Neoadjuvant Melanoma Trials
Data Collection and Endpoint Selection

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Disclosures

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• Stockownership: Uniti Cars, Neon Therapeutics, Forty Seven
International Neoadjuvant Melanoma Consortium

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

Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

The outcome of high risk stage III melanoma patients is poor

After surgery +/- RT the 5 year OS is only 30-60% 1-3

The EFS outcome of high risk stage III melanoma patients is poor

- Adjuvant therapy improved the RFS, but EFS remains poor $^{4,5}$

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Adapted from Menzies et al ASCO 2019
Neoadjuvant versus adjuvant checkpoint inhibition (IPI+NIVO) in macroscopic stage III melanoma – OpACIN

designed by TN Schumacher and CU Blank in 2014
What did we learn from OpACIN?

Neoadjuvant IPI + NIVO:
- Did not delay surgery
- Was superior compared to adjuvant therapy in expanding tumor-resident TCR clones
- The pathologic response rate was high (78%)
- None of the patients with pathologic response have relapsed
- Highly toxic with 90% grade III/IV adverse events

Blank et al., Nat Med, 2018; Blank et al., ESMO 2019
Multicenter Phase 2 Study to Identify the Optimal neo-Adjuvant Combination Scheme of Ipilimumab and Nivolumab – OpACIN-neo

- **Arm A**: 2x IPI 3mg/kg + NIVO 1mg/kg q3wk
- **Arm B**: 2x IPI 1mg/kg + NIVO 3mg/kg q3wk
- **Arm C**: 2x IPI 3mg/kg q3wk + 2x NIVO 3mg/kg q2wk

**Grade 3-4 toxicity**
- **Arm A**: 40%
- **Arm B**: 20%
- **Arm C**: 50%

**Pathologic Response**
- **Arm A**: 80%
- **Arm B**: 77%
- **Arm C**: 65%

18-months Relapse-free survival – **OpACIN-neo**

According to treatment arm

<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>

According to pathologic response

<table>
<thead>
<tr>
<th>Pathologic response</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>64</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
</tr>
</tbody>
</table>

*pRR = pathologic response rate

Pathologic response (pCR, near-pCR, pPR)

No pathologic response

* patient died due to toxicity without signs of melanoma relapse

Pathologic response correlates with outcome!
INMC pooled analysis

• Pooled data from 6 modern NST clinical trials conducted across the INMC.

• Pts with RECIST measurable, surgically resectable, clinical stage III melanoma with nodal metastases who underwent surgery were included.

• Baseline disease characteristics, treatment regimen, pathologic response and RFS were examined.

Adapted from Menzies et al. Presented at ASCO 2019
Personalized Response-driven Adjuvant therapy after Combination of neoadjuvant Ipilimumab and Nivolumab in stage IIIB/C melanoma - PRADO

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

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

Pathological pCR or near CR (0-10% vital tumor cells) → Follow-up CT + ultrasound q12w

Resection of marked lymph node

pPR (10-50% vital tumor cells) → CLND

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

NIVO 52wks q4wk# + start adjuvant RT† CT q12w

Follow-up CT q12w

FU*

FU*

FU*

PET/CT
CT neck thorax abdomen
MRI brain
Lab + PBMC
Feces collection
Tumor biopsy
Lymph node marker placement

CLND = Complete Lymph node dissection

Excision marked lymph node
CT
Lab + PBMC
Feces collection

FT 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
† Adjuvant radiotherapy according to patient's and physician's decision

+ start adjuvant RT† CT q12w

NIVO 52wks q4wk#
The pathologic response in the largest lymph node is representing the whole lymph node bed

*(MeMaLoc substudy of OpACIN-neo)*

### Table 1 Overall results

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patients(^*) (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seed in situ (days)</strong>(^\dagger)</td>
<td>23 (21–27)</td>
</tr>
<tr>
<td><strong>Skin to seed distance on ultrasound imaging (mm)</strong>(^\dagger)</td>
<td>10 (5–15)</td>
</tr>
<tr>
<td><strong>Surgery</strong></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(^\dagger)</td>
<td>98 (90–100)</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td></td>
</tr>
<tr>
<td>Total node count per patient(^\dagger)</td>
<td>24 (16–34)</td>
</tr>
<tr>
<td>Node count with evidence of viable or treated tumour(^\dagger)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td><strong>Response</strong></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>

\(^*\)Schermers et al., BJS 2019
What have we learned from **PRADO** so far?

- IPI1+NIVO3 scheme is again well tolerated
- Pre-treatment application of marker in index LN is feasible
- Fast pathologic evaluation of marked LN is feasible
- Timing of **CLND** within 3 weeks post marked LN resection and start adjuvant therapy (if needed) at week 12 is feasible (NKI & MIA experience)
- Parallel RT to NIVO or DAB+TRAM is feasible
RFS is not advisable in neoadjuvant randomized trials: T-VEC neoadjuvant versus upfront surgery

Arm 1 (T-VEC + Surgery, N = 76): 29.5%
Arm 2 (Surgery Alone, N = 74): 16.5%
Median Follow-up = 31.2 months
Overall $P = 0.070$
Overall HR (80% CI) = 0.75 (0.58, 0.96)

ITT Analysis Set: 150 patients enrolled and randomized
Remaining questions for a phase 3 trial

- Response-driven scheme? Adjuvant versus only FU in MPR patients?
- Primary endpoint EFS?
- Event also non-melanoma death? Elderly populations!
- Index LN approach versus TLND?
- Stratify for BRAF status? How fast BRAF status available
- Stratify continents?

Stage IIIIB/C de novo or recurrent melanoma RECISt 1.1. measurable (≥ 1.5cm short diameter), PA proven

6 weeks neo-adjuvant PD-1 + CTLA-4 blockade

- Pathological pCR or near CR (0-10% vital tumor cells)
- no pathological response (pNR) (> 50% vital tumor cells)

- Resection of marked lymph node
- no CLND
- CLND

- Pathological pCR or near CR
- no CLND

- Follow-up CT + ultrasound q12w
- Follow-up CT q12w

- FU*
- FU*

- Standard adjuvant therapy start no later than w12

- TLND§,#

- Adjuvant PD-1 blockade or BRAF + MEK inhibition

- FU*
Remaining questions for a phase 3 trial

- Timing of CLND within 3 weeks post marked LN resection feasible?
- Start adjuvant therapy (if needed) at week 12 broadly feasible?
- Pathology fast enough? pRR or MPR as surrogate markers?
- Adjuvant RT parallel NIVO or DAB+TRAM in NR patients?
- How to deal with change to other adjuvant therapy in non-MPR which will be reality?
Patients and their families

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