What is the rationale for combining immunotherapy with chemotherapy or TKIs

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DISCLOSURES

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• Research funding: BMS, Novartis, NanoString

• Stockownership: Uniti Cars
Combining Immunotherapy with Chemotherapy
The Cancer Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)
Turning ‘cold’ tumors into ‘hot’ tumors

non-inflamed
• few T cells
• non-clonal T cells
• immunosuppressive TME
• low no. of antigens

inflamed
• many T cells
• clonal T cells
• no immunosuppression
• foreign tumor

Adapted from: Sharma & Allison. Science 2015
Chemotherapy-induced immunogenic cell death

Tesniere et al. Cell Death and Differentiation 2008
Immunomodulatory properties of chemotherapy

Galluzzi et al. Nature Reviews Drug Discovery 2012
Dose, schedule, pretreatment does matter!
Are all chemotherapies equally immunogenic (in humans)?

Rizvi et al. JCO 2017
Immunomodulation by chemotherapy and RT

Rodriguez-Ruiz et al. Trends in Immunology 2018
Combined PD-1blockade and chemotherapy in TNBC – the TONIC-trial

Main inclusion criteria:
- Metastatic TNBC
- Pretreated with chemotherapy
- Max. 3 lines of palliative chemotherapy
- LDH < 2 ULN
- WHO 0 or 1

Non comparative Simon’s two-stage design:
- Interim analysis after 10 “evaluable” patients per cohort
- Continue with cohort when 3/10 no progression at 12 weeks ($n = 17$)

**Voorwerk, Slagter, …, Kok. Nature Medicine 2019**
High response rate in overall cohort
Turning “cold” into “hot” tumors

Adapted from: Sharma & Allison. Science 2015

Non-inflamed

Inflamed
TME of responders on nivo

Upregulation of immune-related genes and higher %T cells in inflamed tumors

Mann-Whitney
Changes in % T cells (TCRseq)

More intratumoral T cells after nivolumab and doxorubicin

Kruskal-Wallis
Responders are depicted with red dots
Treatment-induced changes gene expression

Most favorable changes in gene expression after cisplatin or doxorubicin and nivolumab

Wilcoxon Signed rank
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All patients for participating in the trial
Combining Immunotherapy with TKI (melanoma)
Intra-tumoral CD8+ T cell infiltration, PD-L1 expression and IFN gene signatures are associated with response to anti-PD-1

Tumeh et al., Nature 2014; Ribas et al SITC 2017
The effect of BRAF inhibitors on the tumor immune infiltrate

- Increased CD8 infiltration
- Increased antigen presentation
- Increased PD-L1 expression

Frederick et al., CCR 2013
BRAF+MEK inhibition induces expression of T-cell related genes

Amaria et al, presented at ASCO 2017
Combination BRAFi + MEKi + anti-PD-1 in mice induces superior tumor control

Hu Liskovan et al., Sci Trans Med 2015
Continuous combination of dabrafenib + trametinib + pembrolizumab has been tested in a randomised phase 2 study

Ascierto et al presented at ESMO 2018

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

**Stratification factors**
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

**Randomisation**
- $R (1:1)$
- $N = 120$
- $N = 60$
- $N = 60$

**Treatment Groups**
- **Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD**
- **Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD**

**Endpoints**
- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018
Continuous combination of dabrafenib + trametinib + pembrolizumab is effective, feasible but rather toxic.

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, a mo (95% CI)</th>
<th>HR b (95% CI)</th>
<th>P Value c</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 did not reach statistical significance threshold per study design (required HR for significance ≤0.62, P ≤ 0.025)**

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Ongoing response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + D + T</td>
<td>63%</td>
<td>45%</td>
</tr>
<tr>
<td>Placebo + D + T</td>
<td>72%</td>
<td>35%</td>
</tr>
</tbody>
</table>

1 year OS

79% vs 73%

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a Based on Kaplan-Meier estimate of PFS, per investigator assessment.
b 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.
c One-sided P value based on stratified log-rank test.


Adapted from Ascierto et al., presented at ESMO 2018.
Continuous combination of dabrafenib + trametinib + pembrolizumab is effective, feasible but rather toxic

<table>
<thead>
<tr>
<th>Event</th>
<th>Pembro + D + T n (%)</th>
<th>Placebo + D + T n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>N = 60</td>
<td>N = 60</td>
</tr>
<tr>
<td>Any-grade AE</td>
<td>59 (98)</td>
<td>58 (97)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>40 (67)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Led to death</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>Treatment-related AE</td>
<td>57 (95)</td>
<td>56 (93)</td>
</tr>
<tr>
<td>Grade 3-4</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>

*One patient died due to treatment-related pneumonitis and one died of unknown cause.

Ascierto et al., presented at ESMO 2018
Other triple combinations are also effective

Dabrafenib + Trametinib + Durvalumab

- N = 26
- ORR 69%
- Grade 3/4 toxicity: 46%
- Ongoing response in 16/18 patients

Vemurafenib + Cobimetinib + Atezolizumab

- N = 38
- ORR 81%
- Grade 3/4 toxicity: 41%
- Ongoing response in 18/31 patients

Dabrafenib + Trametinib + Spartalizumab

- N = 9
- ORR 100%
- Grade 3/4 toxicity: Hepatitis (3), verhoogd lipase (2)


Adapted from Dummer, presented at ESMO 2018.
Important questions

1. Combination therapy or sequential therapy?

2. Favorable effect of BRAFi+MEKi on the immune infiltrate, how long does this effect last?
Combination vs sequential therapy

PFS 1 + PFS 2 = Total PFS
Favorable effect of BRAFi and MEKi on the immune infiltrate - how long does this effect last?

Kakavand et al., CCR 2015
Wilmott et al., CCR 2012;
Favorable effect of BRAFi and MEKi on the immune infiltrate - how long does this effect last?

Deken, Gadiot et al., Oncoimmunology 2016
Short-term BRAFi + MEKi is synergistic with anti-PD-1

Deken, Gadiot et al., Oncoimmunology 2016
IMPemBra trial – Study design

Study cohort:
• 32 patients, 8 per arm

Inclusion criteria:
• Irresectable stage III of stage IV melanoma
• BRAF V600E/K positive
• No prior systemic therapy
• Lesion that can be biopsied easily
• No untreated brain metastases

Gestratified according to:
LDH < ULN, >ULN, >2x ULN

Cohort 1:
PEM 200mg Q3W

Cohort 2:
PEM 200mg Q3W
+ 2x 1 week
DAB 150mg BID + TRAM 2mg QD

Cohort 3:
PEM 200mg Q3W
+ 2x 2 weeks
DAB 150mg BID + TRAM 2mg QD

Cohort 4:
PEM 200mg Q3W
+ 6 weeks
DAB 150mg BID + TRAM 2mg QD

Primary endpoints:
• Safety and feasibility of the treatment
• Immune-activating capacity of the treatment schedule

Secondary endpoints:
• ORR (based on modified RECIST) at week 6, 12, 18
• PFS
IMPemBra trial – Study design

Cohort 1
Cohort 2
Cohort 3
Cohort 4:

Week 6  7  8  9  10  11  12
3rd cycle PEM
4th cycle PEM
5th cycle PEM

Pembrolizumab
DAB+TRAM

Biopt  Biopt  Biopt
## Efficacy – Objective response rate

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (n=7) PEM</th>
<th>Cohort 2 (n=7) PEM + 2x1W D+T</th>
<th>Cohort 3 (n=6) PEM + 2x2W D+T</th>
<th>Cohort 4 (n=6) PEM + 6W D+T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W 6</td>
<td>W12</td>
<td>W18</td>
<td>W 6</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>29%</td>
<td>57%</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>29%</td>
<td>57%</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>43%</td>
<td>14%</td>
<td>14%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Efficacy

New lesions are marked with a *
EFFICACY – PATIENT CASE

Week

0

PEM

6

2 x 2 weeks DAB+TRAM

12

PEM

18

PEM

Biopsy: minimal infiltrate lymphocytes

Biopsy: minimal infiltrate lymphocytes

Biopsy: lymphocytes, plasma cells and histiocytic infiltrate, no tumor cells

Biopsy: some lymphocytes and macrophages no tumor cells
Combining Immunotherapy with TKI (RCC)
In RCC high CD8 TIL and high PD-L1 are associated with worse outcome

Zhu et al. Journal of Cancer 2019
Addition of anti-PD-L1 to VEGFi improves PFS in RCC
Axitinib plus Avelumab

Motzer et al., NEJM 2019
Addition of anti-PD-L1 to VEGFtarget improves OS in RCC
Axitinib plus Pembrolizumab

Rini et al., NEJM 2019
Conclusions

• Chemotherapy, RT and TKI can modulate the tumor environment favorably for checkpoint inhibition

• Dosing and duration might play a pivotal role

• Intermittent applications are a undervalued approach

• PFS 1 + PFS 2 analyses need to be standard to establish the best patient benefit (concomitant versus sequential treatment)