NEOADJUVANT IMMUNOTHERAPY IN MELANOMA
The pathway towards personalised immunotherapy

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The Netherlands Cancer Institute, Amsterdam
TARGETED THERAPY AND IMMUNOTHERAPY HAVE IMPROVED 3 year OS of stage IV melanoma patients

*OS rate at 33 months
ONLY A SUBGROUP OF PATIENTS BENEFITS LONG-TERM FROM THE CURRENT THERAPIES...

...and not all need a toxic combination therapy – urgent need for personalisation of immunotherapies

MULTIPARAMETER BIOMARKERS ARE KEY

The Cancer Immunogram

- Tumor foreignness
  - Mutational load
- General immune status
  - Lymphocyte count
- Tumor sensitivity to immune effectors
  - MHC expression
  - IFN- sensitivity
- Absence of inhibitory tumor metabolism
  - LDH, glucose utilization
- Absence of soluble inhibitors
  - IL6->CRP/ESR
- Absence of Checkpoints
  - PD-L1
- Immune cell infiltration
  - Intratumoral T cells

WHICH PATIENTS ALWAYS HAVE A FAVOURABLE CANCER IMMUNOGRAM?

MELANOMA ADJUVANT TREATMENT
Phase 3 studies with checkpoint inhibition and targeted therapy

EORTC 18071
- Ipilimumab 10 mg/kg vs. placebo
  - Stage IIIA-C; RFS HR 0.76, OS HR 0.72

Checkmate 238
- Ipilimumab 10 mg/kg vs. nivolumab
  - Stage IIIB-C + IV; RFS HR 0.65, OS HR NA

EORTC 1325
- Pembrolizumab vs. placebo
  - Stage IIIA-C; RFS HR 0.57, OS HR NA

COMBI-AD
- Dabrafenib + trametinib vs. placebo
  - Stage IIIA-C; RFS HR 0.47, OS HR 0.57

Pembro > Pbo
Nivo > Ipi
D+T > Pbo

Courtesy of Prof O. Michielin. Presented by Olivier Michielin, at ASCO 2018
WHY SHALL WE GO FOR NEOADJUVANT THERAPY?

1. **Therapy efficacy** can be determined **within the individual patient** for possible additional adjuvant therapy
2. **Reduce tumour burden** before surgery
3. Utilise **pathological response** data as surrogate **outcome markers** for relapse free and overall survival
4. **Easier baseline biomarker identification** due to more homogenous patient populations
5. In the case of T cell checkpoint blockade neoadjuvant therapy could induce **stronger and broader tumour-specific T cell response**
NEOADJUVANT VERSUS ADJUVANT CANCER IMMUNOTHERAPY

Adjuvant immunotherapy

Image courtesy of Dr CU Blank, National Cancer Institute ©CU Blank, NKI.

Neoadjuvant immunotherapy
WHY SHOULD WE NOT GO FOR NEOADJUVANT THERAPY?

1. Patients not responding might **deteriorate** and will **not make it to** potential curative **surgery**
2. **irAE** might **hamper surgery**
3. **Neoadjuvant therapy** might **not be better** than adjuvant therapies
4. Neoadjuvant therapies require **more patient management**, timing scans, day clinic appointments and surgery planning
5. **Pseudoprogression** **versus** real progression
IN PRECLINICAL EXPERIMENTS NEOADJUVANT CHECKPOINT INHIBITION IS SUPERIOR TO ADJUVANT APPLICATION

NEO-ADJUVANT VERSUS ADJUVANT CHECKPOINT INHIBITION (IPI+NIVO)

In macroscopic Stage III melanoma – OpACIN

Designed by Dr TN Schumacher and Dr CU Blank in 2014
NEO-ADJUVANT NIVOLUMAB + IPILIMUMAB EXPANDS MORE AND BROADER TUMOUR RESIDENT T CELL CLONES

Reprinted by permission from Springer Nature, Nature Medicine, Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma, Blank CU, et al. Copyright 2018
PATIENTS WITH RELAPSE SEEM TO HAVE A LOWER NUMBER OF NEWLY DETECTED CLONES

Compared to patients without a relapse

- >1-fold expanded clones
- Newly detected clones

Reprinted by permission from Springer Nature, Nature Medicine, Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma, Blank CU, et al. Copyright 2018
PD-1 BLOCKADE PROMOTES EPITOPE SPREADING IN ANTICANCER CD8+ T CELL RESPONSES
By preventing fratricidal death of subdominant clones to relieve immunodomination

Immunodominance IV >> I >= II/III >> V
NEO-ADJUVANT IPI+NIVO

Induces within 6 weeks a high frequency of deep pathologic responses (pRR 78%)

- **pNR**
  - Week 0 Biopsy
  - Week 6 Surgery
  - 2 patients no response

- **pPR**
  - 1 patient pathologic partial response

- **pCR**
  - 4 patients pathologic near complete response (<10% vital tumour)
  - 2 patients pathologic complete response, 1 patient likely but formally not judgeable

Images courtesy of Dr CU Blank, NKI
NEOADJUVANT IPI+NIVO SEEMS TO BE SUPERIOR TO ADJUVANT IPI+NIVO (MIDDLE FU 25MO)

Week 6 pNR

Week 6 pCR, pnCR, pPR

SURVIVAL UPDATE

RELAPSE-FREE SURVIVAL

OVERALL SURVIVAL

80% 60%

90% 70%

Courtesy of Prof C. Blank et al., ESMO 2019
IMMUNE SIGNATURE ANALYSES (HERE ANTI-PD-1 RESPONSES)

Can map the network of anti-tumour immune responses

PATIENTS WITH A HIGH IFN/T-CELL/BATF3 SIGNATURE HAVE A GOOD CLINICAL OUTCOME

Batf3 DC signature¹

T cell signature²

IFN-γ signature³

HIGH/INTERMEDIATE IFN SIGNATURES IDENTIFIES PATIENTS BENEFITTING LONG-TERM

JUDGING RADIOLOGIC RESPONSES
Is hampered by sarcomatoid reactions and interfissure lymph node swelling

Courtesy of Prof CU Blank. NKI.
**Neo-ADJUVANT IPI+NIVO AT STANDARD DOSING IS TOXIC**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All patients (n=20)</th>
<th>Adjuvant (n=10)</th>
<th>Neo-Adjuvant (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades n (%)</td>
<td>Grade 3/4 n (%)</td>
<td>All grades n (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>20 (100)</td>
<td>18 (90)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>17 (85)</td>
<td>5 (25)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>14 (70)</td>
<td>4 (20)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (60)</td>
<td>6 (30)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>GGT increased</td>
<td>11 (55)</td>
<td>3 (15)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Elevated Lipase</td>
<td>11 (55)</td>
<td>8 (40)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (50)</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>10 (50)</td>
<td>5 (25)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (45)</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8 (40)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>Elevated serum amylase</td>
<td>8 (40)</td>
<td>4 (20)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Colitis</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>7 (35)</td>
<td>1 (5)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (30)</td>
<td>2 (10)</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>

PATHOLOGICAL RESPONSE AND SURVIVAL WITH NEOADJUVANT THERAPY IN MELANOMA: A POOLED ANALYSIS FROM THE INTERNATIONAL NEOADJUVANT MELANOMA CONSORTIUM (INMC)

# MODERN MELANOMA NST TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaria (TT)</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Long (TT)</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Blank (OpACIN, IT)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Amaria (IT)</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Huang (IT)</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>Blank (OpACIN-neo, IT)</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Courtesy of Dr. A. Menzies
# MODERN MELANOMA NST TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>pCR (%)</th>
<th>med RFS (mo)</th>
<th>med FU (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaria Lancet Oncol 2018</td>
<td>Dab/Tram</td>
<td>58</td>
<td>19.7</td>
<td>18.6</td>
</tr>
<tr>
<td>Long Lancet Oncol 2019*</td>
<td>Dab/Tram</td>
<td>49</td>
<td>23.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Blank Nat Med 2018</td>
<td>Ipi+nivo</td>
<td>33</td>
<td>NR</td>
<td>32</td>
</tr>
<tr>
<td>Amaria Nat Med 2018</td>
<td>Ipi+nivo</td>
<td>45</td>
<td>NR</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Nivo</td>
<td>25</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Huang Nat Med 2019</td>
<td>Pembro</td>
<td>19</td>
<td>NR</td>
<td>18</td>
</tr>
<tr>
<td>Rozeman Lancet Oncol 2019*</td>
<td>Ipi+nivo</td>
<td>57</td>
<td>NR</td>
<td>8.3</td>
</tr>
</tbody>
</table>

*In press
RESULTS – PCR RATES

![Bar chart showing pCR and no pCR rates for total, immunotherapy, and targeted therapy.

Total: 59, 41
Immunotherapy: 62, 38
Targeted Therapy: 53, 47

Courtesy of Dr A M. Menzies.
RFS AND PATHOLOGICAL RESPONSE

Immunotherapy

Targeted Therapy

*1 pt died from toxicity without recurrence, censored at time of death. Courtesy of Dr A M Menzies.
Neo-adjuvant Nivolumab or Pembrolizumab was less toxic, but pRR was low (30-33%)
Several stage III patients deteriorated and could not undergo surgery anymore, making anti-PD-1 monotherapy unfeasible for neo-adjuvant therapies\textsuperscript{1,2}
Neo-adjuvant Nivolumab or Pembrolizumab was less toxic, but pRR was low (30-33%). Several stage III patients deteriorated and could not undergo surgery anymore, making anti-PD-1 monotherapy unfeasible for neo-adjuvant therapies\textsuperscript{1,2}

Can we reduce toxicity, but preserve efficacy by modulating the Ipilimumab + Nivolumab neoadjuvant scheme?


OPACIN-NEO:
A MULTICENTER PHASE 2 STUDY TO IDENTIFY THE OPTIMAL NEO-ADJUVANT COMBINATION SCHEME OF IPILIMUMAB (IPI) AND NIVOLUMAB (NIVO)

OPACIN-NEO: STUDY DESIGN

Study design:
- Multi-centre phase 2 trial

Study cohort:
- Stage III measurable melanoma
- 86 patients, 30 Arm A and Arm B, 26 in Arm C (closed earlier upon advice of the DSMB)

Stratified according to:
- Study centre

## IMMUNE-RELATED ADVERSE EVENTS IN THE FIRST 12 WEEKS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>A: 2xI3+N1 All grade</th>
<th>Grade 3-4</th>
<th>B: 2xI1+N3 All grade</th>
<th>Grade 3-4</th>
<th>C: 2xI3-2xN3 All grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>29 (97)</td>
<td>12 (40)</td>
<td>29 (97)</td>
<td>6 (20)</td>
<td>26 (100)</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (63)</td>
<td>-</td>
<td>17 (57)</td>
<td>-</td>
<td>14 (54)</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (60)</td>
<td>2 (7)</td>
<td>11 (37)</td>
<td>1 (3)</td>
<td>18 (69)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (40)</td>
<td>-</td>
<td>10 (33)</td>
<td>-</td>
<td>10 (38)</td>
<td>-</td>
</tr>
<tr>
<td>ALT increased</td>
<td>12 (40)</td>
<td>6 (20)</td>
<td>6 (20)</td>
<td>1 (3)</td>
<td>9 (35)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12 (40)</td>
<td>-</td>
<td>2 (7)</td>
<td>-</td>
<td>9 (35)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (23)</td>
<td>1 (3)</td>
<td>4 (13)</td>
<td>1 (3)</td>
<td>11 (42)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (27)</td>
<td>1 (3)</td>
<td>5 (17)</td>
<td>-</td>
<td>4 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (13)</td>
<td>-</td>
<td>4 (13)</td>
<td>1 (3)</td>
<td>7 (27)</td>
<td>-</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6 (20)</td>
<td>-</td>
<td>3 (10)</td>
<td>-</td>
<td>3 (12)</td>
<td>-</td>
</tr>
<tr>
<td>Colitis</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>-</td>
<td>7 (27)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (17)</td>
<td>-</td>
<td>2 (7)</td>
<td>-</td>
<td>3 (12)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (13)</td>
<td>-</td>
<td>1 (3)</td>
<td>-</td>
<td>4 (15)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (7)</td>
<td>-</td>
<td>3 (10)</td>
<td>-</td>
<td>4 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Dry eye</td>
<td>2 (7)</td>
<td>-</td>
<td>3 (10)</td>
<td>-</td>
<td>2 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>1 (3)</td>
<td>-</td>
<td>4 (13)</td>
<td>-</td>
<td>2 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>-</td>
<td>-</td>
<td>5 (17)</td>
<td>-</td>
<td>2 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Serum amylase increased</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>-</td>
<td>-</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>-</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (8)</td>
<td>1 (4)</td>
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<tr>
<td>Radiculitis</td>
<td>-</td>
<td>-</td>
<td>1 (3)</td>
<td>-</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>-</td>
<td>-</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adverse events that occurred in ≥ 7 patients or were grade 3-4 are displayed in the table. Data are presented as n, (%)

## RADIOLOGIC RESPONSE ACCORDING TO RECIST 1.1

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A: 2xI3+N1 (n=30)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>18 (60)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>16 (53)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>10 (33)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>Not evaluable</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

*aFor one patient the target lesion was not pictured on the CT images and could not be evaluated for response.*
CORRELATION RADIOLOGIC/PATHOLOGIC RESPONSE

RADIOLOGIC RESPONSE UNDERESTIMATES PATHOLOGIC RESPONSE

### PATHOLOGIC RESPONSE – CENTRAL REVISION

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>A: 2xl3+N1 (n=30)</th>
<th>B: 2xl1+N3 (n=30)</th>
<th>C: 2xl3-2xN3 (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRR</td>
<td>24 (80)</td>
<td>23 (77)</td>
<td>17 (65)</td>
</tr>
<tr>
<td>pCR</td>
<td>14 (47)</td>
<td>17 (57)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>near pCR</td>
<td>7 (23)</td>
<td>2 (7)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>pPR</td>
<td>3 (10)</td>
<td>4 (13)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>pNR</td>
<td>6 (20)</td>
<td>7 (23)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>-</td>
<td>-</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*a* One patient had only palliative resection of largest lymph node, *b* Surgery was not performed because of toxicity, this patient had a radiologic CR

Data are presented as n, (%).

18 MONTHS EVENT-FREE SURVIVAL PER TREATMENT ARM

- Arm A: 2x IPI3+NIVO1
- Arm B: 2x IPI1+NIVO3
- Arm C: 2x IPI3 - 2x NIVO3

<table>
<thead>
<tr>
<th>Arm</th>
<th>pRR</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>80%</td>
<td>30</td>
</tr>
<tr>
<td>B</td>
<td>77%</td>
<td>29</td>
</tr>
<tr>
<td>C</td>
<td>65%</td>
<td>24</td>
</tr>
</tbody>
</table>

Relapse-free survival (%)

0 25 50 75 100
0 6 12 18 24
0 90%
65% 77% 80%

18 MONTHS RELAPSE FREE SURVIVAL ACCORDING TO PATHOLOGIC RESPONSE

*One patient who achieved a pCR had died due to complications of an immune-related encephalitis without signs of melanoma relapse.
**PD-L1 EXPRESSION IS NO MARKER IN NEOADJUVANT IMMUNOTHERAPY**

<table>
<thead>
<tr>
<th>Pathologic response rate (95% CI)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>86</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>37</td>
</tr>
<tr>
<td>male</td>
<td>49</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>52</td>
</tr>
<tr>
<td>&gt;60</td>
<td>34</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
<td></td>
</tr>
<tr>
<td>T1–T2</td>
<td>38</td>
</tr>
<tr>
<td>T3–T4</td>
<td>24</td>
</tr>
<tr>
<td>Tx</td>
<td>24</td>
</tr>
<tr>
<td><strong>Ulceration</strong></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>39</td>
</tr>
<tr>
<td>yes</td>
<td>21</td>
</tr>
<tr>
<td><strong>Sum of target lesions</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 24</td>
<td>45</td>
</tr>
<tr>
<td>&gt;24</td>
<td>41</td>
</tr>
<tr>
<td><strong>Number of target lesions</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td><strong>PD-L1</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>41</td>
</tr>
<tr>
<td>≥1%</td>
<td>26</td>
</tr>
<tr>
<td>Unknown</td>
<td>19</td>
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</table>
INTERFERON-GAMMA SIGNATURE AND TUMOR MUTATIONAL BURDEN IDENTIFY RESPONDERS

1. Reprinted by permission from Springer Nature: Nature Medicine, Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma, Blank CU, et al. Copyright 2018
LOW BACTERIAL ALPHA DIVERSITY…
...Is associated with severe irAEs upon neoadjuvant immunotherapy

...Is associated with poor anti-melanoma responses upon neoadjuvant immunotherapy

Courtesy of Dr Batten M, et al. AACR 2019 Abstract 2822
Next goal: Confirm high path RR of IPI+NIVO combination scheme

Side goal: Challenge CLND, address a consolidation approach for non-responders – let neoadjuvant IT become the immunotherapeutic knife (PRADO trial)
PRADO

Expansion cohort OpACIN-neo: Personalised Response-driven Adjuvant Combination of Ipilimumab and Nivolumab in stage IIIB/C melanoma -

Stage IIIB/C de novo or recurrent melanoma RECIST 1.1 measurable (≥ 1.5 cm short diameter) PA proven

2 courses Ipilimumab 1mg/kg + Nivolumab 3mg/kg q3wks

Resection of marked lymph node

pCR or pathological near CR (0-10% vital tumor cells)

Follow-up CT q12w

FU*

no CLND

Follow-up CT q12w

FU*

pPR (10-50% vital tumor cells)

CLND

Follow-up CT q12w

FU*

no pathological response (pNR) (> 50% vital tumor cells)

CLND = Complete lymph node dissection

NIVO 52wks q4wk* + start adjuvant RT†

CT q12w

FU*

* According to institutes standard
† BRAF+MEK inhibition in BRAF V600E/K patient is allowed according to patient’s and treating physician’s decision when available.

PET/CT
CT neck thorax abdomen
MRI brain
PBMC tumor biopsy lab
feaces collection lab
Lymph node marker placement

0 6 12 64

Courtesy of Prof CU Blank
MEMALOC SUB STUDY OF OPACIN-NEO

How representative is the pathologic response in the largest lymph node for the whole lymph node bed?

Schermers B, et al. Br J Surg 2019;106(5):519-522. Available under the terms of the Creative Commons Attribution Non-Commercial License CC BY-NC. Available at https://creativecommons.org/licenses/by-nc/4.0/legalcode
THE PATHOLOGIC RESPONSE IN THE LARGEST LYMPH NODE IS REPRESENTING THE WHOLE LYMPH NODE BED

Overall results

<table>
<thead>
<tr>
<th></th>
<th>No. of patients* (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seed in situ (days)†</td>
<td>23 (21-27)</td>
</tr>
<tr>
<td>Skin to seed distance on ultrasound imaging (mm)†</td>
<td>10 (5-15)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Transcutaneous detection</td>
<td>12</td>
</tr>
<tr>
<td>Retrieval rate</td>
<td>12</td>
</tr>
<tr>
<td>System Usability Scale score†</td>
<td>98 (90-100)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Total node count per patient†</td>
<td>24 (16-34)</td>
</tr>
<tr>
<td>Node count with evidence of viable or treated tumour†</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>Index node</td>
<td></td>
</tr>
<tr>
<td>pCR</td>
<td>7</td>
</tr>
<tr>
<td>Near-pCR</td>
<td>3</td>
</tr>
<tr>
<td>pPR</td>
<td>1</td>
</tr>
<tr>
<td>pNR</td>
<td>1</td>
</tr>
<tr>
<td>Total basin</td>
<td></td>
</tr>
<tr>
<td>pCR</td>
<td>7</td>
</tr>
<tr>
<td>Near-pCR</td>
<td>3</td>
</tr>
<tr>
<td>pPR</td>
<td>1</td>
</tr>
<tr>
<td>pNR</td>
<td>1</td>
</tr>
<tr>
<td>Index node congruent with total basin</td>
<td>12</td>
</tr>
</tbody>
</table>

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MR. G, 66 YEARS

Melanoma of unknown primary, Lymph node metastases neck both side

Standard care would be: lymph node dissection on both side (+ possible RT)
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Patient was included in PRADO study neoadjuvant immunotherapy with ipilimumab + nivolumab
MR. G, 66 YEARS

Melanoma of unknown primary, Lymph node metastases neck both side

Standard care would be: lymph node dissection on both side (+ possible RT)

Patient was included in PRADO study neoadjuvant immunotherapy with ipilimumab + nivolumab

PA LN left: only fibrosis, 0% vital tumor -> pCR index LN
Next goal: **Identify** alternative **neoadjuvant combination schemes for** biomarker-unfavourable patients
Addition of HDACi to PD-1 blockade restores responsiveness to checkpoint inhibitor therapy

PERSONALISED COMBINATION THERAPY OF SINGLE OR DOUBLET CHECKPOINT PLUS HDAC INHIBITION

allocated according to IFN-gamma signature (no intermediate patients)

stage III macroscopic de-novo or recurrent melanoma

RECIST measurable (≥1.5cm short diameter)

stratified for PD-L1 expression

IFN-gamma signature, if high or low:
CT neck, thorax, abdomen
PET/CT or MRI brain

Week: -4

0

3

6

12

64

IFN-gamma signature

PET/CT or MRI brain

10 pat

2 x NIVO 240 mg q3W

Domatino 200mg QD, d1-14, q3W
+ 2 x NIVO 240 mg q3W

Domatino 200mg QD, d1-14, q3W
+ 2 x NIVO 240 mg q3W

Domatino 200mg QD, d1-14, q3W
+ 2 x NIVO 240 mg , q3W
+ 2 x IPI 80 mg q3W

10 pat

10 pat

10 pat

TLND = Total Lymph node dissection

52wks NIVO 480mg q4wk*
PET/CT or CT**

2 years FU**

* adjuvant dabrafenib + trametinib in BRAF V600E/K patients is allowed in pathologic non-responders according to the patient’s and treating physician’s decision

** according to the institute’s standard, preferably q3mo

= standard of care

 Courtesy of Prof C. Blank
THE FUTURE OF CANCER THERAPIES:
PERSONALISED IMMUNOTHERAPY

Stage III melanoma/malignancy
NanoString signature analysis
DSP
personalized neo-adjuvant therapy

BRAFi+MEKi + aPD-1 +/- aCTLA-4
Ipilimumab 80mg + NIVO 240 mg q3wk
NKTR-214 + NIVO +/- IPI
Relatlimab + NIVO +/- IPI
STING agonist NIVO +/- IPI
T-VEC + NIVO
HDACi + NIVO +/- IPI

In case of relapse (< vs > 6mo post surgery)
Re-signature analysis + pRR data from neo-adjuvant treatment

NKTR + NIVO +/- IPI
PERSONALISED IMMUNOTHERAPY – STAGE III TREATMENT DECISION

Stage III melanoma/malignancy
NanoString signature analysis
DSP
personalized neo-adjuvant therapy

Stage III

- BRAFi+MEKi + aPD-1 +/- aCTLA-4
- Ipilimumab 80mg + NIVO 240 mg q3wk
- NKTR-214 + NIVO +/- IPI
- Relatlimab + NIVO +/- IPI
- STING agonist NIVO +/- IPI
- T-VEC + NIVO
- HDACi + NIVO +/- IPI

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PERSONALISED IMMUNOTHERAPY – LATE RELAPSE, SAME SIGNATURE

Stage III melanoma/malignancy
NanoString signature analysis
DSP
personalized neo-adjuvant therapy

Stage III

- BRAFi+MEKi + aPD-1 +/- aCTLA-4
- Ipilimumab 80mg + NIVO 240 mg q3wk
- NKTR-214 + NIVO +/- IPI
- Relatlimab + NIVO +/- IPI
- STING agonist NIVO +/- IPI
- T-VEC + NIVO
- HDACi + NIVO +/- IPI

In case of relapse (< vs > 6mo post surgery)
Re-signature analysis + pRR data from neo-adjuvant treatment

Stage IV

- NKTR + NIVO +/- IPI
PERSONALISED IMMUNOTHERAPY – EARLY RELAPSE, ALTERED SIGNATURE

Stage III melanoma/malignancy
NanoString signature analysis
DSP
personalized neo-adjuvant therapy

Stage III

- BRAFi+MEKi + aPD-1 +/- aCTLA-4
- Ipilimumab 80mg + NIVO 240 mg q3wk
- NKTR-214 + NIVO +/- IPI
- Relatlimab + NIVO +/- IPI
- STING agonist NIVO +/- IPI
- T-VEC + NIVO
- HDACi + NIVO +/- IPI

In case of relapse (< vs > 6mo post surgery)
Re-signature analysis + pRR data from neo-adjuvant treatment

Stage IV

- HDACi + NIVO +/- IPI

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THE INTERNATIONAL NEOADJUVANT MELANOMA CONSORTIUM (INMC)

Initiated by MIA, MDA, and NKI: www.melanoma-inc.org

International Neoadjuvant Melanoma Consortium

Advancing treatment for patients with melanoma by facilitating collaborations in neoadjuvant clinical and translational research.

Our Mission

The International Neoadjuvant Melanoma Consortium (INMC) was established in order to bring together key stakeholders across multiple disciplines including medical oncology, surgical oncology, pathology, radiology, and translational research from institutions around the world with the goal of creating an organized approach into the investigation of neoadjuvant treatment in melanoma.

Through this mechanism and with a comprehensive approach to maximizing collaborative opportunities amongst investigators and institutions, the INMC seeks to advance treatment for patients with melanoma.
NEOADJUVANT TRIALS AT THE NKI BEYOND MELANOMA

**Bladder**
NABUCCO
M. vd Heijden

**CRC**
NICHE
M. Chalabi

**H&N**
IMCISION
L. Zuur

**Breast**
BELLINI
M. Kok

**Lung**
W. Theelen
J. de Langen

**RCC**
NEOAVAX
H.v. Thienen.

**RCC**
A. Bex.

**MC, RCC**
J. Haanen
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Patients and their families

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Sylvia ter Meulen
Annemiek Koenen

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Regina von Furstenberg
Lindsay Grijpink
Gabry van Netten
Sandra Visser
Steven Vanhoutvin
Harm van Tinteren
Karolina Sikorska

Department of Pathology
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CFMPB
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Hussein Tawbi

Collaborators OpACIN-Neo trial
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Johan Hanison
James Larkin

Nanostring
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BMS
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Constance Pfeifer
Andrew Evans

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THANK YOU!