Pathologic Response Criteria

Janis M. Taube, MD
Professor, Dermatology, Pathology, and Oncology
Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy

#MelanomaNeoadjuvant
Disclosures

- Research funding from BMS and Akoya Biosciences
- Consultant/Advisor board for BMS, Astra Zeneca, Merck, Akoya Biosciences
Overview

• Assessment of pCR and MPR (near-pCR)
  • Immunotherapy
  • Targeted therapies
Pathologic Complete Response (pCR): No residual viable tumor (RVT)

Major Pathologic Response (MPR)/ “near-pCR”: <10% RVT

Additional provisional terms for melanoma:
“Pathologic Partial Response” (pPR): 10% < RVT < 50%
“Pathologic Non-Response” (pNR): >50% RVT
% residual viable tumor

% Residual viable tumor = \frac{\text{Total area involved by viable tumor}}{\text{Total area where tumor used to be}} \times 100
Radiographic vs. gross (and microscopic) pathologic assessments
% Residual viable tumor by irPRC = \frac{\text{Total area involved by tumor}}{\text{Total tumor bed area}} \times 100

Recognition of regression influences score (80% RVT vs. 40% RVT)
Cottrell, *Ann Oncol*, 2018
Originally defined in NSCLC through comparisons of paired pre vs. on-Rx specimens
Histologic features of immune-mediated tumor regression in melanoma

- Foamy macrophages
- Neovascularization
- Plasma cells
- Proliferative fibrosis
- Hyalinized fibrosis
- Cholesterol clefts

*REPRODUCIBILITY DATA: Inter-reader agreement (5 pathologists) at 10% RVT thresholds. ICC = 0.982, 95% CI [0.965, 0.992]

Scoring categories described include pCR, MPR (near path-CR), partial PR (>10% RVT <50%), and NR (>50% RVT)
How do these features associate with patient outcomes?
Rozeman, Menzies, ..., Long, Blank, et al. ESMO 2019
New concept

$\text{MPR}_{\text{bx}} = \text{Major pathologic response (MPR, } \leq 10\% \text{ residual viable tumor)} \text{ assessed on biopsy, rather than definitive surgical resection}$
pCR\textsubscript{bx} or MPR\textsubscript{bx}

Complete pathologic response
or major pathologic response on biopsy specimen (<10% residual viable tumor)
Discovery cohort:
51 biopsies from CA209-038 cohort, median of 4 weeks (range of 22-36 days) on anti-PD-1 therapy


irPR score in pre- or post-Rx specimens did not vary by whether a patient had received ipi first.
Association of irPR score with overall survival in new validation cohort

- \( pCR/MPR_{bx} \)
- \( RVT \leq 10\% \) (n=7)
- \( 10\% < RVT \leq 90\% \) (n=7)
- \( RVT = 100\% \) (n=15)

\( p=0.03 \)
Overview

• Immunotherapy

• Targeted therapy
Targeted therapy (Dabrafenib + Trametinib) in the neoadjuvant setting

Ongoing analyses:

- Early on-treatment bx compared to resection specimen.

- Assessing distinct histologic features that are associated with disease progression, following pathologic “response”.

Tetzlaff, Ann Oncol, 2018
Conclusions

• Histologic features of immune-mediated pathologic response (irPR) in early on-treatment biopsy specimens following immune checkpoint blockade associate with long-term patient outcomes.

• RFS data for patients treated with ICB lends support to the idea that these features will also be predictive of OS in the neoadjuvant setting.

• Ongoing analyses include assessing clinically meaningful thresholds of RVT beyond pCR for patients treated with ICB, and refining histologic features of response for patients treated with targeted therapies.
Now reviewed over 500 on-treatment specimens from >10 different tumor types from regimens containing anti-PD-(L)1

- Consistent histologic features of immune-mediated pathologic response across examined specimens

### Future Directions

Pan-tumor scoring system for pathologic response

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<thead>
<tr>
<th>Treatment Setting</th>
<th>Tumor type</th>
<th>Treatment</th>
<th>NCT^1</th>
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<td>Advanced Unresectable Disease</td>
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Pan-tumor pathologic response assessment for neoadjuvant immunotherapy
Potomac Ballroom at the Westin National Harbor
Wednesday, November 6, 2019
2:15-3:15 pm
Acknowledgements

JHU – Taube lab
• Julie Stein
• Tricia Cottrell

JHU-BKI
• Evan Lipson
• Drew Pardoll
• Suzanne Topalian
• Patrick Forde

BMS
• Robin Edwards
• Megan Wind-Rotolo

Academic Collaborators
• Michael Tetzlaff
• Richard Scolyer
• Bart van de Wiel
• Margaret Callahan
• George Xu
• Georgina Long
Figure 1. Response rate per subgroup