
   - Ipi + Nivo
   - IO + chemo
   - Enzalutamide + IO

2. Translational based evidence
   - Targeted therapies + IO
   - Other IO/IO combos
   - PARP + IO

So far, Empiric is winning!