Patient Selection and Risk: Benefit Considerations:
A Surgeon’s Perspective

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#MelanomaNeoadjuvant
Disclosures

- Stock Ownership: Pfizer (spouse)
What are the surgical *risks* with neoadjuvant therapy?

1) Will patients lose opportunity to undergo surgery?
   a) Does drug inhibit wound healing?
   b) Side effect which delays surgery
   c) Progression of disease

2) Neoadjuvant treatment change surgical approach?
   a) Major tumor shrinkage- less morbid surgery
   b) Adhesions/fibrosis- increased morbidity

3) Do patients with all patients with radiologic response need surgery?
Comparison of patients received neoadjuvant TKI- surgery versus Surgery

Stopped medicines two weeks prior to surgery
Intraop/postop complications similar
Increased adhesions in neoadjuvant group
Neoadjuvant targeted therapy melanoma

Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial

Drug stopped 48 hours prior to surgery
Restarted within a week
Surgical complications similar
12 patients urothelial bladder cancer
- 6 Ipilimumab 3mg/kg
- 6 Ipilimumab 10mg/kg
4 week after last dose - surgical resection

No severe complications related to therapy
- 1) wound dehiscence/fistula
- 2) UTI x 5
### Table 1. Clinical characteristics of patients with localized urothelial carcinoma who received anti-CTLA-4

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Prior therapy</th>
<th>Adjuvant therapy</th>
<th>Drug-related irAEs</th>
<th>Surgery delay (wk)</th>
<th>Follow-up (mo)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>66</td>
<td>BCG</td>
<td>None</td>
<td>Rash, Gr 1;</td>
<td>None</td>
<td>33.37</td>
<td>NED Alive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea, Gr 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>75</td>
<td>None</td>
<td>Cis, Gem, Ifos chemo</td>
<td>None</td>
<td>5.1 (due to cardiac eval)</td>
<td>32.67</td>
<td>NED Alive</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>71</td>
<td>BCG</td>
<td>None</td>
<td>Amylase and lipase increased, Gr 2;</td>
<td>None</td>
<td>25.83</td>
<td>NED Alive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uveitis, Gr 2;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diarrhea, Gr 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>60</td>
<td>None</td>
<td>MVAC chemo</td>
<td>Rash, Gr 1</td>
<td>None</td>
<td>27.3</td>
<td>NED Alive</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>55</td>
<td>None</td>
<td>None</td>
<td>Rash, Gr 1; Pruritis, Gr 1</td>
<td>None</td>
<td>24.9</td>
<td>NED Alive</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>75</td>
<td>BCG</td>
<td>None</td>
<td>Rash, Gr 2; Pruritis, Gr 2</td>
<td>None</td>
<td>23.1</td>
<td>NED Alive</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>76</td>
<td>None</td>
<td>None</td>
<td>Rash, Gr 1</td>
<td>None</td>
<td>7.7</td>
<td>NED Deceased</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>69</td>
<td>None</td>
<td>None</td>
<td>Testicular swelling/EPididymitis, Gr 2</td>
<td>4.0 (due to irAE)</td>
<td>17.5</td>
<td>NED Alive</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>63</td>
<td>None</td>
<td>None</td>
<td>Transaminitis, Gr 3; Diarrhea, Gr 2</td>
<td>None</td>
<td>17.03</td>
<td>NED Alive</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>68</td>
<td>None</td>
<td>None</td>
<td>Diarrhea, Gr 3 (received only one dose of antibody)</td>
<td>None</td>
<td>12.23</td>
<td>NED Alive</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>71</td>
<td>BCG</td>
<td>Ifos-Adria-Gem chemo</td>
<td>Rash, Gr 1; Pruritis, Gr 1; Elevated AST, Gr 1; Diarrhea, Gr 3</td>
<td>N/A*</td>
<td>9.27</td>
<td>Metastatic disease Alive</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>66</td>
<td>None</td>
<td>Gem-Cis chemo</td>
<td>Diarrhea, Gr 2</td>
<td>None</td>
<td>8.33</td>
<td>Metastatic disease Alive</td>
</tr>
</tbody>
</table>
Safety surgery and Immunotherapy: Melanoma

Retrospective look at patients operated on after Immunotherapy (n=23)

Surgery performed median 25 days after last dose
earliest 1 week after dose
included bowel resections

No grade 3-5 complications

2 doses of Ipilimumab 10 mg/kg (q 3 weeks)

Surgery 6-8 weeks

No reported toxicity

Increased CD8 cells at week 6

Lack of B cells correlated with poor outcome
Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study

Andrea Necchi, Andrea Anichini, Daniele Raggi, Alberto Briganti, Simona Massa, Roberta Luciani, Maurizio Colechia, Patrizia Giammatteo, Roberta Mortarini, Marco Bianchi, Elena Faré, Francesco Monopoli, Renzo Colombo, Andrea Gallina, Andrea Salonia, Antonella Messina, Sinaj M. Ali, Russell Madison, Jeffrey S. Ross, Jon H. Chung, Roberto Salvioni, Luigi Mariani, and Francesco Montorsi

50 patients, cT3, cT2, or cT2-3N1
3 doses of anti-PD1
All patients made it to surgery

42% pT0
# Neoadjuvant Immunotherapy: Lung

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Treatment</th>
<th>STAGE (n)</th>
<th>Surgical Resection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forde et al NEJM 2018</td>
<td>PD1 x 2</td>
<td>I- IIIa (n=21)</td>
<td>95%</td>
</tr>
<tr>
<td>Shu et al ASCO 2018</td>
<td>PDL1 + chemo</td>
<td>IB-IIIa (n=14)</td>
<td>78%</td>
</tr>
<tr>
<td>Neostar ASCO 2019</td>
<td>Nivo</td>
<td>I-IIIa (n=44)</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>IPI Nivo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCM3 ASCO 2019</td>
<td>PDL1</td>
<td>IIIa-b (*mostly) (n=101)</td>
<td>89%</td>
</tr>
</tbody>
</table>
50% of all minimally invasive approaches converted because of fibrosis/inflammation

Bott et al, J Thorac Cardiovasc Surg. 2019
Will patients loose opportunity to undergo surgery?

**Targeted Therapy**
- Good Selection: Limited to patients with known mutation, BRAF V600E/K (melanoma)
- Most responses rapid

**Immune Therapy**
- No selection criteria? PDL1
- Responses can be rapid or slow with pseudoprogression
- Toxicity can be long lasting and interfere with surgery
25 year old with unknown primary and biopsy proven melanoma in axilla
Imaging without evidence of distant disease
On pain meds for terrible neuropathic pain in axilla
BRAF V600E mutation
s/p 6 months of BRAF, followed by surgical resection
Rapid Responses CTLA-4/PD1

s/p one dose (3 weeks)

s/p one dose (6 weeks)

Chapman et al, NEJM, 2015
Neoadjuvant/Adjuvant Checkpoint Blockade: Melanoma

MDACC: Stage IIIB and IIIC and oligometastatic Stage IV

Nivolumab x 4 doses → SURGERY → Adjuvant Nivolumab
Ipilimumab AND Nivolumab x 3 doses → Adjuvant Nivolumab

Amaria, Wargo et al Nature Medicine 2018
Neoadjuvant/Adjuvant Checkpoint Blockade: Melanoma

MDACC: Stage IIIB and IIIC and oligometastatic Stage IV

- Nivolumab x 4 doses
- Ipilimumab AND Nivolumab x 3 doses
- SURGERY
- Adjuvant Nivolumab

Amaria, Wargo et al Nature Medicine 2018
Neoadjuvant Checkpoint Blockade Melanoma: Failure to get to surgery with anti-PD1

2/11 patient progressed and surgery not performed

Amaria, Wargo et al Nature Medicine 2018
74 yo female s/p resection of 8mm buttock(skin) melanoma and 2 positive nodes from superficial groin
relapsed metastatic melanoma pelvic lymph nodes 3 months later

Treated with anti-PD1

Severe pneumonitis- ICU admission
home o2
several courses of steroids, relapse when steroid dose decreased
Balancing surgery and Immunotherapy Side Effects

pelvic nodes with metastatic melanoma

To get to surgery
SLOW prednisone taper and off home O2
Robotic- barotrauma
Open- wound healing
Rapid Responses CTLA-4/PD1

s/p one dose (3 weeks)

s/p one dose (6 weeks)

Does this patient need surgery?

Is there a correlation with radiologic CR and pCR?

Stage IV melanoma: Overall Survival

Larkin et al, NEJM 2019
Stage IV melanoma: Many patients progress after Immunotherapy

4 year follow-up of checkmate 067 study Stage III/IV melanoma

Progression Free Survival

Median PFS
IPI/NIVO 11.5 months
Nivo 6.9 months
Ipi 2.9 months

Hodi et al Lancet Oncology, 2018
Stage IV melanoma: Progression Free Survival

Larkin et al, NEJM 2019
## Treatment after Systemic Immunotherapy

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab Plus Ipilimumab (n=314)</th>
<th>Nivolumab (n=316)</th>
<th>Ipilimumab (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any subsequent therapy, n (%)</td>
<td>135 (43)</td>
<td>182 (58)</td>
<td>236 (75)</td>
</tr>
<tr>
<td>Subsequent systemic therapy</td>
<td>104 (33)</td>
<td>150 (48)</td>
<td>206 (65)</td>
</tr>
<tr>
<td>Subsequent immunotherapy</td>
<td>53 (17)</td>
<td>103 (33)</td>
<td>148 (47)</td>
</tr>
<tr>
<td>Anti-PD-1 agents</td>
<td>36 (12)</td>
<td>47 (15)</td>
<td>143 (45)</td>
</tr>
<tr>
<td>Anti-CTLA-4 agents</td>
<td>19 (6)</td>
<td>91 (29)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Other immunotherapy</td>
<td>7 (2)</td>
<td>12 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>BRAF inhibitor</td>
<td>42 (13)</td>
<td>60 (19)</td>
<td>72 (23)</td>
</tr>
<tr>
<td>MEK/NRAS inhibitor</td>
<td>32 (10)</td>
<td>43 (14)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>Other approved agents</td>
<td>45 (14)</td>
<td>63 (20)</td>
<td>75 (24)</td>
</tr>
<tr>
<td>Other investigational agent</td>
<td>8 (3)</td>
<td>9 (3)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Subsequent radiotherapy</td>
<td>61 (19)</td>
<td>92 (29)</td>
<td>123 (39)</td>
</tr>
<tr>
<td>Subsequent surgery</td>
<td>60 (19)</td>
<td>69 (22)</td>
<td>95 (30)</td>
</tr>
</tbody>
</table>

**Median time from randomisation to subsequent systemic therapy, months (95% CI)**

- **Nivolumab Plus Ipilimumab:** NR
- **Nivolumab:** 25.2 (16.0–43.2)
- **Ipilimumab:** 8.1 (6.5–8.7)

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Hodi et al *Lancet Oncology*, 2018
What is the outcome of patients (initially not resectable) selected for surgery after systemic immunotherapy?

ADJUVANT SURGERY
Neoadjuvant Therapy Prior to Surgery

**Targeted Therapy**

Good Selection: Limited to patients with known mutation, BRAF V600E/K (melanoma)

Most responses rapid

=Ideal group for neoadjuvant therapy
  select for patients most likely to respond
  short window for assessment
  most toxicities reversible quickly

GREAT CANDIDATES FOR NEOADJUVANT

**Immune Therapy**

Selection criteria? PDL1

Responses can be rapid or slow with psuedoprogression

Toxicity can be long lasting and interfere with surgery

BALANCE THE DELAY WITH NEED FOR SURGICAL PALLIATION
Conclusions

Surgery safe in combination with immunotherapy, targeted therapy

Neoadjuvant treatment

- High response rate
- Toxicity manageable - requires multi-disciplinary approach
- Loss of surgical window - what is acceptable amount?
- Do patients with radiologic CR need to have surgery?

Favorable outcomes in advanced patients undergoing surgery with response to immunotherapy consistent with favorable outcomes in neoadjuvant trials

Should surgery become the “Adjuvant?”

*LONG TERM OUTCOMES AND BIOMARKERS NEEDED*