Patient Selection and Risk: Benefit Considerations: An Oncologist’s Perspective

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#MelanomaNeoadjuvant
Disclosures

**Consultant:** Amgen, Array, Astra Zeneca, Aveo, Boehringer-Ingelheim, BMS, Exelixis, Eisai, Ideera, ImmunoCore, Iovance, Merck, Newlink, Novartis, Genentech/Roche, Pfizer

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Topics To Cover

• Type of Trials
• Potential Benefits/Risks of Neoadjuvant Therapy
• Eligibility Criteria for Trials
• Patients Examples
• Future Considerations for such patients
  • Upfront systemic therapy with imaging endpoints and surgical salvage
Types of Neoadjuvant Trials

• Single arm or randomized trials where all get neoadjuvant therapy; surgery at a specified time (3-9 weeks)- RR (path CR), RFS, safety, biomarkers are major endpoints

• Randomized trials where patients get same therapy in either the neoadjuvant or adjuvant setting - RFS, OS, and safety are principal endpoints

• Eligibility criteria might be different for these distinct trials
Potential Benefits of Neoadjuvant Treatment

• Tumor shrinkage $\rightarrow$ decreased surgical morbidity
  • Potentially decreased need for surgery
• Destruction of micrometastases $\rightarrow$ prevention of distant disease spread
  • May be superior to adjuvant treatment (S1801 Trial)
• Objective measure of response to therapy $\rightarrow$ personalization of subsequent adjuvant therapy
• Opportunity to collect high-quality serial biospecimens to facilitate understanding of drug response and resistance; identify surrogate markers
• Potential pathway for new drug evaluation/registration
  • Expedite, rationalize combination drug regimen development
  • Ability to study intralesional therapies
Preclinical Data Suggest Neoadjuvant Checkpoint Inhibition Is Superior to Adjuvant Checkpoint Inhibition
S1801 Schema

Stage III (N1b or higher) Melanoma

N=556

1:1 randomization

Arm A (control)

Surgery

Adjuvant pembrolizumab, 200/kg x 18 cycles

Arm B (experimental)

Neo Adjuvant pembrolizumab, 200/kg x 3 cycles

Surgery

Adjuvant pembrolizumab, 200/kg x 15 cycles

PI: Sapna Patel, MDACC
THE IMMUNED STUDY- STAGE IV NED
RFS in all patients

Schadendorf et al  ESMO 2019

Data cut-off date July 2nd, 2019
Median follow-up time: 28.4 months (n=167)

<table>
<thead>
<tr>
<th></th>
<th>NIVO (n=59)</th>
<th>NIVO+IPI (n=56)</th>
<th>Placebo (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RFS, mo (95% CI)</td>
<td>12.4 (5.30, 33.26)</td>
<td>NR(^1)</td>
<td>6.4 (3.26, 9.61)</td>
</tr>
<tr>
<td>HR (95% CI) vs placebo</td>
<td>0.56 (0.36, 0.88)</td>
<td>0.23 (0.13, 0.41)</td>
<td>-</td>
</tr>
<tr>
<td>HR (95% CI) vs NIVO</td>
<td>-</td>
<td>0.40 (0.22, 0.73)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\) NR: not reached
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INMC Pooled Analysis of Neoadjuvant Trials: RFS by pathological response and drug

**Immunotherapy**

- pCR: 100%
- non-pCR: 72%

Log-rank p < 0.0001

Numbers at risk: 51 42 34 25 20 15 10 9 9 6 2 1

Med f/u 10 mo

**Targeted Therapy**

- pCR: 88%
- non-pCR: 43%

Log-rank p < 0.0001

Numbers at risk: 24 23 22 20 20 19 16 12 10 9 7 6

Med f/u 22 mo

1 pt died from toxicity without recurrence, censored at time of death

Menezes Et al ASCO 2019
Potential Benefits of Neoadjuvant Treatment

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Potential Risks of Neoadjuvant Therapy: Factors favoring Adjuvant Therapy

• Possible loss of some standard prognostic factors: LN #, tumor volume, etc
• Treatment toxicity may limit ability to undergo surgery at scheduled time (may be more than in Stage IV disease)
• Disease growth might make surgery more complicated/impossible
• Disease might spread to distant sites during delay in surgical therapy
### OpACIN-Neo: irAEs in First 12 Weeks

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Nivo 1 mg/kg + Ipi 3 mg/kg (n=30)</th>
<th>Nivo 3 mg/kg + Ipi 1 mg/kg (n=30)</th>
<th>Ipi 3 mg/kg then Nivo 3 mg/kg (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3-4</td>
<td>All grades</td>
</tr>
<tr>
<td>Any</td>
<td>29 (97)</td>
<td>12 (40)</td>
<td>29 (97)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (63)</td>
<td>17 (57)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (60)</td>
<td>2 (7)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (40)</td>
<td>10 (33)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>12 (40)</td>
<td>6 (20)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12 (40)</td>
<td>2 (7)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (23)</td>
<td>4 (13)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (27)</td>
<td>1 (3)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (13)</td>
<td>4 (13)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6 (20)</td>
<td>1 (3)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Colitis</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (17)</td>
<td>2 (7)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (13)</td>
<td>1 (3)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>1 (3)</td>
<td>4 (13)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>5 (17)</td>
<td>2 (8)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Serum amylase increased</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

AEs that occurred in ≥ 10% of patients.
OpACIN-Neo: Pathologic Responses

Pathologic Response

- pCR
- pPR
- near pCR
- pNR

Pathologic Response: Central Review

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Nivo 1 mg/kg + Ipi 3 mg/kg (n = 30)</th>
<th>Nivo 3 mg/kg + Ipi 1 mg/kg (n = 30)</th>
<th>Ipi 3 mg/kg Then Nivo 3 mg/kg (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</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>NE</td>
<td>-</td>
<td>-</td>
<td>1 (4)*</td>
</tr>
</tbody>
</table>

* n = 1, only palliative resection of largest lymph node. †Surgery not performed due to toxicity; patient had a radiologic CR.
Eligibility for Neoadjuvant Trials

- Palpable or radiographically detectable (RECIST measurable) disease (Stage IIIB-Stage IV)
  - Biopsy proven
  - Surgically “resectable” with acceptable morbidity (Stage III incl. in transits, some Stage IV)
  - Medically resectable – pace of disease
    - Normal range LDH
    - “Stable stage”
    - No co-morbidities relevant to surgery, ECOG PS < 2
- No other metastatic sites
- No prior relevant systemic therapies
- Eligible for specific systemic therapies
  - No h/o autoimmune conditions, requirement for immunosuppressive drugs, etc
  - A targetable mutation (if a targeted therapy trial); no CHF, other cancers, etc
- Compliant- willing to follow protocol
Ideal Patient for Neoadjuvant Clinical Trial

• 39-year-old woman with history of T2aN0M0 melanoma of the right upper arm (excised 5/2009)

• Current presentation:
  • Palpated a right axillary mass 5/2016
  • Imaging showed solitary right axillary node
  • Core biopsy revealed melanoma that is BRAF, NRAS, KIT wild type

Slides courtesy of Rodabe Amaria, MD
MD Anderson Cancer Center
Ideal Patient for NeoAdjuvant Clinical Trial

- Patient entered neoadjuvant combination immunotherapy clinical trial
- Randomized to nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for up to 3 doses
- Able to receive all planned neoadjuvant doses
  - Grade 1 diarrhea, grade 2 fevers, grade 2 fatigue
- Scans prior to surgery showed PR (45% reduction); pathology review at surgery shows pCR
- Remains without evidence of disease 31 months after surgery

- 39-year-old woman with history of excised T2aN0M0 melanoma of the right upper arm
- Current presentation: solitary right axillary node mass; core biopsy revealed melanoma that is BRAF, NRAS, KIT wild type
Not Ideal Patient for Some Neoadjuvant Clinical Trials

- 52 yo woman presented 7/2018 with a raised, nodular, bleeding lesion on her left thigh that had been present for over a year
  - Shave bx- at least 1.4 mm thick melanoma transected at base with ulceration and MR of 17/mm2
  - Excisional bx showed 5.35 mm thick lesion with negative margins.
  - PET-CT showed no foci of distant disease

- 2 months later- Underwent WLE and SLN biopsy at MSKCC.
  - Pathology showed 0.5 mm satellite in SQ tissue and 0/2 SLNs involved.
  - Tumor is BRAF V600E and NRASQ61R negative

- 1 month later- presents to MGUH for discussion of subsequent therapy:
  - Adjuvant IO recommended

- 2 months later- presents to begin adjuvant therapy
  - LDH elevated – (278)
  - Imaging shows large PET+ pelvic mass; No other active disease
CT Scan - baseline

Left external iliac node
Not Ideal Candidate for Some Neoadjuvant Trials (cont)

- Patient case was discussed at Multidisciplinary Conference
  - Concern raised about extent of surgery; pace of disease
  - Upfront treatment with nivo/ipi
- She began nivo 3 mg/kg + ipi 1 mg/kg IV q 3 weeks.
- She presented after dose 2 (4 weeks) with acute onset cough and dyspnea (O2 sat 92%)
- Diagnosed with bronchospasm- received HD steroids with improvement in breathing; IO therapy held
- Taper required 8 weeks because recurrent symptoms
- Repeat CT scan at 6 weeks showed major tumor shrinkage.
- Repeat scan at 12 weeks showed additional shrinkage Metabolic-CR
Pet-CT Scan findings

What is the value of subjecting this patient to surgery?
KEYNOTE-006: PFS With Pembrolizumab in Patients Who Completed Protocol

- Randomized, open-label phase III trial of pembrolizumab (Q2W or Q3W) vs ipilimumab for patients with unresectable stage III/IV melanoma (N = 834); current analysis assessed population of patients who completed protocol-specified 2 yrs of pembrolizumab (n = 103)

![Graph showing PFS (%)](Long. ASCO 2018. Abstr 9503.)
Imaging Biomarkers and Response Durability Predictions

- Prospective single center cohort of patients with metastatic melanoma treated with PD-1–based therapy who underwent baseline and 1-yr PET (N = 118)

PFS After 1 Yr by CT Response

- Median NR in both groups
- HR 0.18 (95% CI 0.06-0.56; \(P = .06\))

CR (n = 29)

PR/SD (n = 75)

PFS After 1 Yr by PET/CT Response in Patients With CT-Based PR

- Median NR vs 12.8 mos
- HR: 0.07 (95% CI: 0.02-0.27; \(P < .01\))

PR + CMR (n = 47)

PR + non-CMR (n = 22)

Many “remission” patients do not reach CR by CT scan

CMR by PET likely better at predicting long-term PFS than CT in patients with PR

CMR by PET might guide treatment discontinuation—needs prospective validation

MedStar Georgetown Approach: Create TFS

- Patient example: PET/CT scan with near CR except for residual hypermetabolic disease site negative on excisional biopsy

MedStar Georgetown Approach in Stage IV: Create TFS

- Single institution review of patients with advanced melanoma treated with PD-1–based therapy (pembrolizumab or nivolumab monotherapy or combination therapy with ipilimumab) (N = 96)

Off Treatment Survival Following Tx D/c by Reason

OS for Patients With Tx D/c for Patient/Provider Decision (n = 20)*

*1 PD, 1 death (nonmelanoma related).

Take Home Messages

- Neoadjuvant therapy is currently a research tool in melanoma
  - Useful for understanding biology and potentially expediting drug development
  - Its clinical utility over adjuvant therapy remains to be determined
  - Toxicities might interfere with proposed surgery
  - Risk/benefits need to be discussed with all patients
  - pCR may be more important for immunotherapy/than tumor targeted therapy

- Upfront therapy with surgical salvage is an future alternative
  - Current immunotherapies create sufficient durable responses to make this an option for patients with stage IV or difficult to resect stage III melanoma
    - Improvement in imaging, blood based biomarkers may ultimately guide salvage surgery decision
  - Targeted therapies for patients with BRAF mutant melanoma are reliably effective in making surgery easier; impact on other efficacy outcomes uncertain