Surrogate Endpoints for ICIs in Early-Stage Melanoma: Does an MPR Reliably Predict Patient Outcomes?

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No Relevant Conflicts of Interest to Disclose

I am currently performing central pathology review of neoadjuvant treated surgical specimens for an active clinical trial sponsored by Merck. These trials (design, results, etc.) will not be discussed today.

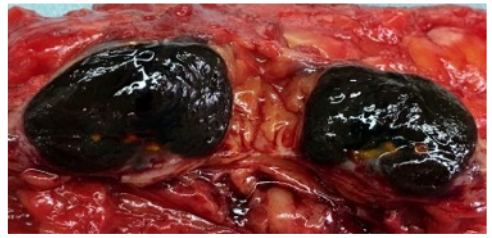
Statement From the Presenter

Neoadjuvant Trial Strategies in Melanoma

Surgically resectable
Stage IIIB-C

Treatment with targeted or immune checkpoint blockade

Surgical resection



Evaluation of the resection specimen

Treatment with targeted or immune checkpoint blockade

- The central premise and advantages of neoadjuvant therapy are the extent to which tumor cells respond to a particular agent:
  - Provides an interval assessment of response that (ideally):
    - Correlates with measures of clinical outcome (PFS, DSS, OS)
    - Guides subsequent treatments in the adjuvant setting
    - Provides tissue for biomarker studies

Neoadjuvant Trial Strategies in Melanoma: *Challenges Faced in Early Trials*

Trial	Population	Regimen	N
NCT02231775 Amaria et al Lancet Oncol 2018	Clinical stage III, resectable IV BRAF V600E/K	Dab/Tram x8w → surgery → Dab/Tram x44w	21
NCT01972347 Long et al Lancet Oncol 2019	Clinical stage III BRAF V600 E/K	Dab/Tram x12w → surgery → Dab/Tram x40w	35
NCT02437279 Blank et al Nat Med 2018	Clinical stage III	I3N1 x2 → surgery → I3N1 x2	10
NCT02519322 Amaria et al Nat Med 2018	Clinical stage III, resectable IV	A: Nivo x4 → surgery → Nivo x13 B: I3N1 x3 → surgery → Nivo x13	A: 12 B: 11
NCT02434354 Huang et al Nat Med 2019	Clinical stage III, resectable IV	Pembro x1 → surgery → Pembro x17	30
NCT02977052 Rozeman et al Lancet Oncol 2019	Clinical stage III	A: I3N1 ×2 → surgery B: I1N3 ×2 → surgery C: Ipi x2 – Nivo ×2 → surgery	A: 30 B: 30 C: 26

- Multiple independent efforts
- Small numbers of patients in each study
- Differing designs
  - Populations
  - Duration

Amaria RN, et al. *Lancet Oncol.* 2018;19(2):181-193.
Long GV, et al. *Lancet Oncol.* 2019;20(7):961-971.
Blank CU, et al. *Nat Med.* 2018;24(11):1655-1661.
Amaria RN, et al. *Nat Med.* 2018;24(11):1649-1654.
Huang AC, et al. *Nat Med.* 2019;25(3):454-461.
Rozeman EA, et al. *Lancet Oncol.* 2019;20(7):948-960.

Neoadjuvant Trial Strategies in Melanoma:
International Neoadjuvant Melanoma Consortium

Come together to harmonize efforts!!

INTERNATIONAL NEOADJUVANT MELANOMA CONSORTIUM
INMC

Our Mission

The International Neoadjuvant Melanoma Consortium (INMC) was established in order to bring together key stakeholders across multiple disciplines including medical oncology, surgical oncology, pathology, radiology, and translational research from institutions around the world with the goal of creating an organized approach into the investigation of neoadjuvant treatment in melanoma.

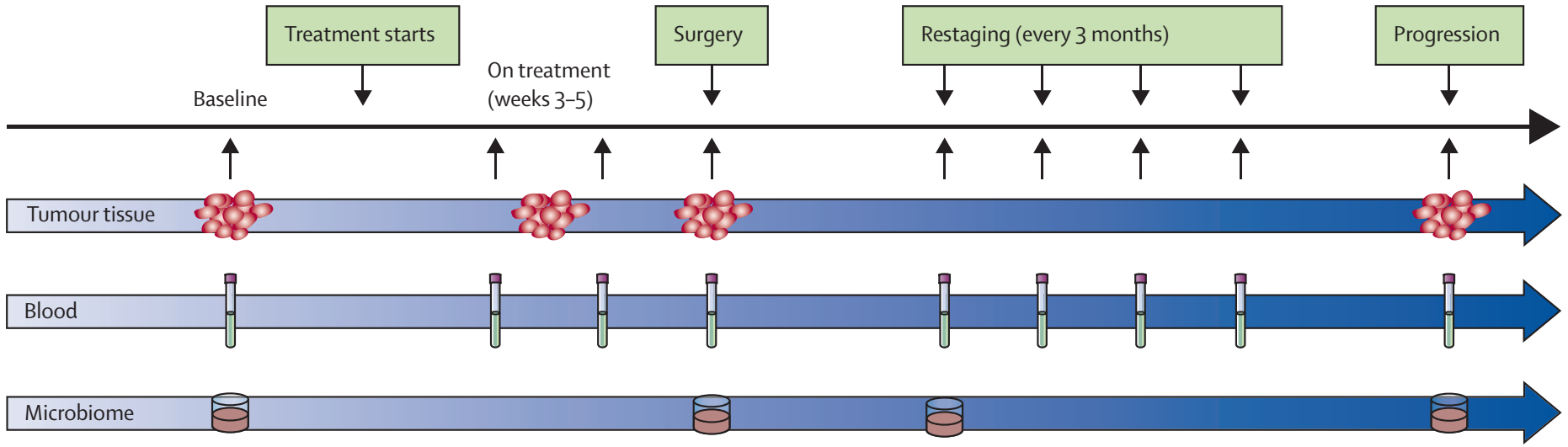
Through this mechanism and with a comprehensive approach to maximizing collaborative opportunities amongst investigators and institutions, the INMC seeks to advance treatment for patients with melanoma.

International Neoadjuvant Melanoma Consortium: *Harmonizing Trial Design*

Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

www.thelancet.com/oncology Vol 20 July 2019

Rodabe N Amaria, Alexander M Menzies*, Elizabeth M Burton*, Richard A Scolyer*, Michael T Tetzlaff*, Robert Antdbacka, Charlotte Ariyan, Roland Bassett, Brett Carter, Adil Daud, Mark Faries, Leslie A Fecher, Keith T Flaherty, Jeffrey E Gershenwald, Omid Hamid, Angela Hong, John M Kirkwood, Serigne Lo, Kim Margolin, Jane Messina, Michael A Postow, Helen Rizos, Merrick I Ross, Elisa A Rozeman, Robyn P M Saw, Vernon Sondak, Ryan J Sullivan, Janis M Taube, John F Thompson, Bart A van de Wiel, Alexander M Eggermont, Michael A Davies, The International Neoadjuvant Melanoma Consortium members†, Paolo A Ascierto‡, Andrew J Spillane‡, Alexander C J van Akkooi‡, Jennifer A Wargo‡, Christian U Blank‡, Hussein A Tawbi‡, Georgina V Long‡*



Amaria RN, et al. *Lancet Oncol.* 2019;20(7):e378-e389.

Challenges for Pathologists in Neoadjuvant Trials in Melanoma

- Pathologic complete response (pCR) is a fundamental endpoint in most clinical trials
  - What is the definition of complete pCR?
  - Be consistent about this early!

- How to process the tissue to determine pathologic response?
  - How much tissue do we need to examine to reliably determine extent of pCR?
  - Standardizing gross assessment facilitates comparison across trials

Challenges for Pathologists in Neoadjuvant Trials in Melanoma

- Pathologic complete response (pCR) is a fundamental endpoint
  i

Important lessons from early neoadjuvant trials in other cancer types: Lack of harmonization resulted in different definitions of pathologic response, nonuniform tissue processing, and thus different interpretations of those results.

- H
  - Standardizing gross assessment facilitates comparison across trials

International Neoadjuvant Melanoma Consortium
Harmonizing Pathologic Assessment

Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

Annals of Oncology 29: 1861–1868, 2018

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†]

- Most cases thus far consist of regional lymphadenectomy specimens +/- primary tumor
  - Primary lesion submitted in toto
  - Lymph nodes submitted according to size of largest nodes

Table 1. Quick reference guide to pathologic assessment of neoadjuvant treated melanoma specimens

Working definitions

- **Tumor bed**
  - The area of the tissue occupied by:
    - Viable tumor and/or
    - Evidence of tumoral regression, including:
      - Necrosis
      - Clusters/sheets of pigmented macrophages
      - Fibrosis/fibroinflammatory stroma
- **Pathologic complete response (pCR)**
  - Complete absence of viable tumor in the treated tumor bed
- ***Major PR/near pCR***
  - *< 10% of viable tumor in the treated tumor bed*
    - *This may represent a meaningful end point in the context of neoadjuvant immune checkpoint blockade*
- **Partial pathologic response (pPR)**
  - Less than 50% of the treated tumor bed is occupied by viable tumor cells. Note: percent tumor regression associated with improved patient outcomes for both targeted therapy and immunotherapy is an area of active investigation.

Gross evaluation of the surgical specimen after neoadjuvant therapy

- Three-dimensional macroscopic measurement of the ***largest grossly positive lymph node identified*** should be provided in the gross description.
- If the ***largest grossly positive lymph node measures ≤ 5 cm in greatest dimension:***
  - Each lymph node should be *submitted entirely at 3–4 mm serially sectioned intervals* (Figure 1A).
- For ***any grossly positive lymph node measuring > 5 cm in greatest dimension***, representative sections of the largest lymph nodes may be utilized.
  - For nodes >5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node (Figure 1B).
  - All lymph nodes <5 cm in specimens where the largest node(s) >5 cm should be submitted entirely (Figure 1A).

Microscopic templates:

(1) For viable melanoma

MELANOMA, METASTATIC TO **XX** OF **YY** LYMPH NODES (XX/YY).
Largest tumor deposit size:___×___mm[a]
Location: Subcapsular/Intraparenchymal
Extracapsular extension: Present/Not identified
See comment.

[a]For the measurements, we recommend including the following:

- Microscopic measurement of the largest deposit of continuous viable tumor in two dimensions (AA x BB mm)

(2) If no viable melanoma

FIBROSIS AND/OR NODULAR AGGREGATES OF PIGMENTED MACROPHAGES AND/OR (COMPLETELY) NECROTIC TUMOR CONSISTENT WITH MELANOMA (COMPLETELY REGRESSED WITH TREATMENT EFFECT), METASTATIC TO **XX** OF **YY** LYMPH NODES (XX/YY).
Largest tumor deposit size: ___×___mm (CORRESPONDS TO LARGEST AREA OF REGRESSED/NECROTIC MELANOMA—Gross measurement preferred over microscopic)
Location: Subcapsular/Intraparenchymal
Extracapsular extension: Present/not identified (corresponds to pigmented macrophages/fibrosis consistent with completely regressed melanoma)
See comment.

Comment:

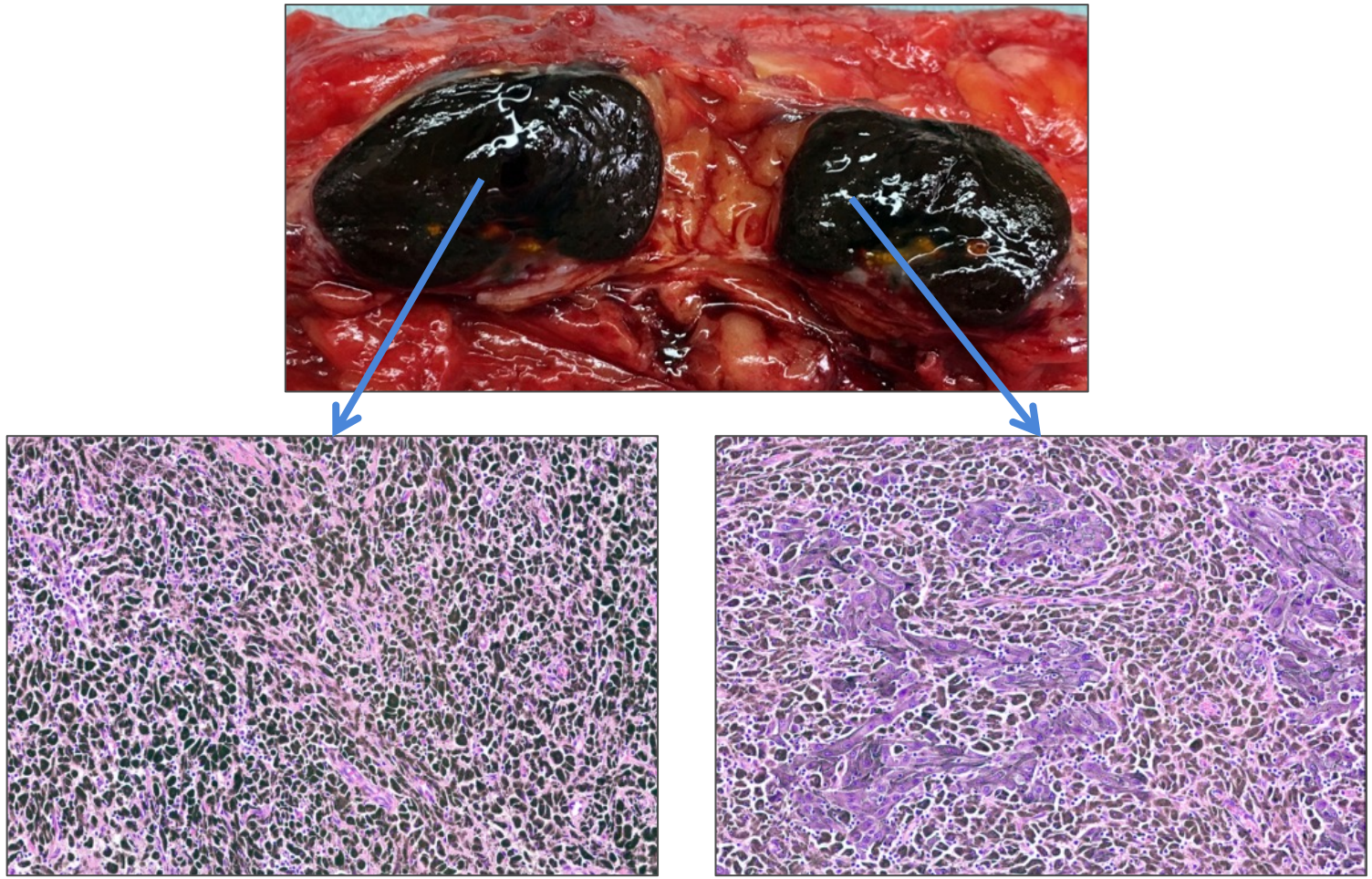
Sections reveal (viable/partially viable/completely regressed) melanoma involving XX of YY lymph nodes. An evaluation of the complete tumor bed reveals[a, b]:

- AA% viable tumor
  - *This would correspond to the % of the tumor bed surface area that is occupied by viable tumor cells*
- Tumoral melanosis/necrosis: Present/not identified
  - *Extent: (% of the tumor bed occupied by tumoral melanosis and pigmented macrophages/necrosis)*
- Fibrosis/fibroinflammatory stroma: Present/absent
  - Extent: (% of the tumor bed occupied by fibrosis/fibroinflammatory stroma)

[a]The sum of these three elements (% viable tumor, % tumoral melanosis/necrosis, and fibrosis/fibrinflammatory stroma should equal 100%).
[b]If multiple nodes or nodal basins are involved by disease (whether completely or partially necrotic), a summary statement should estimate the combined percentages of viable tumor cells, necrosis/melanosis and fibrosis occupying the surface area encompassed by the tumor bed comprising each of the involved nodes.

Tetzlaff MT, et al. *Ann Oncol.* 2018;29(8):1861-1868.

Determining Extent of Pathologic Response After Neoadjuvant Therapy in Melanoma Requires Careful Assessment



How much of the treated tumor bed consists of viable tumor?

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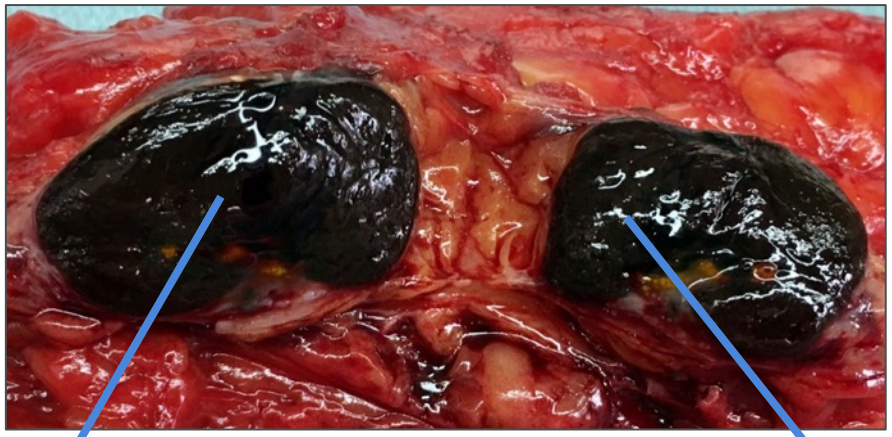
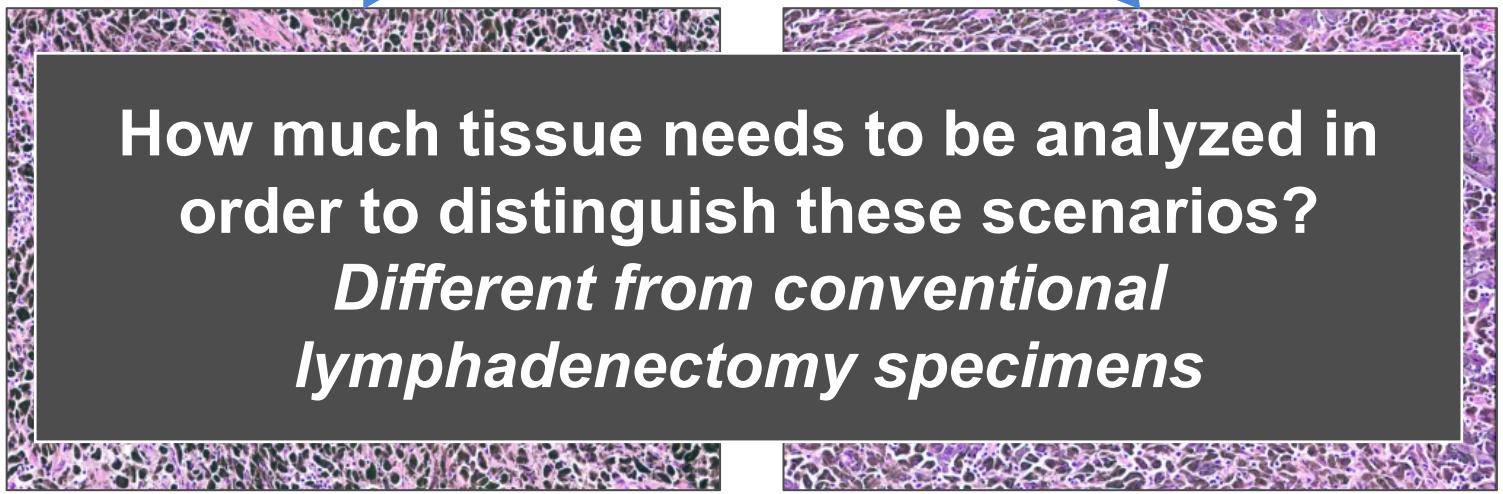
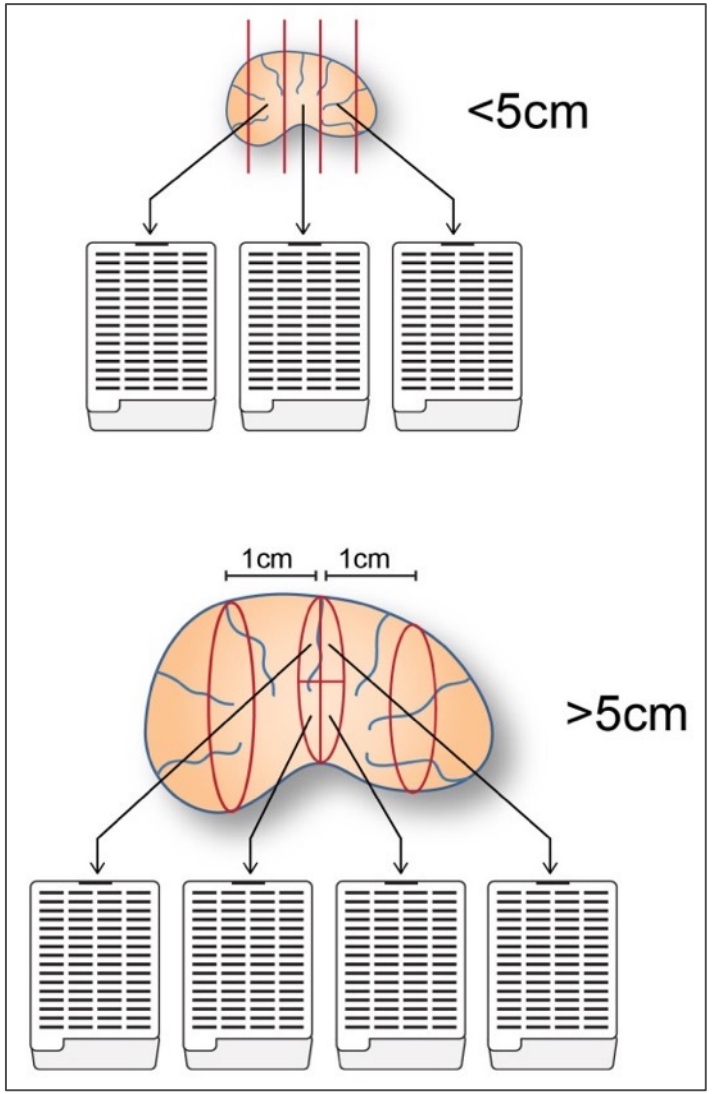
Determining Extent of Pathologic Response After Neoadjuvant Therapy in Melanoma Requires Careful Assessment



How much tissue needs to be analyzed in order to distinguish these scenarios?
Different from conventional lymphadenectomy specimens





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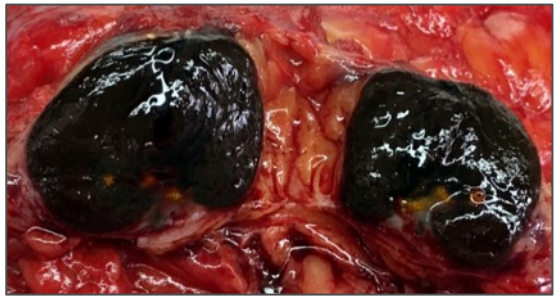

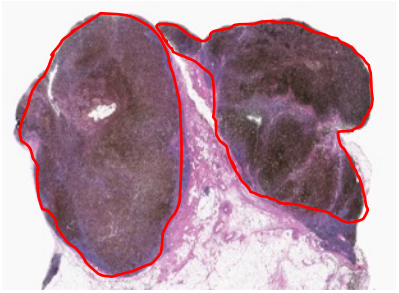

- **Definition of pathologic Complete Response (pCR)**
  - ***Complete absence of viable tumor in the treated tumor bed***
  - **May consist of a variable admixture of:**
    - **Fibrosis (hyalinized and/or proliferative)**
    - **Necrosis**
    - **Pigmented macrophages (tumoral melanosis)**
    - **Inflammatory infiltrate (composition)**
- **Definition of near pathologic Complete Response (near pCR)**
  - **Treated tumor bed occupied by ≤ 10% viable tumor**
- **Definition of partial Pathologic Response (pPR)**
  - **Tumor bed occupied by ≤ 50% viable tumor**
- **Definition of Pathologic non-Response (pNR)**
  - **Treated tumor bed occupied by > 50% viable tumor**

All of these are *empirical cutoffs that are not data driven or validated*

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Neoadjuvant Trial Strategies in Melanoma

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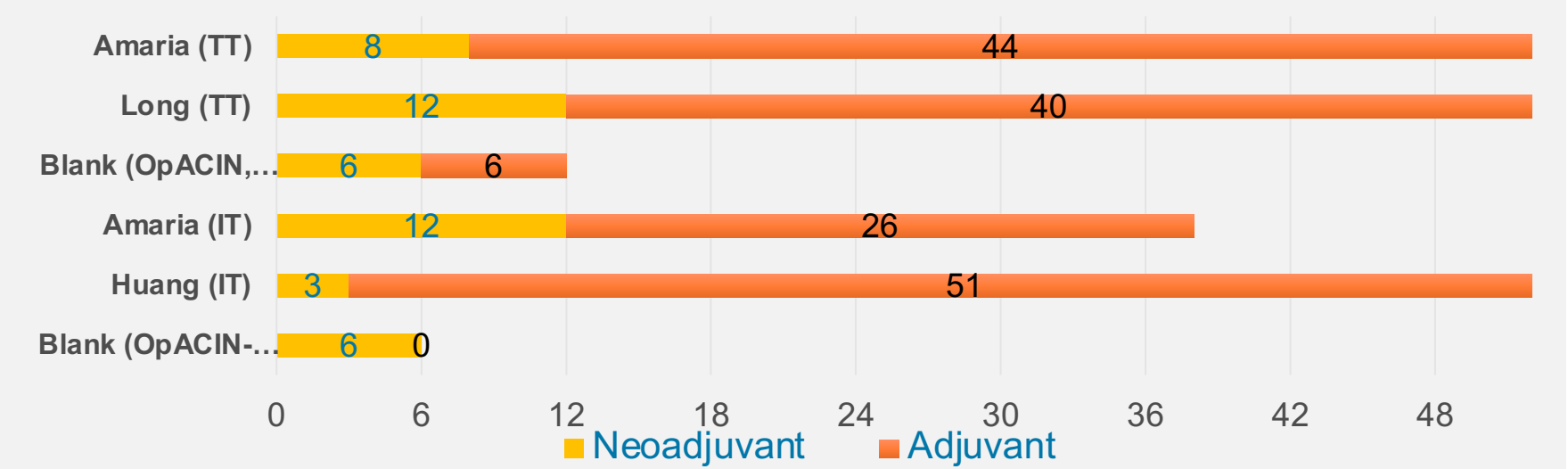

Menzies AM, et al. *Nat Med.* 2021;27(2):301-309.

Pooled analysis from all trials

Amaria RN, et al. *Lancet Oncol*. 2018;19(2):181-193.
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Blank CU, et al. *Nat Med*. 2018;24(11):1655-1661.
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Huang AC, et al. *Nat Med*. 2019;25(3):454-461.
Rozeman EA, et al. *Lancet Oncol*. 2019;20(7):948-960.

Survival (RFS) Differs According to Targeted Versus Immune Checkpoint Blockade and According to Pathologic Response

Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

NATURE MEDICINE https://doi.org/10.1038/s41591-020-01188-3

Alexander M. Menzies[1,2,3,12], Rodabe N. Amaria[4,12], Elisa A. Rozeman[5,12], Alexander C. Huang[6,7,12], Michael T. Tetzlaff[4,12], Bart A. van de Wiel[5,12], Serigne Lo[1,2,12], Ahmad A. Tarhini[8], Elizabeth M. Burton[4], Thomas E. Pennington[1,2,9], Robyn P. M. Saw[1,2,9], Xiaowei Xu[6], Giorgos C. Karakousis[6], Paolo A. Ascierto[10], Andrew J. Spillane[1,2,3], Alexander C. J. van Akkooi[5], Michael A. Davies[4,13], Tara C. Mitchell[6,13], Hussein A. Tawbi[4,13], Richard A. Scolyer[1,2,11,13], Jennifer A. Wargo[4,13], Christian U. Blank[5,13] and Georgina V. Long[1,2,3,13] ✉

- Pooled analysis from 6 trials
- 192 patients
  - 141 treated with immunotherapy
  - 51 treated with targeted therapy
- Pathological response categories
  - pCR = no viable tumor
  - near pCR ≤10% viable tumor
  - pPR ≤50% viable tumor
  - pNR >50% viable tumor

Baseline patient characteristics

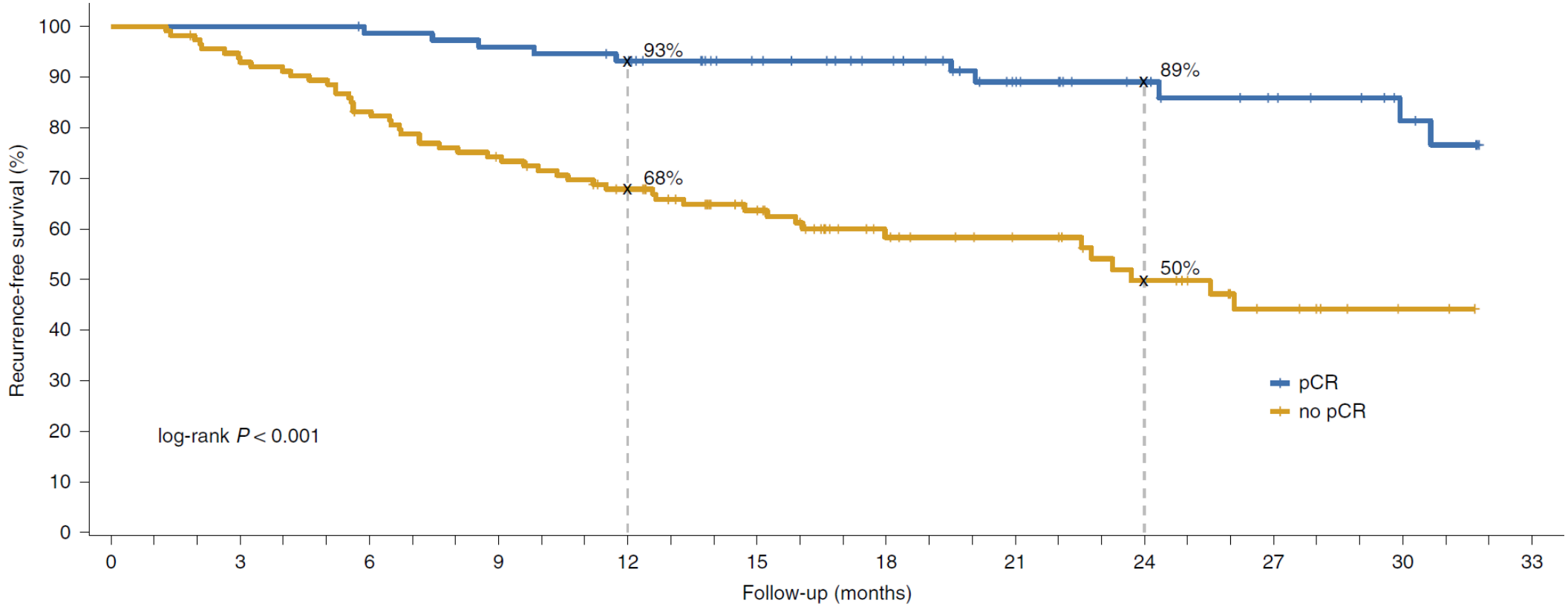
Characteristics	Overall ($n = 192$)	Immunotherapy ($n = 141$)	Targeted therapy ($n = 51$)	P value[a]
Sex				
Female	79 (41.1%)	54 (38.3%)	25 (49.0%)	0.182
Male	113 (58.9%)	87 (61.7%)	26 (51.0%)	
Age at NST start				
Median (range)	57.2 (18.0, 87.0)	58.0 (18.0, 85.0)	57.0 (22.2, 87.0)	0.423
BRAF status				
Wild type	60 (31.3%)	60 (42.6%)	0 (0.0%)	< 0.001
V600E	103 (53.6%)	55 (39.0%)	48 (94.1%)	
V600K	3 (1.6%)	0 (0.0%)	3 (5.9%)	
Other	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Unknown	25 (13.0%)	25 (17.7%)	0 (0.0%)	
NRAS status				
Wild type	136 (70.8%)	87 (61.7%)	49 (96.1%)	< 0.001
Mutated	27 (14.1%)	27 (19.1%)	0 (0.0%)	
Unknown	29 (15.1%)	27 (19.1%)	2 (3.9%)	
AJCC v7 stage (IIIB, IIIC)				
IIIB	100 (52.1%)	81 (57.4%)	19 (37.3%)	0.013
IIIC	92 (47.9%)	60 (42.6%)	32 (62.7%)	
Nodal disease sites				
Neck	36 (18.8%)	30 (21.3%)	6 (11.8%)	0.014
Multiple	11 (5.7%)	6 (4.3%)	5 (9.8%)	
Axilla[b]	81 (42.2%)	66 (46.8%)	15 (29.4%)	
Groin	63 (32.8%)	38 (27.0%)	25 (49.0%)	
Epitrochlear	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Baseline SoD targets (SoD largest node)				
Median (range)	22.0 (9.0, 65.0)	22.0 (9.0, 64.0)	24.0 (12.0, 65.0)	0.135
Time to surgery (weeks)				
Median (range)	7.0 (2.0, 28.0)	6.0 (2.0, 28.0)	10.0 (7.0, 23.0)	< 0.001
Post-surgery follow-up time (months)				
Median (range)	18.8 (1.1, 52.5)	17.9 (1.1, 41.9)	22.8 (9.5, 52.5)	< 0.001
Follow-up time from neoadjuvant therapy (months)				
Median (range)	20.9 (1.8, 54.2)	19.3 (1.8, 43.3)	25.9 (11.6, 54.2)	< 0.001

[a]Comparing immunotherapy to targeted therapy groups. [b]One patient had an epitrochlear node only. NST, neoadjuvant systemic therapy.

Menzies AM, et al. *Nat Med.* 2021;27(2):301-309.

Neoadjuvant Therapy for Melanoma

Recurrence-Free Survival Differs According to Extent of Pathological Response



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Neoadjuvant Therapy for Melanoma

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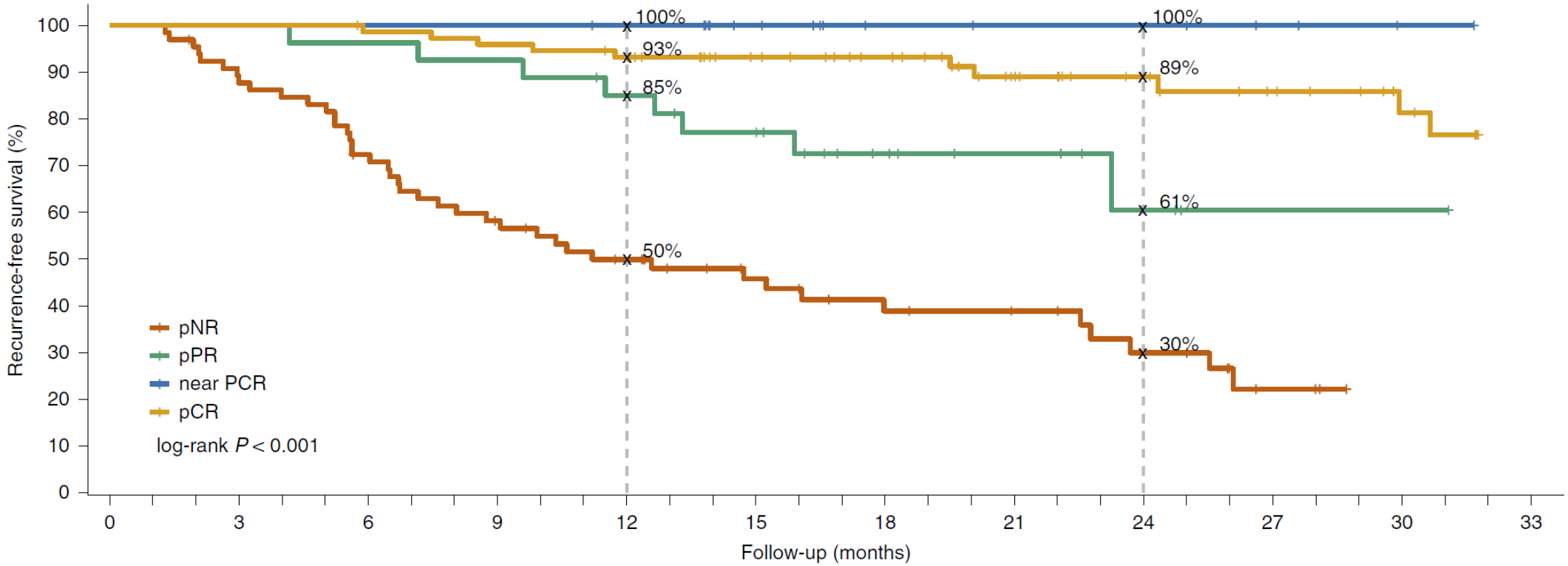

Numbers at risk

pNR	66	57	46	36	29	21	16	14	10	4	1	1
pPR	27	27	26	25	22	19	11	8	5	3	3	2
near PCR	21	21	21	21	20	15	9	8	8	6	4	3
pCR	75	75	73	71	68	58	52	39	29	24	18	13

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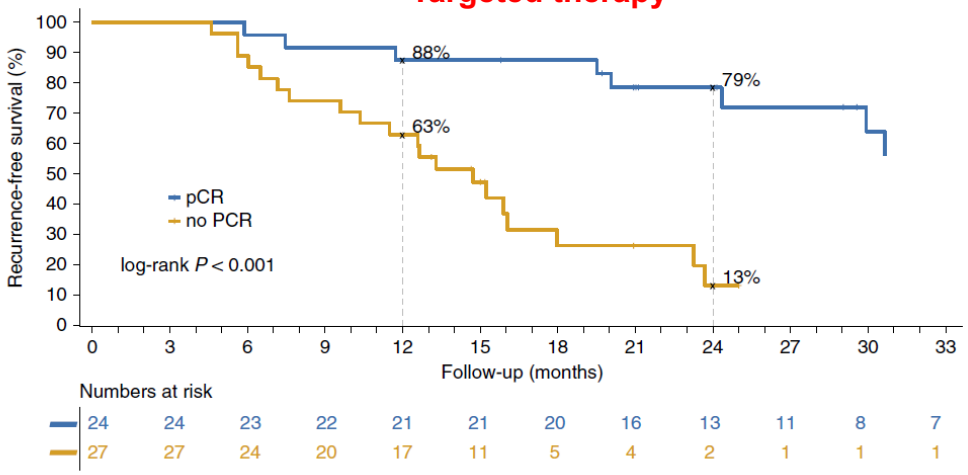
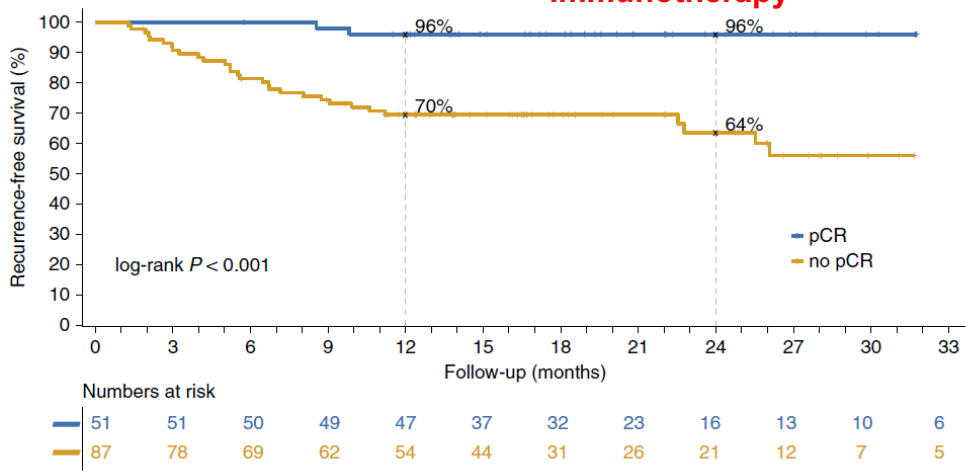
Neoadjuvant Therapy for Melanoma

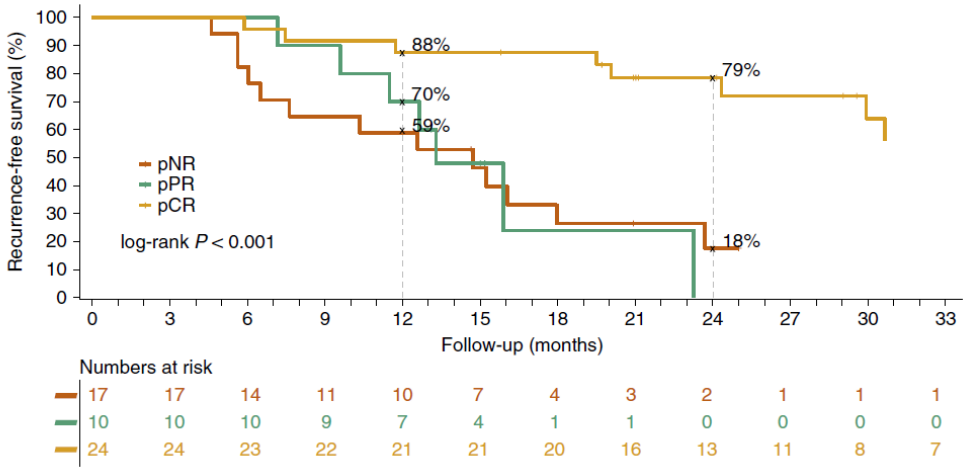
Recurrence-Free Survival Differs According to Pathological Response and Therapy

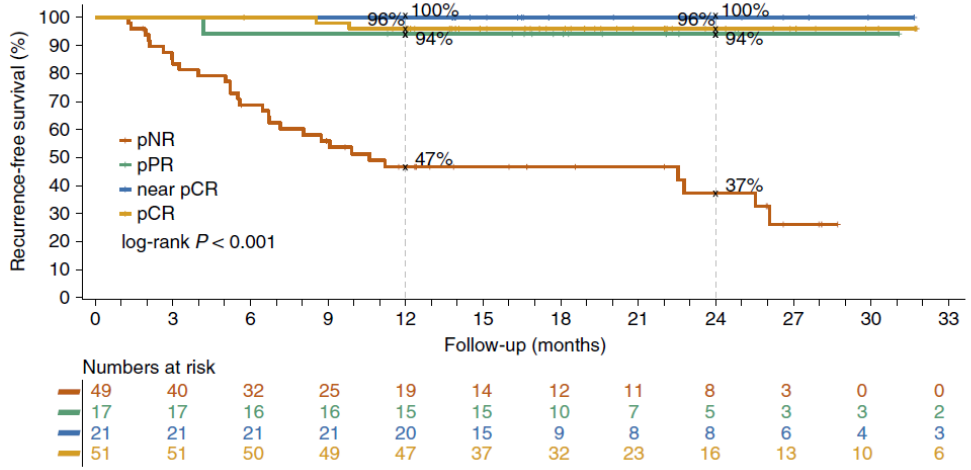
Targeted therapy



Immunotherapy







Underscores the importance of reliably establishing pathologic response

Menzies AM, et al. *Nat Med*. 2021;27(2):301-309.

Neoadjuvant Therapy in Melanoma and the Importance of the Pathologic Assessment

- Accurately determining the extent of pathologic response is critical to optimizing patient management and outcomes following neoadjuvant therapy in melanoma

- The extent of pathologic response correlates with RFS following neoadjuvant therapy
  - Immune checkpoint shows greater efficacy than targeted therapy
  - Achieving a pCR is more important in targeted therapy than immune checkpoint blockade

Thank You

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- Dr. Serigne Lo
- Dr. Georgina Long
- Dr. Alex Menzies
  - Melanoma Institute of Australia
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- Dr. Hussein Tawbi
- Dr. Michael A. Davies
- Dr. Roda Amaria
  - MDACC, Melanoma Medical Oncology

- Dr. Jeff Gershenwald
- Dr. Merrick Ross
- Dr. Jennifer Wargo
  - MDACC, Surgical Oncology, Genomic Medicine and Cancer Biology

- Dr. Fraser Symmans
  - MDACC, Pathology and Translational and Molecular Pathology

INTERNATIONAL NEOADJUVANT MELANOMA CONSORTIUM
INMC

- Dr. Phil LeBoit
- Dr. Thaddeus Mully
- Dr. Jeff North
- Dr. Laura Pincus
- Dr. Richard Jordan

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