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### Surgical Oncology for General Surgeon - Disclosures Reported

#### Speakers / Moderators / Discussants / Authors

| Name                                      | Affiliation                                                                 | Disclosures                                                                 |
|-------------------------------------------|-------------------------------------------------------------------------------|                                                                            |
| Flavio Rocha, MD, FACS, FSSO              | Oregon Health & Science University/Knight Cancer Institute                     | (moderator) Nothing to disclose                                             |
| Genevieve Boland, MD, PhD, FACS           | Nektar Therapeutics, Honorary from Novartis, Sponsored Research Agreement from Palleon Pharmaceuticals, Sponsored Research Agreement from Olink Proteomics Massachusetts General Hospital | (speaker) Scientific Advisory Board/Steering Committee at Nektar Therapeutics, Honorarium from Novartis, Sponsored Research Agreement from Palleon Pharmaceuticals, Sponsored Research Agreement from Olink Proteomics Massachusetts General Hospital |
| Sepideh Gholami, MD, FACS                 | UC Davis Health                                                               | (speaker) Nothing to disclose                                              |
| Arpana Naik, MD, FACS                     | Oregon Health & Science University                                            | (speaker) Nothing to disclose                                              |

#### Planning Committee / Editorial Committee

| Name                                      | Affiliation                                                                 | Disclosures                                                                 |
|-------------------------------------------|-------------------------------------------------------------------------------|                                                                            |
| Judy Boughey, MD, FACS                    | Mayo Clinic                                                                  | Research funding support for clinical trial from Eli Lilly                 |
| Christina Roland, MD, FACS                | MD Anderson Cancer Center                                                     | Research funds to institution from Bristol Myers Squibb                    |
| Asa Carter, MBA, CTR                      | American College of Surgeons                                                 | Nothing to disclose                                                       |
| Amanda Francescatti, MS                   | American College of Surgeons                                                 | Nothing to disclose                                                       |
| Linda Zheng                               | American College of Surgeons                                                 | Nothing to disclose                                                       |
Program Objectives

Target Audience

✓ Breast surgeons
✓ Cancer registrars
✓ Colorectal surgeons
✓ General surgeons
✓ Nurses
✓ Nurse practitioners
✓ Other advanced practice professionals
✓ Physician assistants
✓ Physicians in cancer accredited centers and programs
✓ Surgical oncologists

Learning Objectives

✓ Review the indications and application of (neo)adjuvant therapy and molecular profiling for solid tumors of the breast, skin and colon.
✓ Understand the technical tips and operative standards for solid tumors of the breast, skin and the colon.
✓ Discuss recent clinical trial findings and outline the application of results to patient management.
Introducing our Moderator

Flavio G Rocha, MD, FACS, FSSO
Chief of the Division of Surgical Oncology
Oregon Health and Science University (OHSU)
Portland, OR
Introducing our Presenters

Sepideh Gholami, MD, FACS
Assistant Professor, Department of Surgery
UC Davis Comprehensive Cancer Center
Sacramento, CA

Genevieve Boland, MD, PhD, FACS
Section Head, Melanoma/Sarcoma Surgery
Surgical Director, Termeer Center for Targeted Therapies
Director, Therapeutic Intrallesional Program
Massachusetts General Hospital
Boston, MA
Introducing our Presenters

Arpana Naik, MD, FACS
Associate Professor of Surgery, Division of Surgical Oncology, School of Medicine
Oregon Health and Science University
Portland, OR
Surgical Oncology for the General Surgeon

Recent Clinical Trial Findings and Application to Patient Care in Colon Cancer

Sepideh Gholami, MD, FACS
Overview

• Clinical trials on management for colon cancer
  ➢ FOxTROT
  ➢ KEYNOTE-177
  ➢ New EPOC

• Novel biomarkers: ctDNA as a prognostic marker for colon cancer
FOxTROT - Background

• Potential benefits of neoadjuvant chemotherapy seen in various solid tumors (increased complete resection and reduced potential for micrometastatic disease by earlier treatment)

• Patients with RAS-wildtype may have better response to preoperative chemotherapy with the addition of EGFR-targeted monoclonal antibodies

• FOxTROT trial aimed to compare efficacy of 6 weeks of neoadjuvant chemotherapy before resection followed by chemotherapy
Patients with operable, non-obstructed colon cancer CT-predicted stage T3-4, N0-2, M0, and were fit for FOLFOX and surgery

Arm A: 6 weeks FOLFOX (N=555) + Panitumumab

Arm B: 6 weeks FOLFOX (N=134) + Panitumumab

Arm C: 24 weeks FOLFOX (N=354)

Endpoints

Primary:
• Freedom from recurrent or persistent disease after 2 years

Secondary:
• Safety
• Histological stage
• Completeness of resection
• Overall survival

Recurrence

2-year recurrence, pre vs postop:
12.6% (95/698) vs 17.2% (61/354)
HR=0.75 (95% CI 0.55, 1.04), p=.08

Conclusion

- Neoadjuvant chemotherapy can be used in appropriately selected patients with colon cancer to improve surgical outcomes - did not increase perioperative morbidity - Increased pathologic response rates and R0 resections

- Long term survival data needed
KEYNOTE 177 - Background

- Patients with microsatellite-instability-high (MSI-H) or mismatch-repair deficient (dMMR) tumors have shown clinical benefit from the programmed death 1 blockade (PD-1) compared to standard therapy.

- Pembrolizumab is a PD-1 inhibitor that has led to substantial response with previously treated patients with MSI-H-dMMR metastatic colorectal cancer.

- KEYNOTE-177 aimed to compare the safety and efficacy of pembrolizumab as first line therapy to standard chemotherapy in this patient population.
KEYNOTE-177

Patients with MSI-H–dMMR stage IV colorectal cancer, with measurable disease
ECOG PS 0 or 1
Treatment naive

Arm A: Investigator’s choice chemotherapy (N=154) Q2W
- mFOLFOX6
- mFOLFOX6 +bevacizumab
- mFOLFOX6 +cetuximab
- FOLFIRI
- FOLFIRI +bevacizumab
- FOLFIRI +cetuximab

Optional crossover to pembrolizumab 200 mg Q3W for up to 35 cycles for patients with centrally verified PD

Arm B: Pembrolizumab, 200 mg every 3 weeks for up to 35 cycles (N=153)

Endpoints

Primary:
• Progression-free survival
• Overall survival

Secondary:
• Overall response

Safety and survival follow-up

Primary:
• Progression-free survival
• Overall survival

Secondary:
• Overall response
Progression-Free Survival


Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.
Duration of Response

- Median time to response (range) was 2.2 mo (1.8-18.8) and 2.1 (1.7-24.9) for patients in the pembrolizumab and chemotherapy arms

Data cut-off: 19Feb2020; Duration of Response assessed per RECIST v1.1 by BICR.
Conclusion

• For patients with MSI-H mCRC, pembrolizumab provided a more durable response compared to chemotherapy

• PFS was significantly improvement in pembrolizumab compared to chemotherapy group

• For patients with MSI-H mCRC, pembrolizumab may be considered a new first-line therapy

New EPOC

- EPOC study demonstrated improved PFS in patients with colorectal liver metastases who received perioperative chemotherapy compared to resection alone

- The New EPOC study assessed the benefits of adding an anti-EGFR antibody (cetuximab) to perioperative chemotherapy

- The study was closed to recruitment in 2012 after interim analysis showed the addition of cetuximab resulted in a shorter PFS (20.5 months vs 14.1 months)

- Recent analysis was conducted to assess overall survival

New EPOC

Patients with histologically confirmed KRAS exon 2 wild-type colorectal cancer with primary R0 resection or resectable primary tumor

Primary:
- Progression-free survival

Secondary:
- Preoperative response
- Surgical margins
- Safety
- Quality of life
- Cost-effectiveness

Arm A: FOLFOX (6 cycles) (N=117)
Arm B: FOLFOX + cetuximab (6 cycles) (N=119)

Surgery

Arm A: FOLFOX (6 cycles) (N=117)
Arm B: FOLFOX + cetuximab (6 cycles) (N=119)

Progression Free Survival

Hazard ratio 1.17 (95% CI 0.87-1.56)
Overall Survival


Hazard ratio 1.45 (95% CI 1.02-2.05)

Number at risk (number censored)
Chemotherapy alone group
Chemotherapy plus cetuximab group

<table>
<thead>
<tr>
<th>Time since randomisation (months)</th>
<th>Chemotherapy alone group</th>
<th>Chemotherapy plus cetuximab group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>128 (3)</td>
<td>128 (11)</td>
</tr>
<tr>
<td>10</td>
<td>125 (16)</td>
<td>117 (25)</td>
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<td>20</td>
<td>112 (24)</td>
<td>103 (38)</td>
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<td>30</td>
<td>104 (33)</td>
<td>90 (48)</td>
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<tr>
<td>40</td>
<td>95 (43)</td>
<td>80 (60)</td>
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<td>50</td>
<td>85 (52)</td>
<td>65 (68)</td>
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<tr>
<td>60</td>
<td>55 (54)</td>
<td>40 (70)</td>
</tr>
<tr>
<td>70</td>
<td>33 (56)</td>
<td>23 (72)</td>
</tr>
<tr>
<td>80</td>
<td>18 (58)</td>
<td>12 (72)</td>
</tr>
<tr>
<td>90</td>
<td>2 (58)</td>
<td>4 (72)</td>
</tr>
<tr>
<td>100</td>
<td>1 (58)</td>
<td>1 (72)</td>
</tr>
</tbody>
</table>
Conclusion

• Cetuximab accelerated disease progression and possibly led to a more aggressive disease biology

• Cetuximab should not be used in the neoadjuvant setting for patients with resectable colorectal liver metastases

• Translational studies are needed to help explain these observations

ctDNA - Background

- Tumors release small **cell-free DNA** fragments
- ctDNA is frequently detected in metastatic solid malignancies\(^1\)
- Has been explored as a marker for **minimal residual disease** after surgery (lung\(^2\), breast\(^3\), pancreas\(^4\))
- Can test for ctDNA through next generation sequencing or PCR panel of mutations detected in patient primary tumors

Stage II Recurrence-Free Survival

HR: 18 (95% CI: 7.9 – 40), p < 0.001

Tie et al. Sci Transl Med 2016
ctDNA to stratify patients with colon cancer

1. Detect MRD and stratify patients into high- and low risk of recurrence
2. Assess post-therapy relapse risk in ctDNA-positive patients.
3. Determine lead time of ctDNA detection compared to CT recurrence.

- Patients with Stage I-III CRC who underwent resection (n = 260)
- 165 patients received adjuvant chemotherapy
- Plasma samples collected at various time points (median follow-up 28.4 months)
Postoperative ctDNA Detection


Recurrence rates

Modified by ACT?
Time to Recurrence

- Molecular recurrence was detected about 8 months before radiological detection of recurrence

ctDNA vs CEA in predicting RFS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>CEA PostOP</td>
<td>175</td>
<td>1.3 (0.56-3.2)</td>
<td>0.524</td>
</tr>
<tr>
<td>CEA PostACT</td>
<td>99</td>
<td>1.4 (0.44-4.2)</td>
<td>0.596</td>
</tr>
<tr>
<td>CEA Longitudinal</td>
<td>197</td>
<td>4.9 (3.2-15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ctDNA Longitudinal</td>
<td>197</td>
<td><strong>95.7 (28-322)</strong></td>
<td><strong>&lt;0.0001</strong></td>
</tr>
</tbody>
</table>

- Longitudinal testing with ctDNA outperformed CEA as a biomarker for disease relapse
## Ongoing/Upcoming Trials evaluating ctDNA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE-IT</td>
<td>II</td>
<td>Stage I or II colorectal cancer after resection</td>
<td>Adjuvant chemotherapy if + ctDNA</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT03748680</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRG GI005 (COBRA)</td>
<td>II/III</td>
<td>Stage II colon cancer; MD deems suitable for observation</td>
<td>Adjuvant FOLFOX if + ctDNA</td>
<td>1. Phase II: clearing rate of ctDNA 2. Phase III: DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT04068103</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRACC</td>
<td>n/a</td>
<td>Stage II and III colorectal cancer after surgery</td>
<td>Evaluation of ctDNA status &amp; clinical outcomes</td>
<td>1. Incidence of ctDNA 2. Correlation of detectable ctDNA &amp; DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT04050345</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

• FDA recently approved single-agent pembrolizumab as first-line treatment for dMMR/MSI-H mCRC

• Neoadjuvant chemotherapy for resectable colon cancer showed increased rates of pCR and complete R0 resection

• Cetuximab should not be used in the neoadjuvant setting for patients with resectable colorectal liver metastases

• ctDNA is a promising new strategy to detect patients at highest risk for colon cancer recurrence
  • Need to determine how to best use ctDNA to guide therapy
THANK YOU
Surgical Management in Melanoma: Where are we going?

Genevieve Boland, MD, PhD, FACS
Section Head, Melanoma/Sarcoma Surgery
Associate Professor of Surgery, Harvard Medical School
Melanoma Background

- Melanoma is the rarest form of skin cancer (accounting for ≈ 4% of skin cancer)\(^1\)

- However, it is responsible for ≈ 90% of deaths due to skin cancer\(^2\)

- Cutaneous melanoma occurs anywhere on the skin, but is most commonly located on the trunk\(^3\)
  - It is less common than non-melanoma skin cancers, however, it is much deadlier because of its propensity to metastasize\(^4\)

Global Incidence of Melanoma\textsuperscript{1, 2}

- In 2012, there were $\approx 232,130$ cases of melanoma worldwide; $\approx 55,489$ deaths due to melanoma were reported\textsuperscript{1}.

- In the US, $91,270$ new cases and $9320$ deaths from melanoma are estimated to occur\textsuperscript{4}.

- Unlike other cancers, the incidence of melanoma is increasing.
  - Between 2000 and 2009, the incidence has climbed 1.9% annually\textsuperscript{1}.

## Surgical Management of Melanoma: Wide Local Excision

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Groups (tumor thickness)</th>
<th>Resection Margins</th>
<th>Follow-Up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization Cascinelli N, et al. Semin Surg Oncol. 1998;14:272-275.</td>
<td>612</td>
<td>&lt; 1 mm 1.01-2.00 mm</td>
<td>1 cm 3 cm</td>
<td>Median, 12 years</td>
<td>NS</td>
</tr>
<tr>
<td>Swedish Melanoma Study Group Cohn-Cedarmark G, et al. Cancer. 2000;89:1495-1501.</td>
<td>989</td>
<td>0.8-2.0 mm</td>
<td>2 cm ≥ 5 cm</td>
<td>Median for OS, 11 years (7-17 years)</td>
<td>HR for OS, 0.96 (NS) HR for RFS, 1.02 (NS)</td>
</tr>
<tr>
<td>Melanoma Institute Australia Haydu LE, et al. Ann Surg Oncol. 2016;23:1071-1081.</td>
<td>2131</td>
<td>1.01-2.0 mm</td>
<td>&lt; 8 mm 8-16 mm</td>
<td>Median, 46 months Mean, 57 months</td>
<td>RFS (P = .044) OS (NS)</td>
</tr>
<tr>
<td>United Kingdom Melanoma Study Group Thomas JM, et al. N Engl J Med. 2004;350:757-766.</td>
<td>900</td>
<td>≥ 2 mm</td>
<td>1 cm 3 cm</td>
<td>Median, 60 months</td>
<td>HR for locoregional recurrence, 1.26 (P = .05) HR for OS, 1.07 (NS)</td>
</tr>
<tr>
<td>United Kingdom Melanoma Study Group Hayes AJ, et al. Lancet Oncol. 2016;17:184-192.</td>
<td>900</td>
<td>≥ 2 mm</td>
<td>1 cm 3 cm</td>
<td>Median 8.8 years (106 months)</td>
<td>HR for MSS, 1.24 (P = .041) HR for OS 1.14 (NS)</td>
</tr>
</tbody>
</table>
Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial

Andrew J Hayes, Lauren Maynard, Gillian Coombes, Julia Newton-Bishop, Michael Timmons, Martin Cook, Jeffrey Theaker, Judith M Bliss*, J Meirion Thomas*, for the UK Melanoma Study Group, the British Association of Plastic, Reconstructive, and Aesthetic Surgeons, and the Scottish Cancer Therapy Network

UK Trial of 1 vs 3 cm margins for melanoma >2 mm thick 1992-2001

Incidence of melanoma-specific death

HR 1.24 (95% CI 1.01-1.52); p = 0.036

median f/u 8.8 years
Melanoma Margins Trial-II (MelmarT-II) Investigating 1cm v 2cm Margins for Primary Cutaneous Melanoma (NCT03860883)

**Inclusion:**
- Age 18+, ECOG PS 0-1
- Invasive primary cutaneous melanoma pT2b-4b (>2mm, or 1-2mm +ulcer)
- 2 cm margin must be anatomically feasible.

**Exclusion:**
- WLE already done
- ineligible for SNBx.
- desmoplastic/neurotropic or subungual melanoma
- microsatellites
- planned radiation therapy
- immune suppression

Power calcs: Non-inferiority log-rank test for 90% power (α 0.05) for non-inferiority HR of 1.25

**Primary Endpoint:** Disease-free survival

**Secondary Endpoints:**
- Local Recurrence
- DDFS, MSS, OS
- QOL, Neuropathic pain
- Surgical AEs
- Costs

Open Dec 2019:
- Australia, Canada,
- New Zealand,
- Sweden,
- U.K., U.S.,
- Target n = 2998.

pT2b-4b cutaneous melanoma

(A) WLE 1 cm margin + SNBx

(B) WLE 2 cm margin + SNBx
MSLT-I: Sentinel Node Biopsy vs Nodal Observation Following Wide Excision—Phase 3

**Melanoma-Specific Survival, Intermediate Thickness Melanomas**

<table>
<thead>
<tr>
<th>Time, Years</th>
<th>OBS</th>
<th>SNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>500</td>
<td>770</td>
</tr>
<tr>
<td>2</td>
<td>448</td>
<td>700</td>
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<tr>
<td>4</td>
<td>390</td>
<td>611</td>
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<tr>
<td>6</td>
<td>351</td>
<td>530</td>
</tr>
<tr>
<td>8</td>
<td>318</td>
<td>467</td>
</tr>
<tr>
<td>10</td>
<td>191</td>
<td>262</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI, 0.64-1.09)  
\[ P = .18 \]

**Melanoma-Specific Survival, Thick Melanomas**

<table>
<thead>
<tr>
<th>Time, Years</th>
<th>OBS</th>
<th>SNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>117</td>
<td>173</td>
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<tr>
<td>2</td>
<td>94</td>
<td>143</td>
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<td>4</td>
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<td>8</td>
<td>57</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR 1.12 (95% CI, 0.76-1.67)  
\[ P = .56 \]

MSLT-I, Multicentre Selective Lymphadenectomy Trial I; OBS, observation.  
# Prognostic Significance of the Sentinel Node

In the biopsy group, sentinel-node status was the strongest predictor of disease recurrence or death from melanoma

## Multivariate Hazard Ratios for Disease Recurrence and Death Among Patients With Intermediate-Thickness Melanoma Who Underwent Sentinel-Node Biopsy, According to Prognostic Indicator

<table>
<thead>
<tr>
<th>Sentinel-node status (positive vs negative)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sentinel-node status (positive vs negative)</td>
<td>2.64 (1.92-3.64)</td>
<td>&lt; .001</td>
<td>2.40 (1.61-3.56)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Breslow thickness (per 1-mm increase)</td>
<td>1.62 (1.31-2.01)</td>
<td>&lt; .001</td>
<td>1.59 (1.21-2.09)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ulceration (present vs absent)</td>
<td>1.40 (1.04-1.89)</td>
<td>.03</td>
<td>1.79 (1.24-2.58)</td>
<td>.002</td>
</tr>
<tr>
<td>Site of melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm or leg(^a)</td>
<td>1.00</td>
<td>.03</td>
<td>1.01</td>
<td>.07</td>
</tr>
<tr>
<td>Head or neck</td>
<td>1.20 (0.77-1.86)</td>
<td>.42</td>
<td>1.19 (0.65-2.16)</td>
<td>.58</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.94 (0.70-1.26)</td>
<td>.66</td>
<td>1.22 (0.82-1.79)</td>
<td>.32</td>
</tr>
<tr>
<td>Age (per 1-year increase)</td>
<td>1.01 (1.00-1.02)</td>
<td>.07</td>
<td>1.01 (0.99-1.02)</td>
<td>.33</td>
</tr>
<tr>
<td>Clark level (IV or V vs III)</td>
<td>1.27 (0.94-1.71)</td>
<td>.12</td>
<td>1.07 (0.74-1.54)</td>
<td>.73</td>
</tr>
</tbody>
</table>

\(^a\) This group served as the reference group.
ASCO and SSO Guideline on SLN Biopsy

Per the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) Clinical Practice Guideline:

- **SLN biopsy is recommended** for intermediate-thickness melanomas (> 1.0 to 4.0 mm; T2 or T3)

- Following a discussion with the patient on the potential benefits and risks of harm associated with the procedure, SLN biopsy:
  - **May be recommended** for thick melanomas (> 4.0 mm; T4);
  - **May be considered** for thin melanomas that are **T1b** (0.8 to 1.0 mm or < 0.8 mm with ulceration)

MSLT-II: Study Design

**Phase 3 Trial Evaluating CLND vs Observation With Nodal Ultrasonography in Node-Positive Melanoma**

**Key eligibility criteria**
- Aged 18 to 75 years with clinically localized cutaneous melanoma
- Tumor-positive sentinel nodes
- ECOG PS 0 or 1

**Stratified by**
- Breslow thickness
- Ulceration
- Metastasis detection method (standard pathological assessment or RT-PCR)
- Enrollment at an MSLT-I center

**N = 1755**

- **Completion Lymph Node Dissection** (n = 824)
- **Nodal Observation** (n = 931)

**Primary endpoint:** MSS

**Key secondary endpoints:** OS, DFS, survival without recurrence of regional nodal metastases, DMFS, and extent of nodal involvement

Sentinel node basin monitored by nodal ultrasonography at each visit for the first 5 years (observation group only)

CLND, complete lymph node dissection; DFS, disease-free survival; DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; MSLT-II, Multicentre Selective Lymphadenectomy Trial II; MSS, melanoma-specific survival; OS, overall survival; RT-PCR, reverse transcription–polymerase chain reaction.


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MSLT-II: Key Results

**CLND Was Not Associated With Improved Melanoma-Specific Survival vs Observation in Patients With Sentinel Node Metastases**

MSLT-II: Key Results

CLND Was Associated With Slightly Higher Disease-Free Survival vs Observation Based on Increased Rate of Disease Control in Regional Nodes

In patients with newly diagnosed stage III melanoma and clinically positive node(s), the National Comprehensive Cancer Network® (NCCN®) recommends:

**Workup**
- Biopsy needed: FNA, core, incisional, or excisional biopsy
- Imaging for baseline staging and to evaluate specific signs or symptoms

**Primary Treatment**
- Wide excision of primary tumor
- Complete therapeutic lymph node dissection
Stage III Melanoma With Non-Nodal Regional Disease

Microsatellites – one or more discontinuous nests of neoplastic cells > 0.05mm, clearly separated from normal dermis

Satellite metastases – cutaneous and/or subcutaneous metastases within 2 cm of the primary tumor

In-transit metastases – cutaneous and/or subcutaneous metastases at a distance > 2 cm from the primary melanoma in the region between the primary and first echelon of regional lymph nodes

Workup

- Tissue Diagnosis: FNA, core, incisional, or excisional biopsy
- Imaging for baseline staging and to evaluate specific signs or symptoms

Primary Treatment - Local or Regional Therapy Options

- Local therapy options:
  - Complete surgical excision to clear margins, if feasible
  - Intralesional talimogene laherparepvec (T-VEC)

- Regional therapy options:
  - Isolated limb infusion/perfusion with melphalan

Importance of a Multidisciplinary Approach

**Treatment Goals**

1. Reduce the risk of relapse and mortality by targeting residual micrometastatic disease
2. Align on treatment strategy and provide clear communication to the patient
3. Reduce the risk of relapse and mortality by targeting residual micrometastatic disease

**Treatment Approach**

**Adjuvant Treatment**

Reduce the risk of relapse and mortality by targeting residual micrometastatic disease

**Systemic Therapy**

Reduce the risk of relapse and mortality by targeting residual micrometastatic disease

**Surgery**

Excision of the tumor, including excisional biopsy to obtain a pathology specimen and to evaluate margins for residual tumor

---

Is Durable Control Possible?

Ribas et al CCR, 2012
Impact of Current Therapies

Recent therapies have translated into a marked survival advantage in metastatic melanoma

Historical Survival Trends in Metastatic Melanoma

Historical OS¹

Current OS With Available Therapies²,a

1-year OS, 25.5%

Adjuvant Therapy in Melanoma

**Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma**


**Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma**

Adjuvant Therapy Failure Patterns in the Modern Era of Melanoma Management

Daan Jan Willem Rauwerdink¹, George Molina, MD, MPH¹, Dennie Tompers Frederick, MS¹, Tanya Sharova, MD¹, Harrison Carmichael, BS¹, and Genevieve Marie Boland, MD, PhD¹,²

A Kaplan-Meier Recurrence Free Survival

B

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Patients</th>
<th>Local Recurrence</th>
<th>Distant Recurrence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Only</td>
<td>26</td>
<td>0.40 (0.16-0.96)</td>
<td>0.40 (0.16-0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>46</td>
<td>0.23 (0.07-0.72)</td>
<td>0.23 (0.07-0.72)</td>
<td>0.01</td>
</tr>
<tr>
<td>BRAF/MEK</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Anti-PD1* Reports 7.70% 3.30% 3.60% 2.40% 4.36% 7.63%

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The OpACIN-neo study identified neoadjuvant IPI 1 mg/kg + NIVO 3 mg/kg as the optimal treatment scheme.

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%

*courtesy of Prof. dr. C.U. Blank, presented ASCO 2020


Rozeman et al., Lancet Oncology, 2019
Promising RFS after 2 years follow-up and pathologic response predicts outcome

(near-)pCR = (near) pathologic complete response, pPR = pathologic partial response, pNR = pathologic non-response

*patient died due to toxicity without signs of melanoma relapse

*Rozeman et al., abstract 10015, ASCO 2020

*courtesy of Prof. dr. C.U. Blank, presented ASCO 2020
MeMaloc substudy of OpACIN-neo

The pathologic response in the largest lymph node (index node) represents the entire lymph node bed.

<table>
<thead>
<tr>
<th>Pathologic response</th>
<th>Index node</th>
<th>Total basin</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Near-pCR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>pPR</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>pNR</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Index node congruent with total basin = 12/12 cases

2 courses IPI+NIVO ➔ TLND

*courtesy of Prof. dr. C.U. Blank, presented ASCO 2020

Schermers et al., BJS 2019
Objectives of PRADO extension cohort

To confirm the high pathologic response rate and safety of IPI 1 mg/kg + NIVO 3 mg/kg combination scheme (OpACIN-neo)

Show that patients with pCR or near-pCR in index lymph node can be safely spared a TLND without affecting RFS

➢ Use a marked index node as representative for the response in entire lymph node basin

Prolong RFS at 24 months for patients with pNR by an additional adjuvant therapy

*courtesy of Prof. dr. C.U. Blank, presented ASCO 2020
# Surgery-related adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Total cohort (n=96)</th>
<th>Index node procedure only (n=63)</th>
<th>Subsequent TLND (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grade (%)</td>
<td>Grade 3 (%)</td>
<td>All grade (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>52 (54)</td>
<td>6 (6)</td>
<td>26 (41)</td>
</tr>
<tr>
<td>Seroma</td>
<td>30 (31)</td>
<td>–</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>11 (11)</td>
<td>3 (3)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>7 (7)</td>
<td>–</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>6 (6)</td>
<td>–</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Wound complication</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>–</td>
</tr>
<tr>
<td>Difficulty mobilizing</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>–</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>–</td>
</tr>
<tr>
<td>Postoperative hemorrhage</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>–</td>
</tr>
</tbody>
</table>

Adverse events that occurred in ≥3 patients or were grade 3-4 are displayed in the table.

1. One patient did not undergo surgery because of toxicity, 2 patients because of distant metastases.
2. Two patients had an additional small surgery to remove 1-3 lymph nodes and were therefore excluded from the surgical subgroup analysis.

*courtesy of Prof. dr. C.U. Blank, presented ASCO 2020*
Management of primary melanoma

- Wide local excision is definitive treatment for primary melanoma
- Sentinel lymph node biopsy is recommended for staging and prognostic information in intermediate thickness and thick melanomas, and worthy of discussion in T1b melanomas.

Management of the regional nodal basin

- MSLT-II changed the management of regional nodal metastases of SLNB positive micrometastatic disease – now active nodal surveillance with nodal ultrasounds a reasonable alternative to CLND
- Clinically positive, palpable nodal disease still treated up front with therapeutic LND
- In transit disease remains challenging, but with many additional options now including intralesional therapies
- Adjuvant therapies available for stage III disease, both targeted and immunotherapies
- Neoadjuvant trials ongoing, increasing enthusiasm for this approach (on trial)

Management of stage IV melanoma (oligometastatic progression)

- Surgery for stage IV disease can be considered on a case-by-case basis as part of multimodality management strategy
Surgical Oncology for the General Surgeon
Breast Cancer

Arpana Naik, MD, FACS
February 11, 2021
Why Neoadjuvant Chemotherapy (NAC)?

Historically:

• Downstage disease to allow for surgery in inoperable cases (e.g., IBC)
• Downstage to allow for BCT

Evolving:

• Downstage axilla
• Evaluate novel agents in clinical trials (e.g., I-SPY2)
• Obtain prognostic information
• Guide additional postop adjuvant therapy depending on pathologic response and residual disease
Who should receive NAC?

Clinically:

- Locally advanced breast cancer
  - Skin or chest wall involvement
  - Node-positive
- Inflammatory breast cancer
- If need to delay surgery (e.g., Covid, medical co-morbidities, awaiting genetic testing, reconstruction planning).

Conventional histopathology:

- Triple-negative → chemotherapy
- HER2-positive → biologic therapy
- Other factors to consider: grade 2/3, elevated Ki-67
What about Hormone Receptor-Positive Breast Cancer?

• Neoadjuvant chemotherapy (NAC) has been traditionally used, and is still often used in pre-menopausal patients.

• Increasing consideration of neoadjuvant endocrine therapy (NET)
  • Tumors known not to respond well to NAC (e.g. Luminal A, ILC)
  • Similar rates of downstaging with both NET and NAC in hormone receptor-positive cancers

• How to decide which neoadjuvant approach to take?
  • Multidisciplinary team review
  • Is patient a good candidate for BCT with downstaging?
  • Would treatment plan require adjuvant chemotherapy anyway?

• Can use core biopsy to obtain genomic assay result to help guide treatment (e.g. I-SPY2 trial)
Case Examples

- **50 yo screen-detected 1.7cm Grade 2 IDC, node-negative**
  - ER+ (100%) PR+ (7%) HER2-, Ki67 82%
  - Oncotype DX sent: RS 31
  - NAC recommended

- **64 yo 3cm Grade 2 IDC, palpable with nipple retraction**
  - ER+ (>95%), PR+ (50-90%), HER-2-, Ki67 10%.
  - Oncotype DX sent: RS 8
  - NET with letrozole recommended (for at minimum ~4-6 months for downstaging)
Genomic Assay as a Predictive Tool

- Currently limited data using genomic assays to predict response to NAC

**Oncotype DX® Recurrence Score as a Predictor of Response to Neoadjuvant Chemotherapy**

Alison M. Pease, MD\(^1\), Luis A. Riba, MD\(^2\), Ryan A. Gruner, MD\(^3\), Nadine M. Tung, MD\(^4\), and Ted A. James, MD, MHCM\(^5\)

\(^1\)Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; \(^2\)Department of Surgery/Linsey BreastCare Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; \(^3\)Department of Medicine/Division of Hematology – Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

- National Cancer Database used to identify 989 T1-3, ER+/HER2- invasive breast cancers, with available RS who underwent NAC
- pCR in 4.3% of patients
- Significant association between pCR and high RS
- Oncotype DX can be used to select ER+ patients for NAC
Genomic Assay as a Predictive Tool

- National Cancer Database used to identify 158 T1-2, N1/2, ER+/HER2- IDC with available RS who underwent NAC
- Axillary pCR in 23 (14.6%) patients
- 27.5% of high RS had axillary pCR (compared to 9.7% and 10.7% in intermediate and low RS groups) (p =0.0268)
- Oncotype DX RS independent predictor of axillary pCR in ER+HER2- IDC undergoing NAC and can help guide management of the axilla
Surgical Considerations: De-escalating Surgery

• De-escalation of axillary surgery for *node-positive* breast cancer after neoadjuvant therapy

• De-escalation of breast surgery for exceptional responders
Planning Breast Surgery after NAC

- Clip placement *prior* to neoadjuvant treatment
- Post-treatment breast imaging (mammogram, U/S, MRI)
  - Pattern of response may affect surgical planning
- Resect residual lesion (not the volume of the original lesion)
- Plan localization (bracketing if needed) and margin (re)excisions depending on pattern of response
### Sentinel Node Biopsy post NAC in cN1 Patients

Can SLNB safely be used post NAC if the axilla appears downstaged from node-positive to clinically node-negative to spare patients unnecessary ALND?

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>SLN identification rate</th>
<th>FNR</th>
<th>FNR with &gt;2 nodes removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z1071</td>
<td>92.9%</td>
<td>12.6%</td>
<td>9.1%</td>
</tr>
<tr>
<td>SENTINA</td>
<td>80.1%</td>
<td>14.2%</td>
<td>9.6%</td>
</tr>
<tr>
<td>SN FNAC</td>
<td>87.6%</td>
<td>8.4%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

**Z1071:**
Lower FNR (10.8%) with dual tracer (blue dye AND radiolabelled colloid) vs. single-method (20.0%). FNR lower if clipped node was also excised (6.8%).

**SN FNAC:**
IHC-positive nodes included as node-positive

---

Boughey et al. JAMA 2013 Oct 9;310(14):1455-61
Kuehn et al. Lancet Oncol. 2013; 14 (7); 609-18
MDACC Targeted Axillary Dissection (TAD): Clipping positive node for Targeting after NAC

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Node +</th>
<th>pCR</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clipped node</td>
<td>191</td>
<td>120</td>
<td>37%</td>
<td>4.2% (95%CI 1.4-9.5)</td>
</tr>
<tr>
<td>SLN</td>
<td>118</td>
<td>74</td>
<td>37%</td>
<td>10.1% (95%CI 4.2-19.8)</td>
</tr>
<tr>
<td>SLN + clipped node</td>
<td>118</td>
<td>74</td>
<td>37%</td>
<td>1.4% (95%CI 0.03-7.3)</td>
</tr>
</tbody>
</table>

Note: a clipped node was **not** retrieved as a SLN in ~20% pts.

“Targeted Axillary Dissection (TAD)”= SLNB + excision of clipped node

Caudle AS et al JCO 2016;34(10):1072-8
Clip Identification Techniques in OR for TAD

Localize clipped node prior to surgery (various methods: wire, ink, radioactive seed, non-radioactive localizers)

Identify clipped node in O.R. (with carbon ink)

Confirm excision of clipped node with radiograph.
Ongoing Trials for Axillary Management: Node-positive Breast Cancer post NAC

**Alliance 11202**

**N+ NAC**

**Post-NAC SLN+**
- ALND + (non-Axillary) Nodal XRT
- **Can axillary RT safely replace ALND?**

**Post-NAC SLN-**
- No ALND + Axillary & Nodal XRT
- No Regional Nodal XRT
- Regional Nodal XRT
- **Can response to NAC be used to select patients who do not need PMRT or extended nodal RT?**

**NSABP B-51 RTOG 1304**
De-escalating Breast Surgery after NAC: Omission of Breast surgery in Exceptional Responders

• 40 patients, triple-negative or HER2+; T1-3, N0-3

• FNR 5% with combination of FNA/VACB. Other studies report unacceptably high FNR with core biopsy of the residual site

• May be able to identify patients who are very high responders (eg HER2+) and can omit surgery

Questions?
ACS Cancer Research Program (CRP) Educational Series

How to Utilize Social Media to Create a Meaningful Impact in Your Practice
Thursday, February 25

Emerging Diagnostic and Treatment Opportunities for Neuroendocrine Tumors of the Gastrointestinal Tract
Thursday, March 11

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