LESSONS LEARNT FROM THE DEVELOPMENT OF IMMUNOTHERAPY

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Details of the DOI for all authors are listed at the end of this presentation
ABBREVIATIONS

Ab: antibody
CR: complete response
CRC: colorectal cancer
CRT: chemoradiotherapy
CT: clinical trials
HPD: hyperprogressive disease
ICPi: immune checkpoint inhibition
IrAE: Immune related adverse events
MSI: microsatellite instability
NSCLC: non small cell lung cancer
OS: overall survival
PFS: progression free survival
PR: partial response
PsPD: pseudoprogression
Pts: patients
SCLC: small cell lung cancer
TIL: tumor infiltrating lymphocytes

TKI: tyrosine kinase inhibitor
TMB: tumor mutational burden
TME: tumor microenvironment
TGR: tumor growth rate
OVERVIEW

- Biomarkers for anti-tumour response
- Response patterns
- Toxicity
- Combination of immunotherapy with other agents
- Clinical trial organisation
- Conclusions and perspectives
BIOMARKERS FOR RESPONSE
BIOMARKERS: MICROENVIRONMENT MATTERS

Inflamed

Immune excluded

Cold

‘Ideal’ microenvironment: highly infiltrated with CD8 T cells that can be activated by immune checkpoint blockade

OVERVIEW OF POTENTIAL BIOMARKERS

PDL1 expression

TIL

e.g. NSCLC

e.g. bladder CA

TMB

e.g. NSCLC

MSI

e.g. CRC


2) Reprinted from The Lancet Oncology, 19(9), Sun R, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study, 1180-1191, Copyright 2018, with permission from Elsevier.

3) Hellman MD, et al. 2018, Cancer Cell 33, 843–852. Under Creative Commons Attribution (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/
BIOMARKER: PDL1 IS CURRENTLY THE BEST WE HAVE

- NSCLC: PDL1 is used as a biomarker for pembrolizumab but not for nivolumab
- Other tumour types: clinical value of PDL1 expression is less clear compared to NSCLC, however, important data for e.g. gastric cancer: ORR for PDL1+: 50% vs. 0% in PDL1- pts
- Explanation for differences:
  - Technical reasons (i.e. different antibodies, platforms, and cut-offs across studies)
  - Biological differences (expression changes over time, heterogeneity within tumour lesions, differences in immunogenicity between tumour types)

For more information see slide set of Dr Castelo-Branco

BIOMARKERS OF INTEREST:
TUMOUR MUTATIONAL BURDEN (TMB) IS A NEW BIOMARKER

- Most evidence in NSCLC
- Assessment needs to be further defined:
  - How to assess (WES/WGS vs. targeted platform), Where to assess (primary tumour or met)
  - When to assess (anytime or only just prior to treatment start)

Figure from Hellman MD, et al. Cancer Cell 2018;32(5):843–52, DOI:https://doi.org/10.1016/j.ccell.2018.03.018, under Creative Commons Attribution (CC BY 4.0).
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BIOMARKERS OF INTEREST: THE MORE TILS THE BETTER

Anti-PD(l)1 is reinvigorating pre-existing immunity

UBC treated with atezolizumab: CD8 T Cell presence is associated with more CR and longer OS

Bladder CA

Further prospective validation is required as well as practical utility


BIOMARKERS OF INTEREST: THE MORE TILS THE BETTER

Anti-PD(l)1 is reinvigorating pre-existing immunity: Potential for radiomics

CD8 cell score determined by analysis of CT scan might predict OS upon immune checkpoint therapy

Reprinted from The Lancet Oncology, 19(9), Sun R, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study, 1180–91, Copyright 2018, with permission from Elsevier.
BIOMARKER: NEGATIVE ASSOCIATION WITH RESPONSE

The presence or absence of certain molecular alterations or pathways involved in the CD8 T cell anti-tumour response might be good biomarkers for determining which patients will not benefit from ICPI monotherapy.

JAK1/JAK2 mutations prevent IFNγ
anti-tumour response

Loss of B2M expression prevents CD8 T cell killing upon ICPI treatment

TGFβ expression is inversely correlated with anti-tumour response with ICPI


RESPONSE PATTERNS
PATIENTS HAVING A COMPLETE RESPONSE SEEM TO HAVE A LONGER OVERALL SURVIVAL

All tumour types phase I patients

There is a striking difference in survival between partial and complete responders

OS and PFS for CR from their first complete response

Median crPFS (months): NR (IQR=17-NR)
Median crOS (months): NR (IQR=NR-NR)

PATIENTS HAVING A COMPLETE RESPONSE ARE STILL RESPONDING 2 YEARS AFTER CESSION OF ICPI

Melanoma

PSEUDOPROGRESSION (PSPD) IS RARE

Hodi et al. Abstract #3008 ASCO 2008

HYPERPROGRESSION (HPD) EXISTS, IT IS PROBABLY LETHAL BUT REMAINS TO BE DEFINED

Several tumour types

It should be discussed if HPD should be considered a severe side effect


TOXICITY
Autoimmune toxicity might be indicating activation of immune response and be associated with outcome.

Melanoma

Reprinted from Clinical Cancer Research, 2016, 22(4): 886-894, Freeman-Keller m, et al. Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes, with permission from AACR.

Retrospective analysis of RCC and melanoma patients treated with ICPi shows no difference in OS in patients that stopped ICPi because of toxicity.

**Melanoma**

- Discontinued because of drug-related AEs during induction
- Did not discontinue because of drug-related AEs

PRE-EXISTING AUTOIMMUNE DISEASE SHOULD NOT BE AN ABSOLUTE CONTRAINDICATION FOR IMMUNOTHERAPY

Retrospective analysis of patients with pre-existing autoimmunity who were treated with ICPi shows a clear difference in the OS without occurrence of IrAE. In this study patients with pre-existing autoimmune disease experience twice a much IrAE


COMBINATION OF IMMUNOTHERAPY WITH OTHER AGENTS
**Systemic treatments**
- Chemotherapy
- Targeted therapy
- Anti-angiogenic therapy
- Other immunotherapies

**Local treatments**
- Radiotherapy
- Surgery
- Intratumoural injection of therapeutics
Phase III studies confirming interest in NSCLC
- Tolerance is good: no overlapping toxicity


Hazard ratio for death, 0.49 (95% CI, 0.38-0.64)
P<0.001
Toxicity profile depends on combination partners

- Vemurafenib (anti-BRAF) + ipilimumab (anti-CTLA4): study stopped for hepatitis problems
- Osimertinib + durvalumab: stopped for pneumonitis (TATTON TRIAL: up to 64% of pts developed pneumonitis)

... 

- Clinical interest of combining TKI + ICPI remains to be demonstrated

See also: Hamid O, et al. 2015, SMR (melanoma).
Phase I/II studies demonstrating clear clinical interest good clinical tolerance: confirmation in phase III study: combination of bevacizumab with atezolizumab is superior to sunitinib in 1st line RCC (Immotion151)

- No overlapping toxicity

1st line RCC: bevacizumab + atezolizumab


COMBINATION OF IMMUNOTHERAPY

- Echo 301 trial (anti-IDO + pembro): negative
- Nivolumab + ipilimumab: interesting for melanoma patients with brain mets: cave toxicity
- Nivolumab + ipilimumab (1 mg/kg): superior OS compared to sunitinib in RCC
- Many combination trials are ongoing

Radiotherapy influences local and systemic immune responses
- It is feasible to combine SBRT with ICPI, no toxicity concerns
- Responses at distance of irradiated sites may be seen: abscopal effect

Neoadjuvant setting:
Interesting results in early CTs

NSCLC (image below), bladder CA (PURE-1), merkel cel CA (checkmate 358), melanoma, ...

Adjuvant setting:
Phase III evidence

- Melanoma stage > III: nivolumab
- NSCLC treated by CRT: durvalumab (PACIFIC)

IMMUNOTHERAPY + INTRATUMOURAL INJECTIONS

A way to modulate the tumour microenvironment (TME)

IMMUNOTHERAPY + INTRATUMOURAL INJECTIONS

- Phase I studies showing interest and good tolerance
  - Oncolytic viral therapy (talimogene laherparepvec)
    - + pembrolizumab (21 pts, phase Ib, DCR 76%)
    - + ipilimumab (Phase II)
      (n=198, ORR 39% v 18%, p =0.002)
  - Revival of TLR agonists
    - BCG (TLR 4)
    - Imiquimod (TLR7)

Twumasi-Boateng et al, 2018, NRC.

CLINICAL TRIAL ORGANISATION
IMMUNOTHERAPY IS CHANGING THE CLINICAL TRIAL LANDSCAPE

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<th>Patients number</th>
<th>Cytotoxic chemotherapy</th>
<th>Molecularly Targeted Agents</th>
<th>Immuno-stimulatory Antibodies</th>
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<td>30-50 unselected patients</td>
<td>30-200 molecularly selected patients</td>
<td>100-1000 immunologically selected patients</td>
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<th>Route of administration</th>
<th>IV &gt; Oral</th>
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<th>Novel routes of administration (intra-tumoral)</th>
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<th>Toxicity</th>
<th>MTD quasi-systematically reached</th>
<th>MTD unconstantly reached</th>
<th>MTD rarely reached</th>
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<th>PK/PD - biomarkers</th>
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<th>Drug approval</th>
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| Drug development timeframe | 10 years | 5-8 years | <5 years |

EXCLUSION CRITERIA FROM CLINICAL TRIALS NEED TO BE ADAPTED

- Brain metastasis can respond
- Hepatitis C RNA can decrease, no reactivation found
- Pre-existing autoimmune disease is not always reactivated
- Recent radiotherapy does not induce more toxicity
- Lymphopenia is not related to non-response
- Oncogeriatric patients do not seem to experience greater toxicity
- Tumour responses have been seen in patients with bad performance status (PS 2)
- Some transplant patients do not reject their graft while treated with ICPI

→ IMMUNOTHERAPY IS THESE SETTINGS SHOULD BE THOROUGHLY DISCUSSED WITH THE PATIENT AND HIS FAMILY

→ PROSPECTIVE CLINICAL TRIALS SHOULD CONFIRM THESE DATA

CONCLUSIONS AND PERSPECTIVES
CONCLUSION

- Biomarkers for anti-tumour response:
  - Highly needed, PDL1 is the best we have, TMB is at its infancy
- Response patterns
  - Durable responses: hope for cure. Even in metastatic setting?
- Toxicity
  - Early identification and treatment is key
- Combination of immunotherapy with other agents
  - Seems feasible for chemotherapy, anti-angiogenic Ab and radiation, much more challenging for TKI
- Clinical trial design
  - No clear dose/response/toxicity relationship
  - More insight needed to define the optimal dose/schedule and treatment duration
FUTURE PERSPECTIVES

- Biomarkers for anti-tumour response:
  - Potential candidates: TILs, JAK1/2 mutations (cfr NSCLC, melanoma)
- Response patterns
  - Possibility to stop immunotherapy after CR (cfr melanoma).
  - Pseudoprogression and hyperprogression need to be precised
- Toxicity
  - Pharmacodynamic parameter of tumour response (cfr melanoma, NSCLC)
- Combination of immunotherapy with other agents
  - Combination with local treatments is promising
- Clinical trial organisation
  - Exclusion criteria need to be revised
THANK YOU!

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**DISCLOSURES**

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