Pathologic Response Criteria

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#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

Definitions

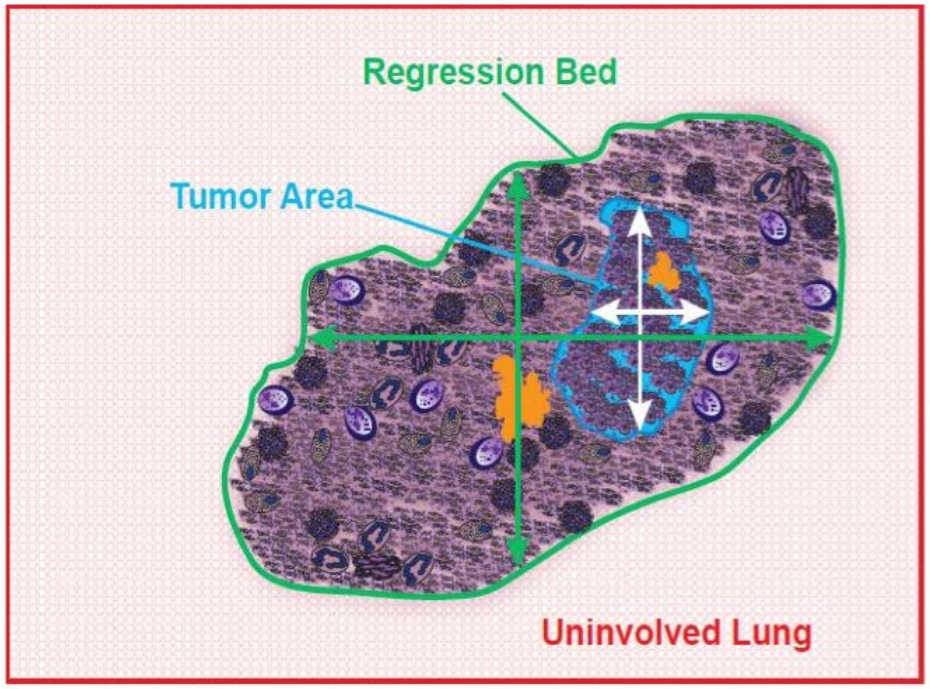
Pathologic Complete Response (pCR): No residual viable tumor (RVT)

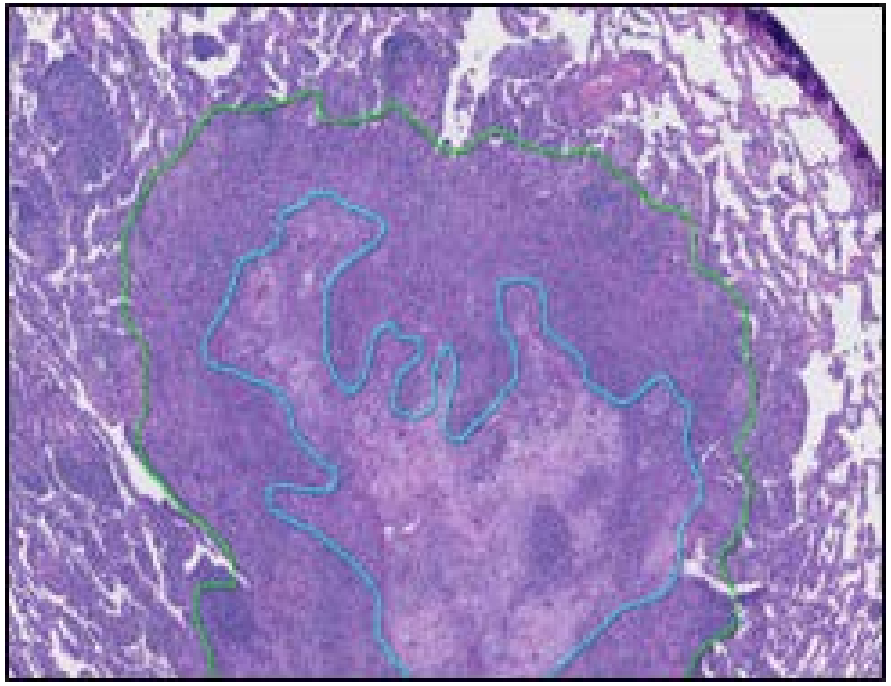
Major Pathologic Response (MPR)/ “near-pCR”: ≤10% RVT

Additional provisional terms for melanoma:

- “Pathologic Partial Response” (pPR): 10% < RVT ≤ 50%
- “Pathologic Non-Response” (pNR): >50% RVT

% residual viable tumor

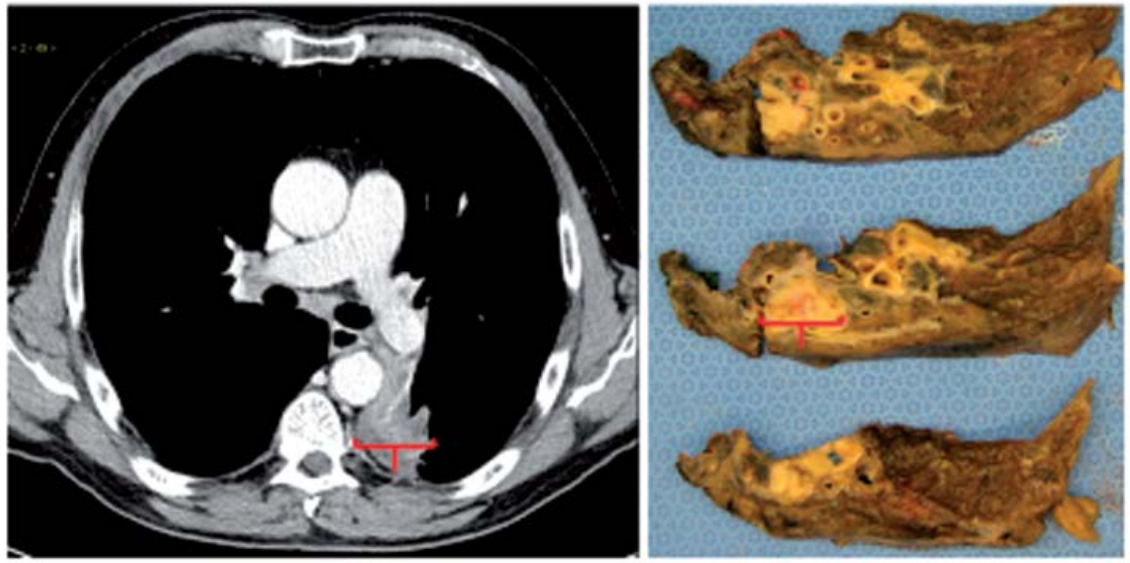


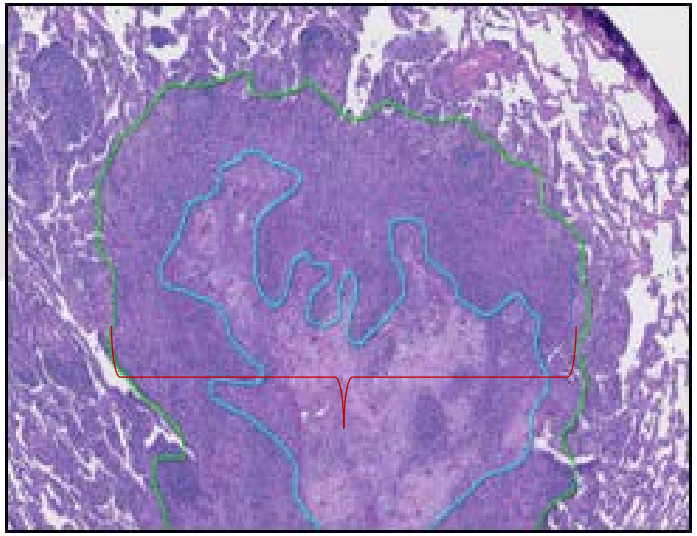


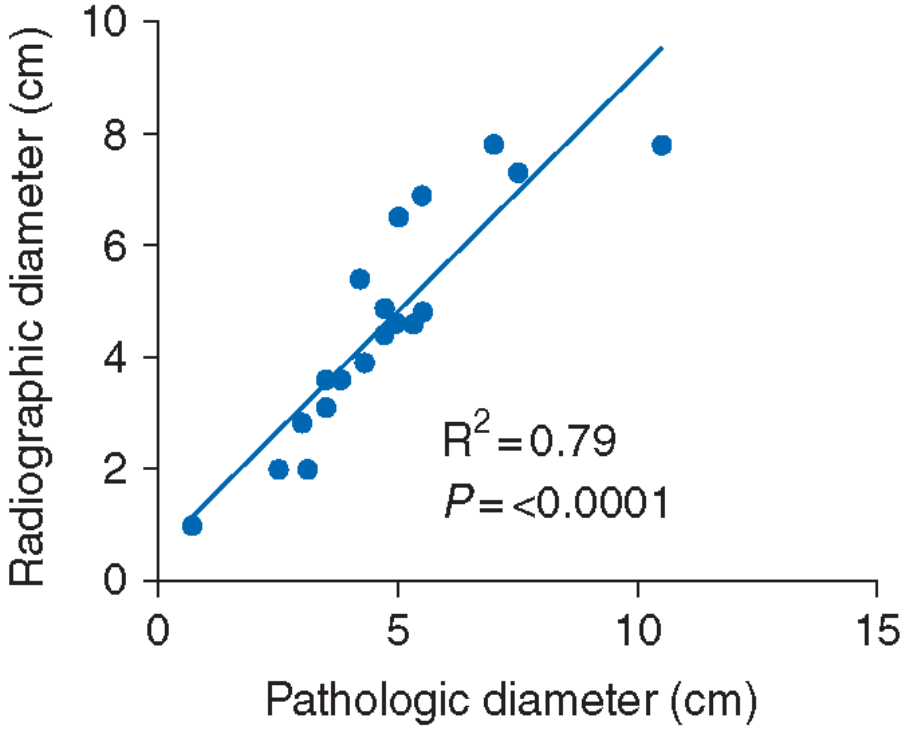
% Residual viable tumor = Total area involved by viable tumor/Total area where tumor used to be x 100

Cottrell, *Ann Oncol*, 2018

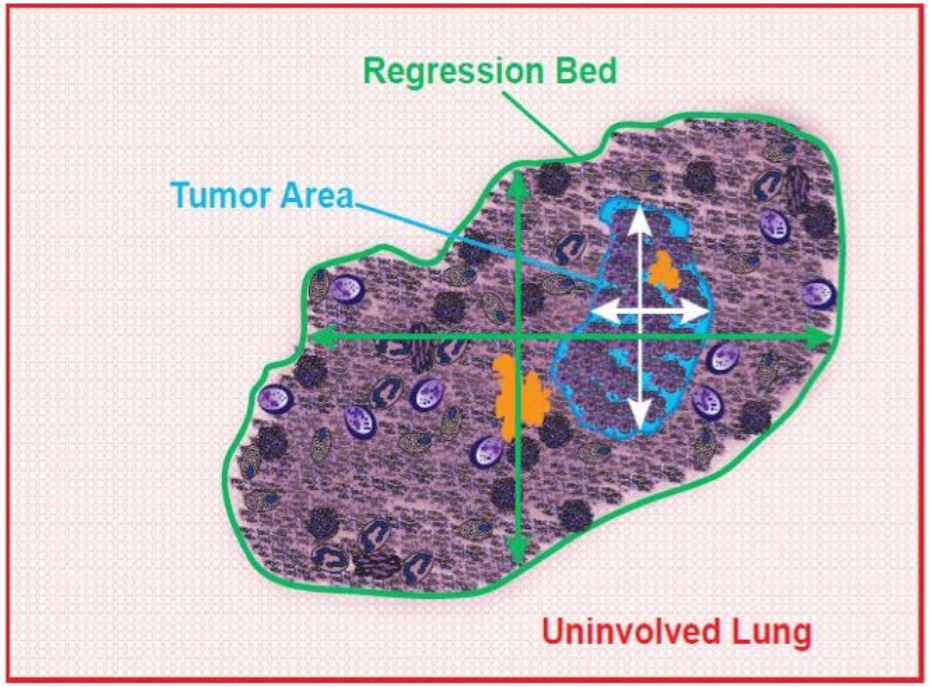
Radiographic vs. gross (and microscopic) pathologic assessments

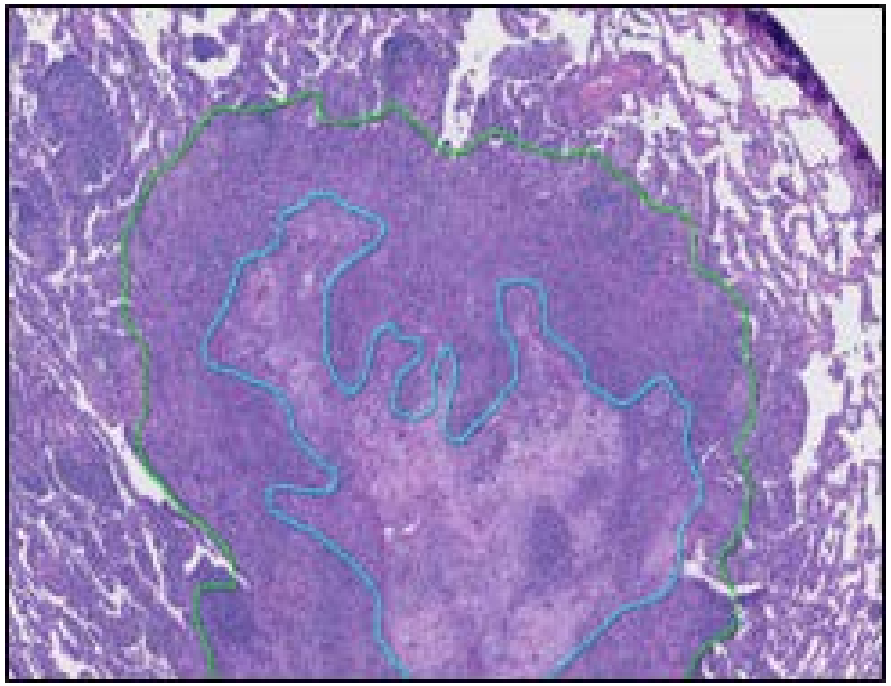






Immune-mediated regression

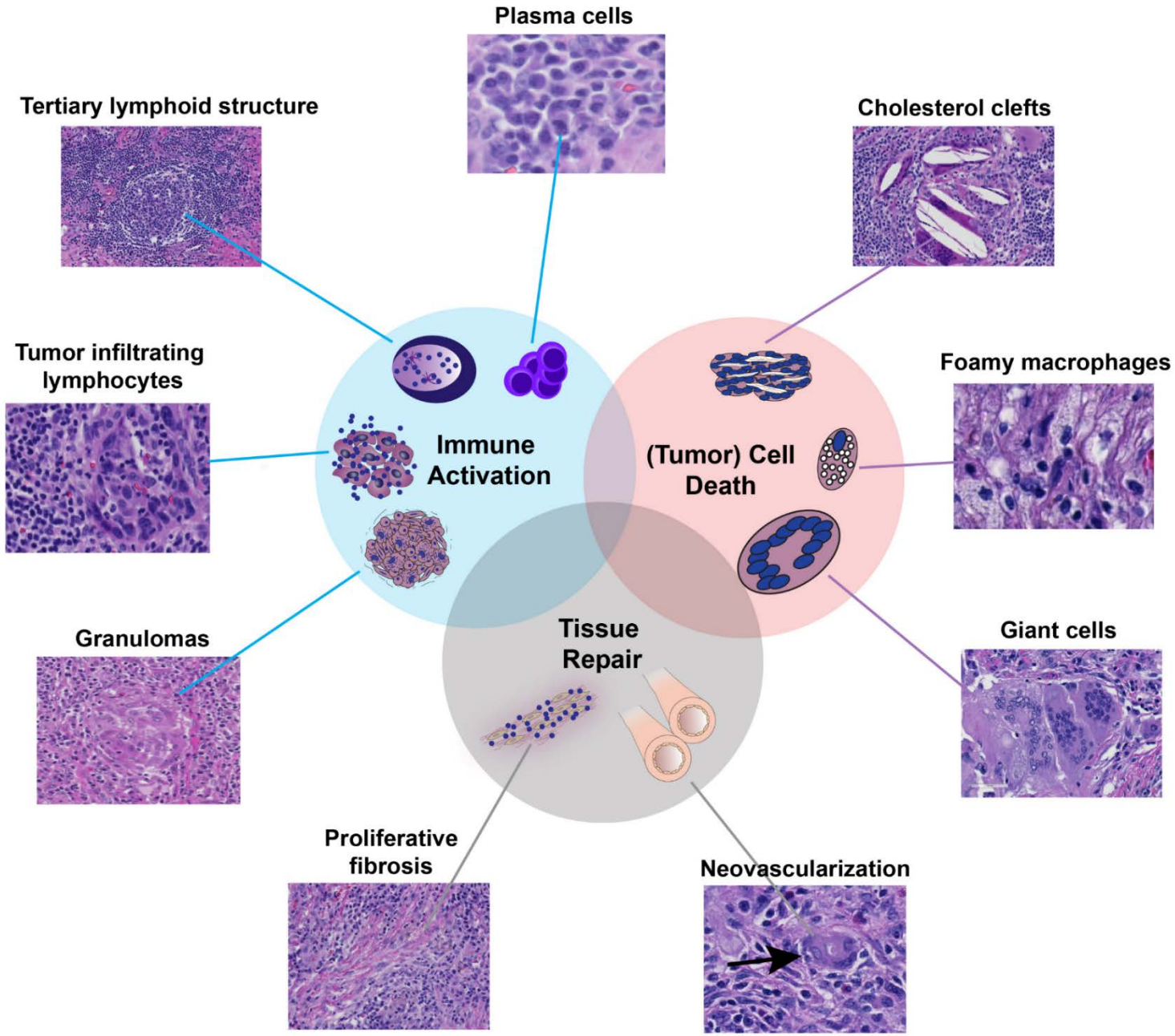




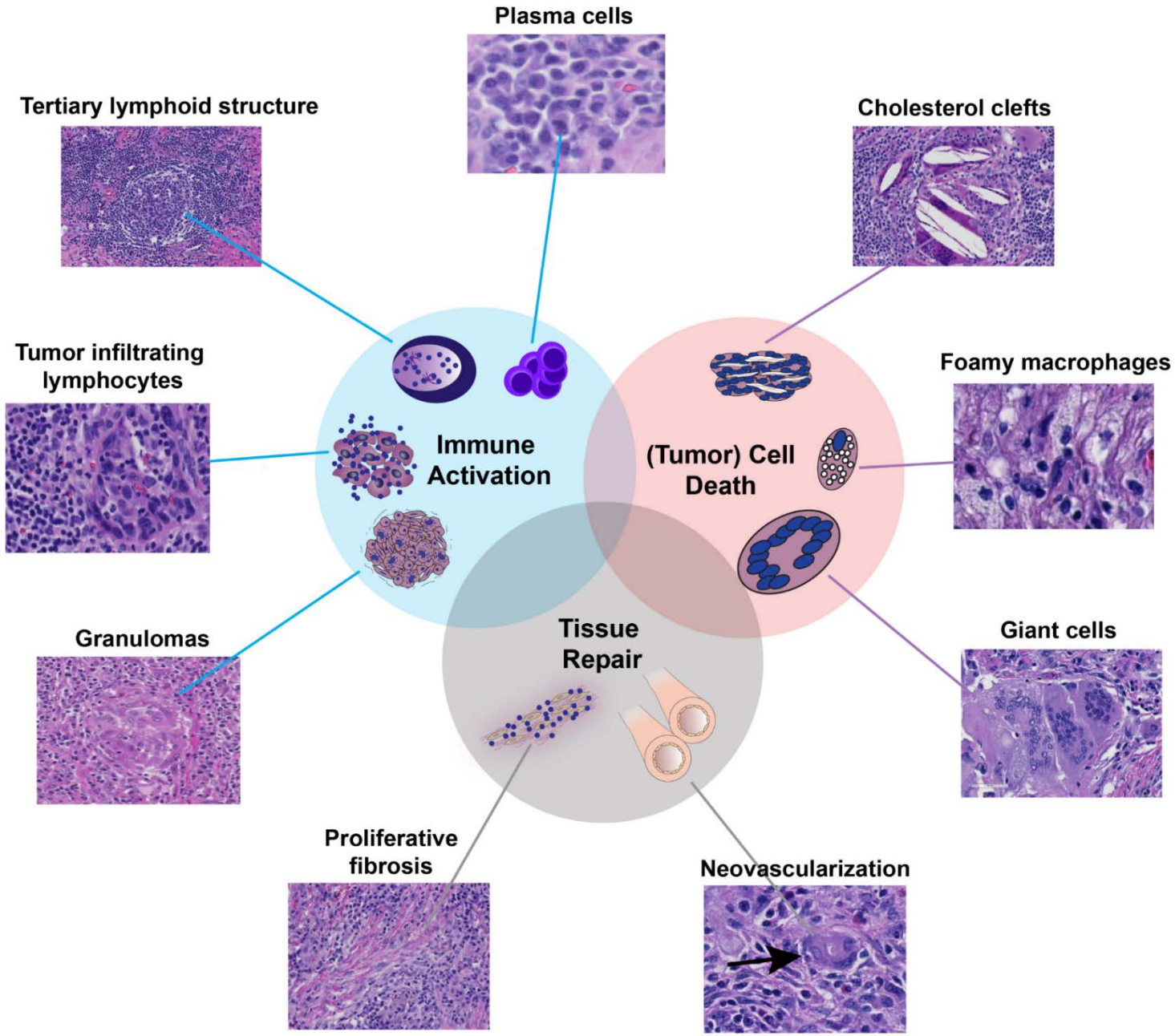
% Residual viable tumor by irPRC = Total area involved by tumor/Total tumor bed area x 100

Recognition of regression influences score (80% RVT vs. 40% RVT)

Cottrell, *Ann Oncol*, 2018



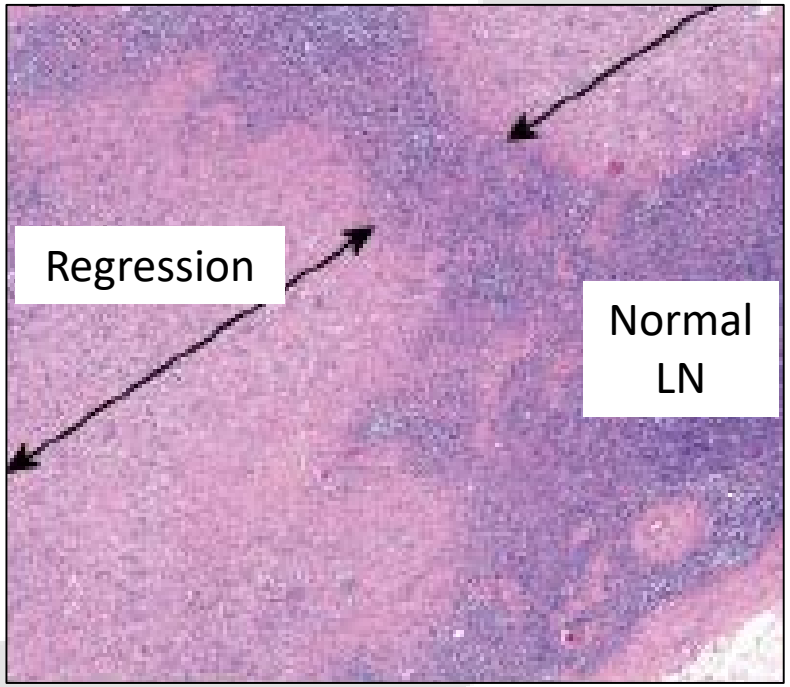
Cottrell, *Ann Oncol*, 2018

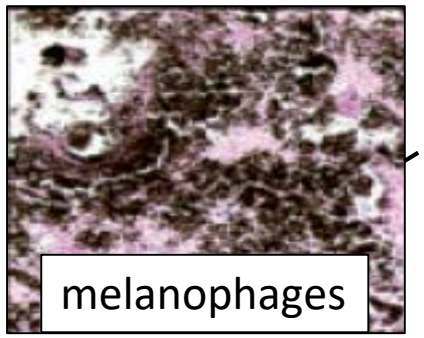


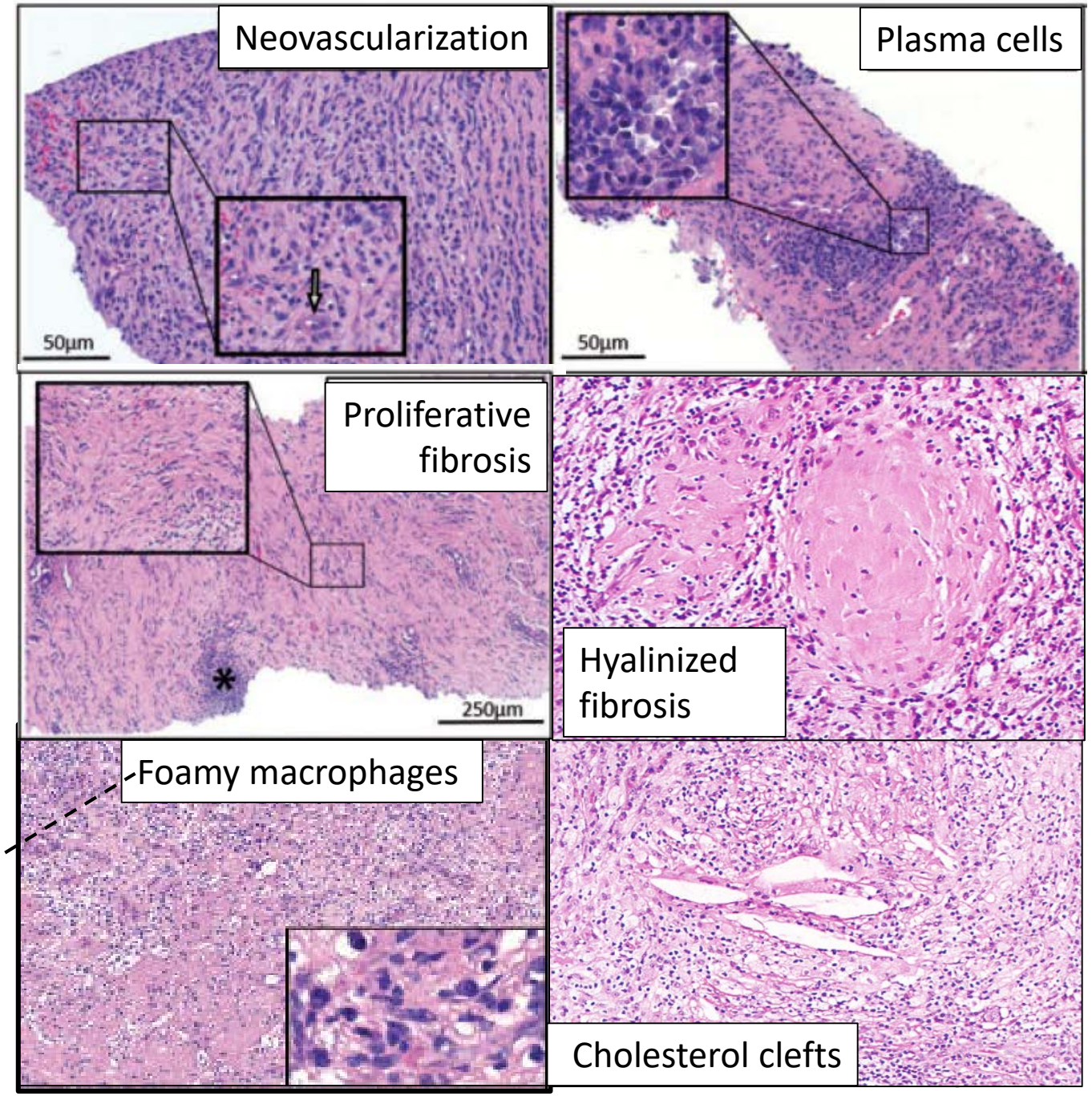
*Originally defined in NSCLC through comparisons of paired pre vs. on-Rx specimens

Cottrell, *Ann Oncol*, 2018

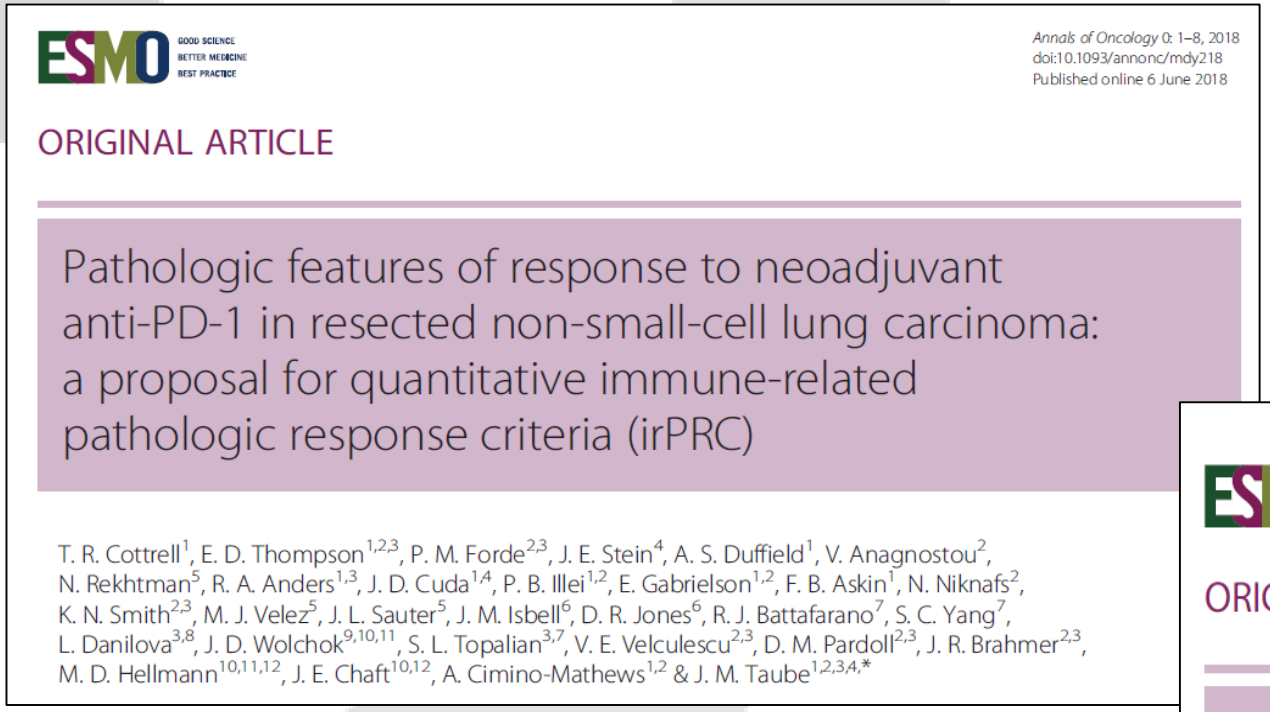
Histologic features of immune-mediated tumor regression in melanoma







Tetzlaff, *Ann Oncol* 2018; Stein, *Ann Oncol* 2019



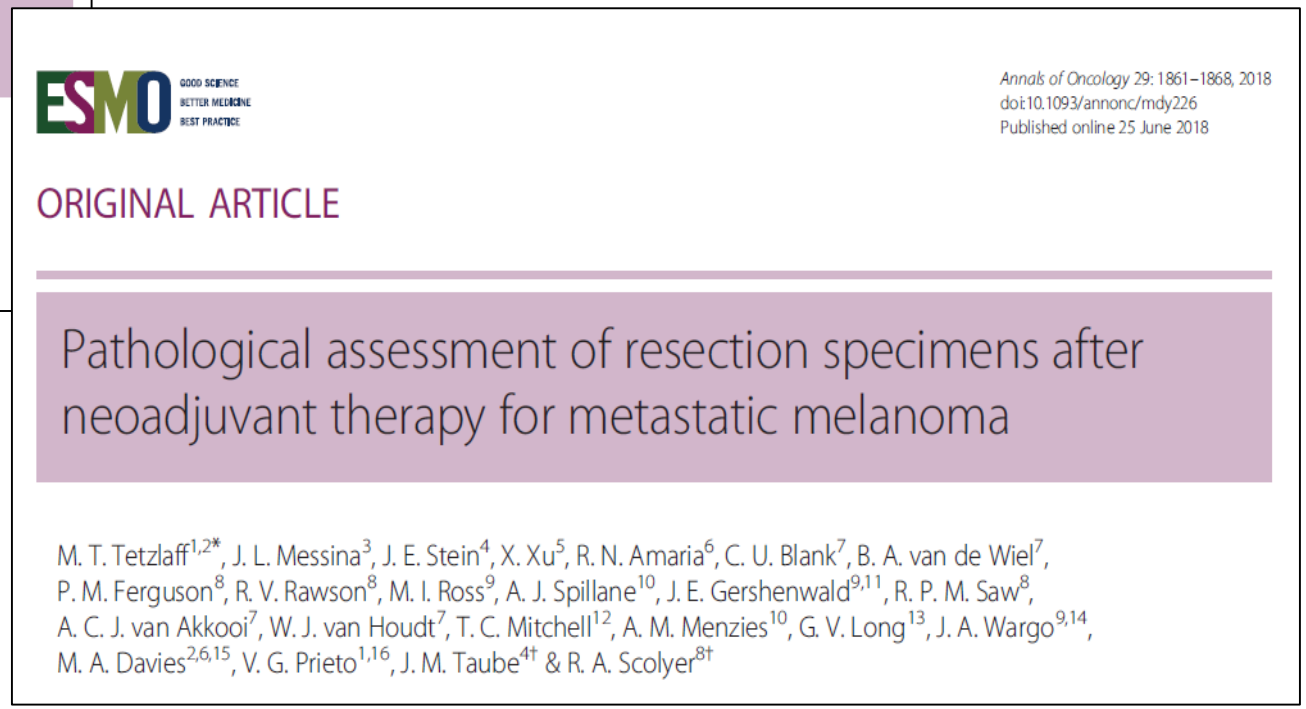
Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy218
Published online 6 June 2018

ORIGINAL ARTICLE

Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC)

T. R. Cottrell[1], E. D. Thompson[1,2,3], P. M. Forde[2,3], J. E. Stein[4], A. S. Duffield[1], V. Anagnostou[2], N. Rekhtman[5], R. A. Anders[1,3], J. D. Cuda[1,4], P. B. Illei[1,2], E. Gabrielson[1,2], F. B. Askin[1], N. Niknafs[2], K. N. Smith[2,3], M. J. Velez[5], J. L. Sauter[5], J. M. Isbell[6], D. R. Jones[6], R. J. Battafarano[7], S. C. Yang[7], L. Danilova[3,8], J. D. Wolchok[9,10,11], S. L. Topalian[3,7], V. E. Velculescu[2,3], D. M. Pardoll[2,3], J. R. Brahmer[2,3], M. D. Hellmann[10,11,12], J. E. Chaft[10,12], A. Cimino-Mathews[1,2] & J. M. Taube[1,2,3,4,*]

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



Annals of Oncology 29: 1861–1868, 2018
doi:10.1093/annonc/mdy226
Published online 25 June 2018

ORIGINAL ARTICLE

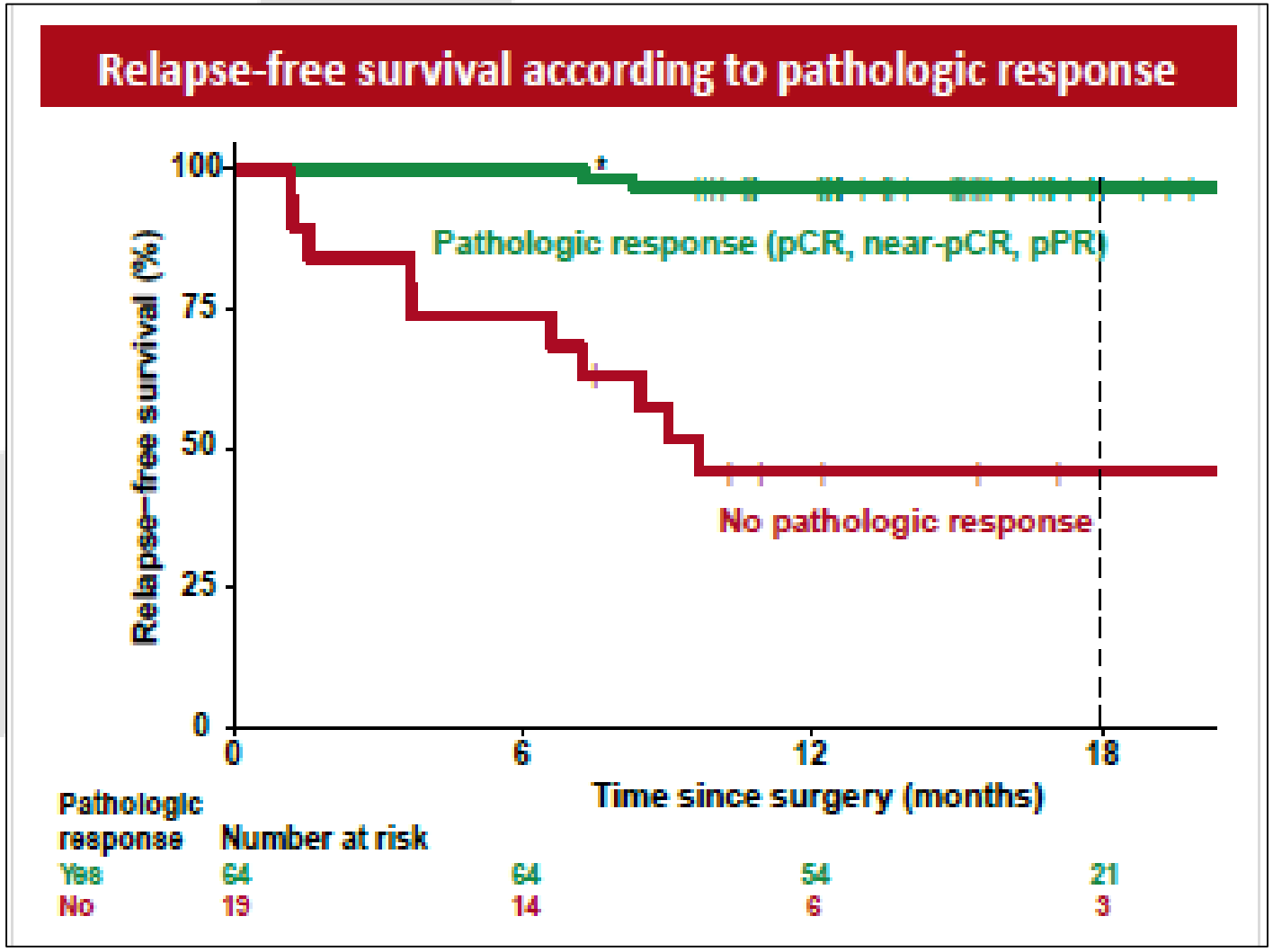
Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

M. T. Tetzlaff[1,2*], J. L. Messina[3], J. E. Stein[4], X. Xu[5], R. N. Amaria[6], C. U. Blank[7], B. A. van de Wiel[7], P. M. Ferguson[8], R. V. Rawson[8], M. I. Ross[9], A. J. Spillane[10], J. E. Gershenwald[9,11], R. P. M. Saw[8], A. C. J. van Akkooi[7], W. J. van Houdt[7], T. C. Mitchell[12], A. M. Menzies[10], G. V. Long[13], J. A. Wargo[9,14], M. A. Davies[2,6,15], V. G. Prieto[1,16], J. M. Taube[4†] & R. A. Scolyer[8†]

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?

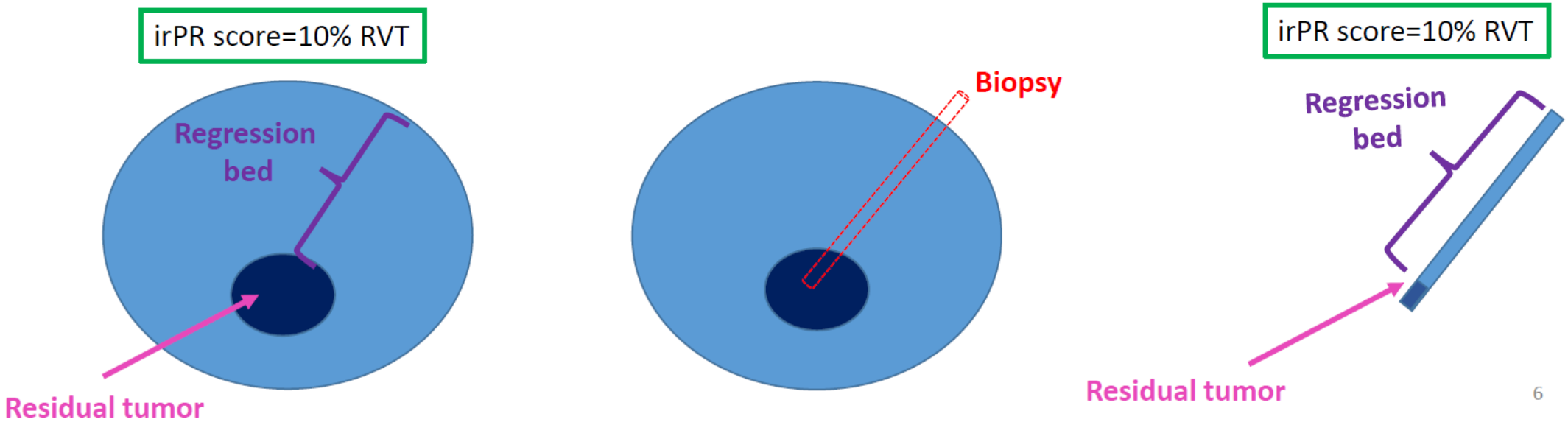
OpACIN-neo



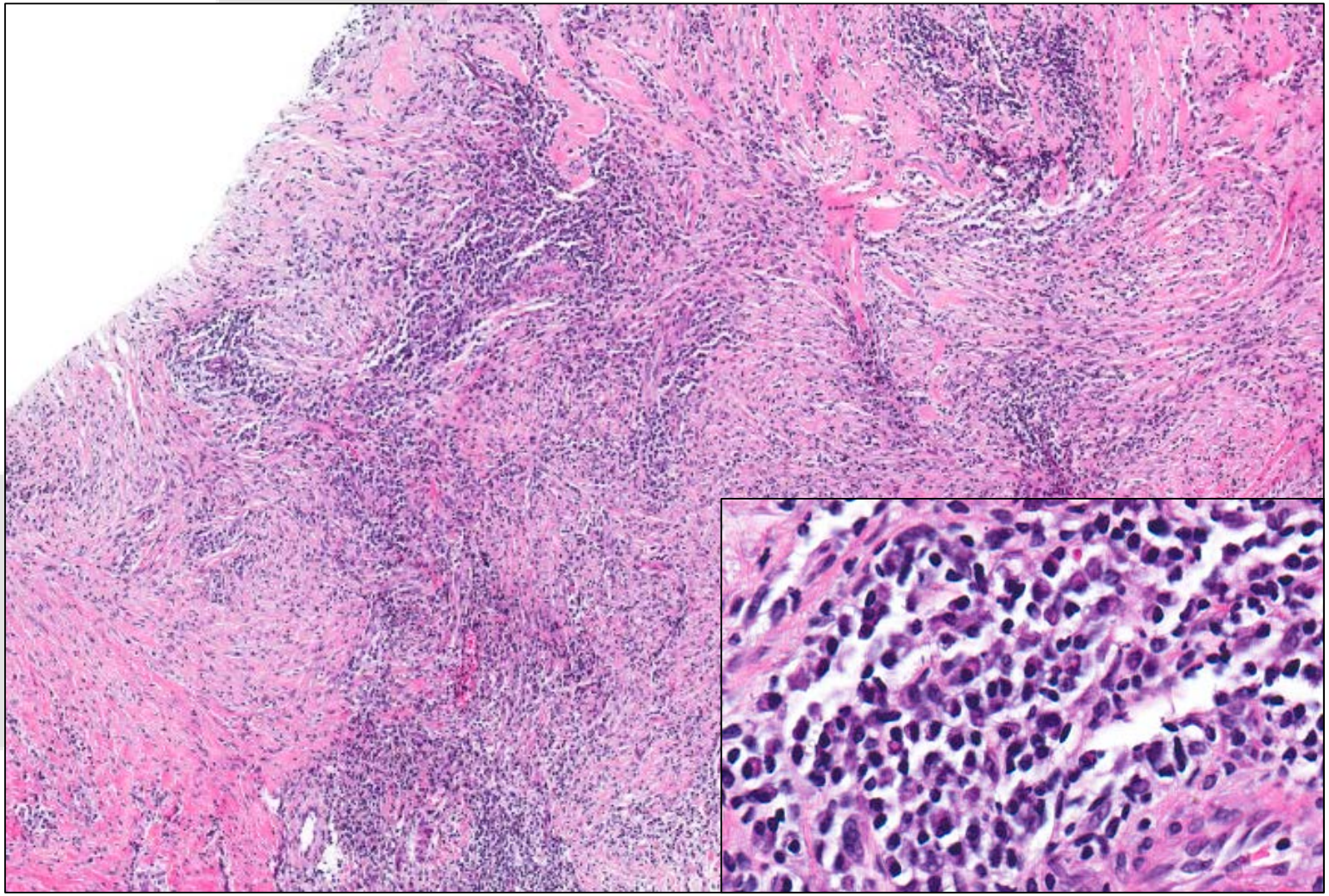
Rozeman, Menzies, ….Long, Blank, et al. ESMO 2019

New concept

MPR_{bx} = Major pathologic response (MPR, ≤10% residual viable tumor) assessed on biopsy, rather than definitive surgical resection

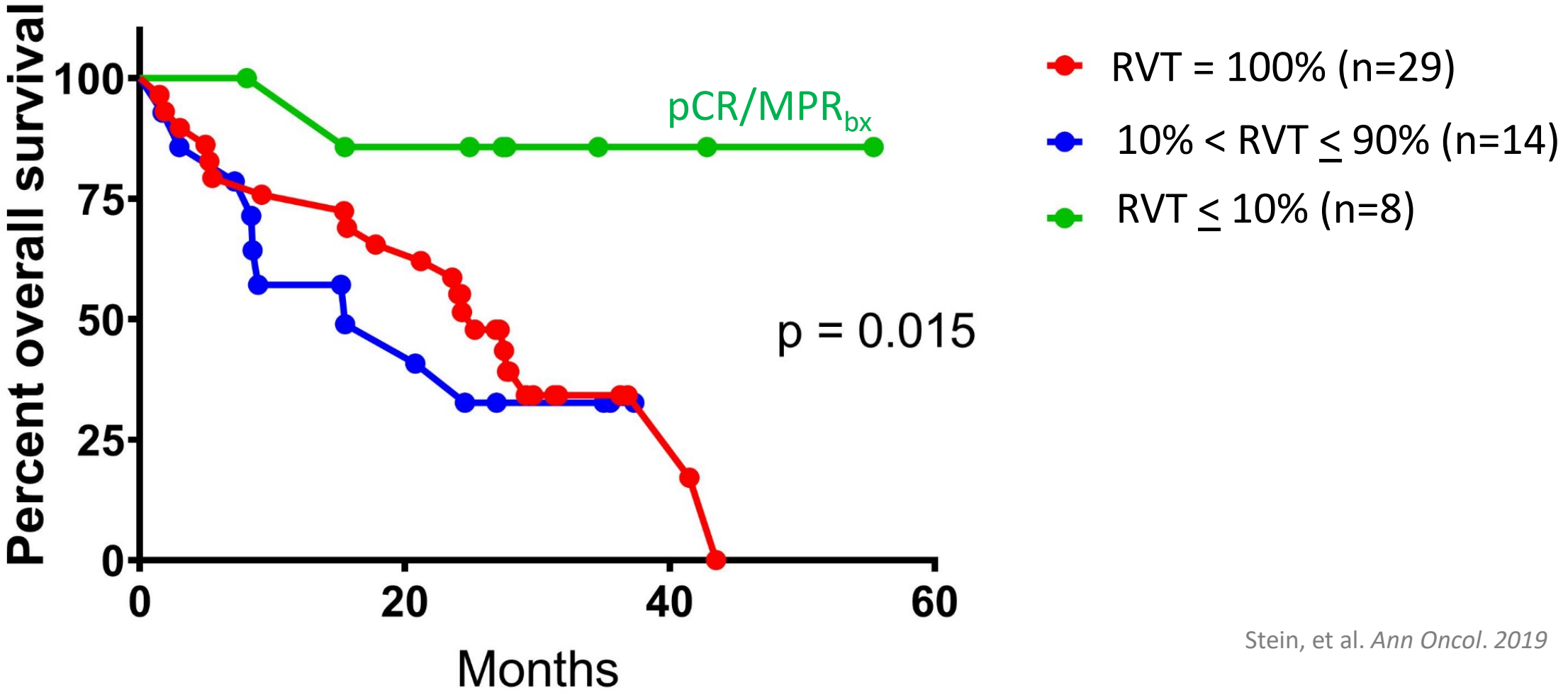


pCR_{bx} or MPR_{bx}



Complete pathologic response
or major pathologic response on biopsy specimen (≤10% residual viable tumor)

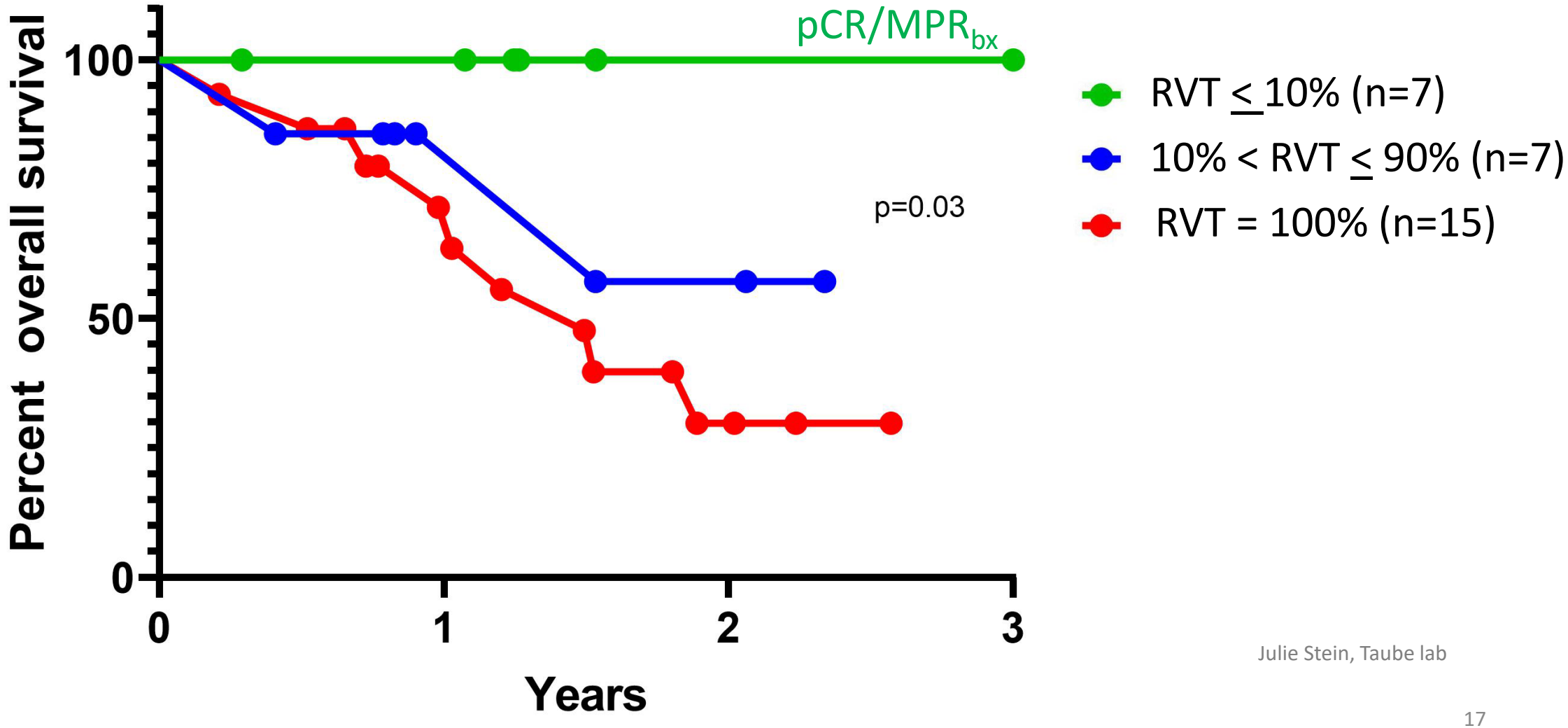
Discovery cohort:
51 biopsies from CA209-038 cohort, median of 4 weeks (range of 22-36 days) on anti-PD-1 therapy



Stein, et al. *Ann Oncol*. *2019*

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

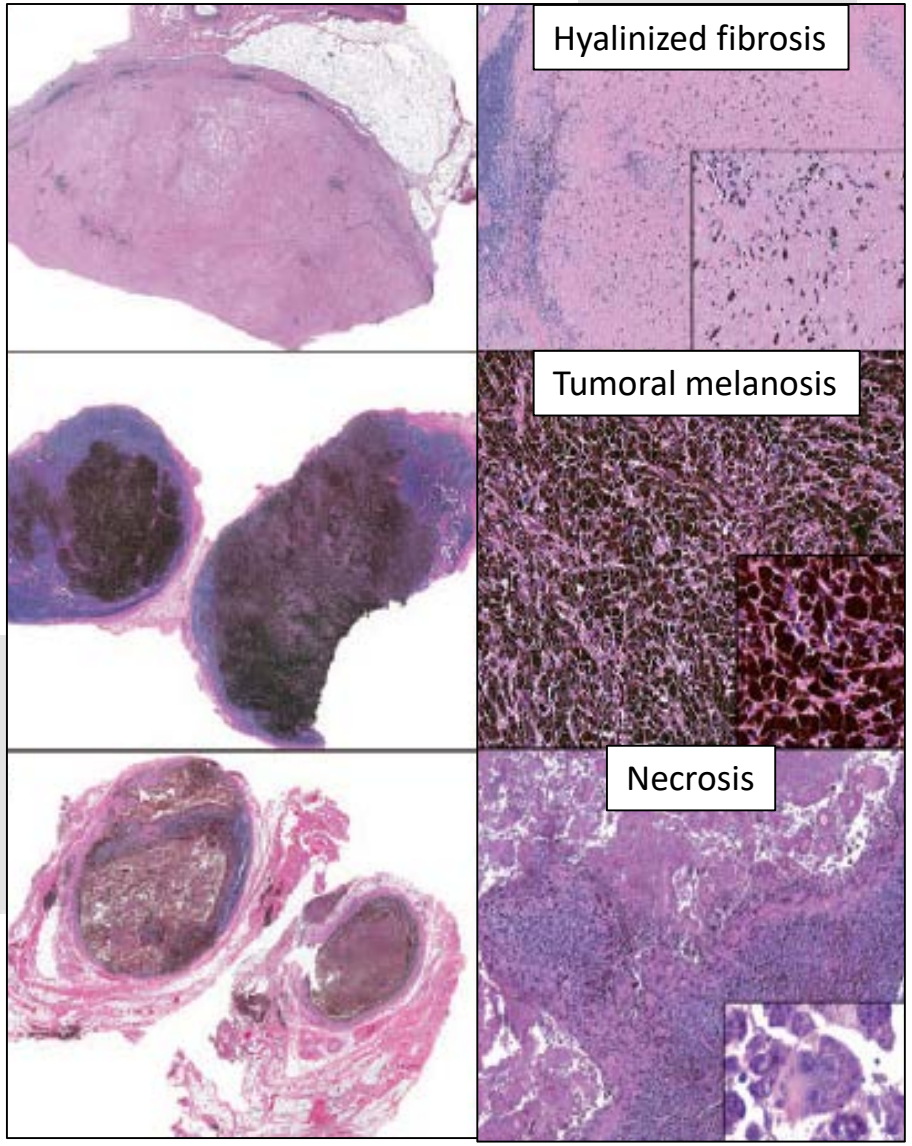


Julie Stein, Taube lab

Overview

- Immunotherapy
- Targeted therapy

Targeted therapy (Dabrafenib + Trametinib) in the neoadjuvant setting



Tetzlaff, *Ann Oncol*, 2018

<u>Ongoing analyses</u>:

- Early on-treatment bx compared to resection specimen.
- Assessing distinct histologic features that are associated with disease progression, following pathologic “response”.

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.

Future Directions

Pan-tumor scoring system for pathologic response

- 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

Treatment Setting	Tumor type	Treatment	NCT*
Neoadjuvant	Cervical cancer	Nivolumab	NCT02488759
	Head and neck squamous cell carcinoma	Nivolumab	NCT02488759[1]
	Melanoma	Nivolumab	NCT02519322[2,3]
	Merkel cell carcinoma	Nivolumab	NCT02488759[4]
	Non-small-cell lung carcinoma	Nivolumab	NCT02259621[5,6]
	Renal cell carcinoma	Nivolumab	NCT02575222
	Vulvovaginal carcinoma	Nivolumab	NCT02488759
Advanced Unresectable Disease	Basal cell carcinoma	Nivolumab	NCT03521830
	Cervical cancer	Nivolumab	NCT02488759
	Cutaneous squamous cell carcinoma	Pembrolizumab; nivolumab	Off-label
	Head and neck squamous cell carcinoma	Nivolumab	NCT02488759
	Melanoma	Nivolumab; pembrolizumab	NCT01621490[7]; standard of care
	Merkel cell carcinoma	Nivolumab	NCT02488759
	Microsatellite instability-high colorectal cancer	Pembrolizumab	NCT01876511[8]
	Nasopharyngeal carcinoma	Nivolumab	NCT02488759
	Non-small-cell lung carcinoma	Nivolumab; pembrolizumab	Standard of care
	Renal cell carcinoma	Nivolumab	NCT01358721
	Vulvovaginal carcinoma	Nivolumab	NCT02488759

Stein, et al *Clin Can Res*, 2019

Pan-tumor pathologic response assessment for neoadjuvant immunotherapy

Potomac Ballroom at the Westin National Harbor

Wednesday, November 6, 2019

2:15-3:15 pm

Society for Immunotherapy of Cancer

Acknowledgements

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BMS

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- Megan Wind-Rotolo

Academic Collaborators

- Michael Tetzlaff
- Richard Scolyer
- Bart van de Wiel
- Margaret Callahan
- George Xu
- Georgina Long

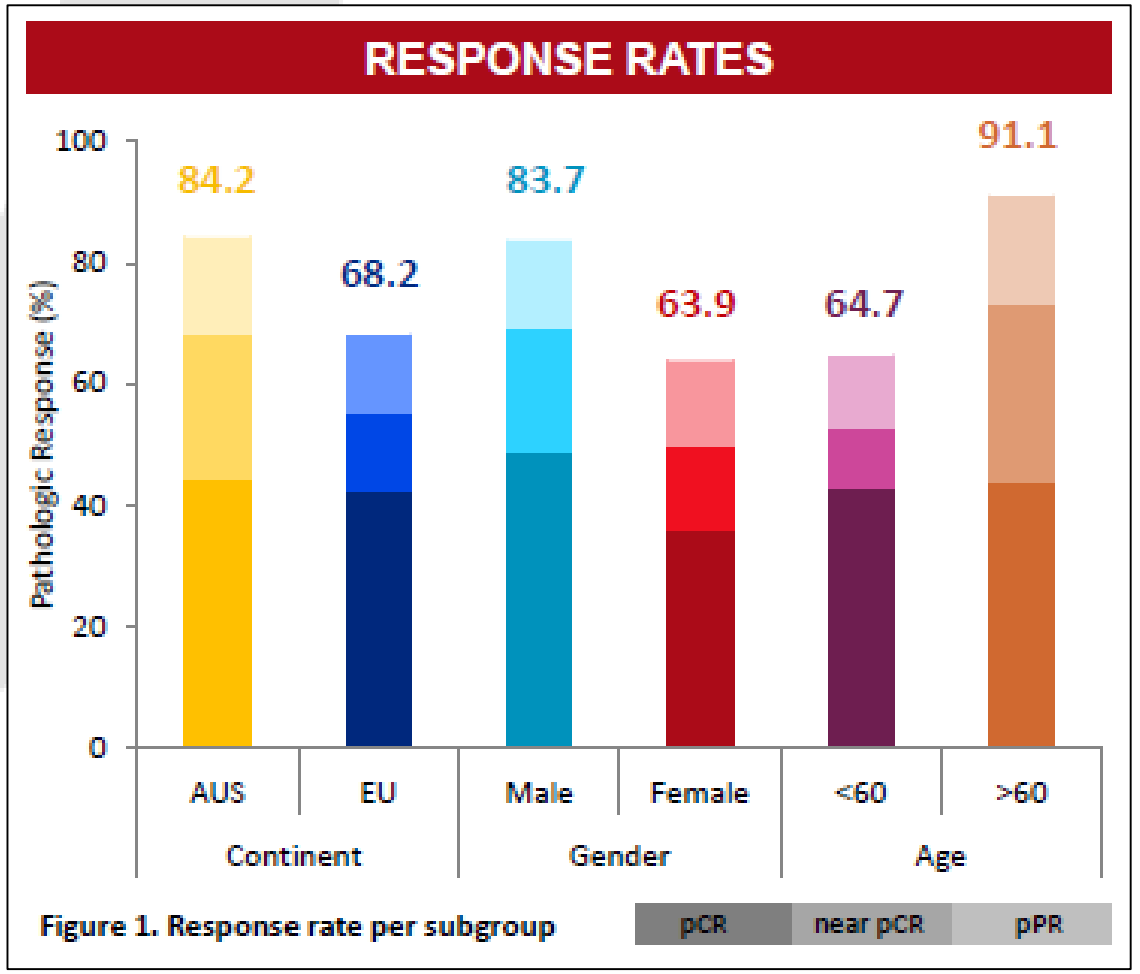

Figure 1. Response rate per subgroup

Reijers, Rozeman, Blank, et al. ESMO 2019