Combination of immunotherapy and other systemic pharmacotherapy

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Brain Mets 2017, Marseille
Number of tumor-infiltrating lymphocytes (TILs) in breast cancer brain metastases compared to matched breast primaries.
Narloch et al, ASCO 2017, n. 2049

- 66 matched primary tumors and Breast Cancer Brain Metastases tissue
- Median %sTILS was significantly different between all primary tumors (15, IQR 5-20) and brain metastases (10, IQR 5-10), p = 0.001.
- The Triple Negative Breast Cancer subtype (n = 11) showed the largest decrease in %sTILs between primary tumors (20, IQR 10-20) and brain metastases (5, IQR 5-10), p = 0.022
PD-L1/PD-1 binding inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

Pembrolizumab
Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

<table>
<thead>
<tr>
<th></th>
<th>Melanoma (n=18)</th>
<th>NSCLC (n=18)</th>
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<tbody>
<tr>
<td>Number of total brain lesions per patient</td>
<td>8 (4-12)</td>
<td>6 (3-18)</td>
</tr>
<tr>
<td>Number of target brain lesions per patient</td>
<td>2 (1-4)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Size of all target lesions (mm)</td>
<td></td>
<td></td>
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<tr>
<td>Previously untreated (mm)</td>
<td>10 (7-13)</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td>Progression after previous SRS or WBRT (mm)</td>
<td>14 (10-19)</td>
<td>10 (6-11)</td>
</tr>
<tr>
<td>Total number of target brain lesions in all patients</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Total previously untreated</td>
<td>32 (13 patients)</td>
<td>43 (16 patients)</td>
</tr>
<tr>
<td>Total progressing after previous SRS or WBRT</td>
<td>13 (5 patients)</td>
<td>3 (2 patients)</td>
</tr>
<tr>
<td>Progression after previous WBRT</td>
<td>6 (2 patients)</td>
<td>3 (2 patients)</td>
</tr>
<tr>
<td>Progressing after previous SRS</td>
<td>7 (3 patients)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are median (IQR), unless otherwise stated. NSCLC=non-small-cell lung cancer. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy.

* or progressive
Best brain metastasis response by modified RECIST in assessable patients

- 28% (10/36) responders (i.e. 30% or more decrease in lesion size)
- 4 complete responses (NSCLC patients)
Goldberg et al, Lancet Oncol 2016

Time to brain metastasis response and duration of treatment

Bars represent individual patients who achieved a brain metastasis response or remained on trial for 6 months or longer.
Results of the phase II study CheckMate 204 (Tawbi et al, ASCO 2017, n. 9507)

- MEL pts with ≥1 measurable BMt 0.5-3.0 cm and no neurologic symptoms received NIVO 1 + IPI x 4 and the NIVO3 only until progression or toxicity. The primary endpoint was intracranial (IC) clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD] > 6 months).
- Median number of induction doses was 3; 26 pts (35%) received 4 NIVO+IPI doses and 38 pts (51%) began NIVO maintenance. Median follow-up of 6.3 months.
- Rx-related grade 3/4 AEs occurred in 48% of pts, 8% neurologic,. 3 pts (4%) stopped Rx for Rx-related neurologic AEs. One pt died of immune-related myocarditis.

<table>
<thead>
<tr>
<th>Best overall response, n (%; 95% CI)</th>
<th>Global</th>
<th>Intracranial</th>
<th>Extracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (3, 0–9)</td>
<td>14 (19, 11–29)</td>
<td>4 (5, 1–13)</td>
</tr>
<tr>
<td>PR</td>
<td>40 (53, 41–65)</td>
<td>28 (37, 26–49)</td>
<td>33 (44, 33–56)</td>
</tr>
<tr>
<td>SD &gt;6 months</td>
<td>5 (7, 2–15)</td>
<td>6 (8, 3–17)</td>
<td>2 (3, 0–9)</td>
</tr>
<tr>
<td>ORR, n (%; 95% CI)</td>
<td>42 (56, 44–68)</td>
<td>42 (56, 44–68)</td>
<td>37 (49, 38–61)</td>
</tr>
</tbody>
</table>
A randomized phase 2 study of nivolumab and nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases: The Anti-PD1 Brain Collaboration (ABC Study) (Long et al, ASCO 2017, n. 9508)

Pts with asymptomatic melanoma brain mets with no prior local brain therapy were randomised to cohort A or cohort B. Cohort C had brain mets 1) that failed local therapy, 2) were neurologically symptomatic and/or 3) with leptomeningeal disease.

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<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICR % (95% CI)</td>
<td>44 (24, 65)</td>
<td>20 (7, 41)</td>
<td>6 (0, 30)</td>
</tr>
<tr>
<td>ICR Complete Response</td>
<td>16 (24, 65)</td>
<td>12 (7, 41)</td>
<td>0</td>
</tr>
<tr>
<td>ECR % (95% CI)</td>
<td>38 (18, 62)</td>
<td>26 (10, 48)</td>
<td>21 (5, 50)</td>
</tr>
<tr>
<td>6-mo PFS % (95% CI)</td>
<td>50 (33, 75)</td>
<td>29 (15, 56)</td>
<td>0</td>
</tr>
<tr>
<td>6-mo OS % (95% CI)</td>
<td>76 (59, 97)</td>
<td>59 (41, 86)</td>
<td>44 (25, 76)</td>
</tr>
</tbody>
</table>

Ipi+nivo had reduced activity in pts who progressed on BRAFi.
Immunogenic tumor cell death

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**A**

Tumor Cell

- Anthracyclines
- Cyclophosphamide
- Oxaliplatin

- HMGB1
- CRT
- CRTR
- Tumor antigen

- dsRNA
- Type I IFN
- IFNAR
- ATP
- MHC
- CD8+ T cell

- Dying tumor cell

- HMGB1

- Immature DCs
- TLR4R
- NRLP3
- proIL1β
- P2RX7
- IFNAR

- CRTR
- CRT

- ATP

- IFN

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**B**

- Anthracyclines

- Tumor antigen-specific CD8+ T cells

- IL1β secretion

- IFN

- Type I IFNs

- MHC

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*Image credit: American Association for Cancer Research*
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

- 123 patients enrolled; 60 randomly assigned to the pembro + chemo and 63 to chemo alone.
- 33 (55%; 95% CI 42-68) of 60 pts in the pembro + chemo group achieved an objective response compared with 18 (29%; 18-41) of 63 pts in the chemo alone group (estimated treatment difference 26% [95% CI 9-42%]; p=0.0016).
- Incidence of grade 3 or worse treatment-related adverse events similar between groups.

However, no data on brain mets: 9 (15%) in pembro + chemo, 6 (10%) in chemo only
Four cohorts (125 patients)
(A) BRAF V600E -positive, asymptomatic melanoma brain metastases, with no previous local brain therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (76 pts);
(B) BRAF V600E -positive, asymptomatic melanoma brain metastases, with previous local brain therapy, and an ECOG performance status of 0 or 1 (16 pts);
(C) BRAF V600D/K/R -positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0 or 1 (16 pts);
(D) BRAF V600D/E/K/R -positive, symptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2 (17 pts).
Dabrafenib plus trametinib was active with a manageable safety profile.

The median duration of response was relatively short.

These results provide evidence of clinical benefit with dabrafenib plus trametinib in melanoma brain metastases.
Pembrolizumab in melanoma brain mets (Goldberg et al, 2016)

- 4/18 melanoma pts not assessable for brain met response (3 extracerebral progression; 1 intralesional haemorrhage).
- 4 pts with partial responses (29% of evaluable pts).
- Responses were durable.
- No BRAF mutation in responders (n=6).

Dabrafenib+Trametinib in BRAF V600 mutant melanoma brain mets (Davies et al, 2017)

- 44-59% responders in the 4 cohorts.
- 58% in cohort A resembling pts of Goldberg et al: ECOG 0-1, no previous local brain therapy.
- Median duration of response was relatively short.
Phase II Randomized Trial of Temozolomide and Concurrent Radiotherapy in Patients With Brain Metastases

D. Antonadou, M. Paraskevaldis, G. Sarris, N. Collarakis, I. Economou, P. Karageorgis ...

Temozolomide for the Treatment of Brain Metastases Associated With Metastatic Melanoma: A Phase II Study

Sanjiv S. Agarwala, John M. Kirkwood, Martin Gore, Brigitte Dreno, Nicholas Thatcher, Beate Czarnetski, Michael Atkins, Antonio Buzaid, Dimosthenis Skarlos, and Elaine M. Rankin

ONCOIMMUNOLOGY
2016, VOL. 5, NO. 5, e1108513 (13 pages)
http://dx.doi.org/10.1080/2162402X.2015.1108513

The multidrug-resistance transporter Abcc3 protects NK cells from chemotherapy in a murine model of malignant glioma

Sara Pessinaa, Gabriele Cantinib, Dimos Kapetisb, Emanuela Cazzatoa, Natalia Di iannia, Gaetano Finocchiaroa, and Serena Pellegattaa
The recent discovery of the extracellular role of **HMGB1** as a proinflammatory cytokine has opened up a new field of research to study the role of HMGB1 in inflammatory diseases, including **severe sepsis** and arthritis. 

http://flipper.diff.org/app/items/info/6907

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**Anti-septic effects of dabrafenib on HMGB1-mediated inflammatory responses**

Byeongjin Jung¹, Hyejin Kang¹,‡, Wonhwa Lee¹,², Hyun Jin Noh³, You-Sun Kim³, Min-Su Han⁴, Moon-Chang Baek⁵,*, Jaehong Kim⁶,*, & Jong-Sup Bae¹,*
Caloric Restriction Leads to Increased Tumor Cell Death via Immunogenic Pathways
Gut microbiota can mediate immune anticancer effects of chemotherapy
The gut microbiome

Franca B. Alphin, Duke University