Patient Selection and Risk:Benefit Considerations: An Oncologist's Perspective

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#MelanomaNeoadjuvant

Disclosures

Consultant: Amgen, Array, Astra Zeneca, Aveo, Boehringer-Ingelheim, BMS, Exelixis, Eisai, Ideera, ImmunoCore, Iovance, Merck, Newlink, Novartis, Genentech/Roche, Pfizer
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Topics To Cover

- Type of Trials
- Potential Benefits/Risks of Neoadjuvant Therapy
- Eligibility Criteria for Trials
- Patients Examples
- Future Considerations for such patients
  - Upfront systemic therapy with imaging endpoints and surgical salvage

Types of Neoadjuvant Trials

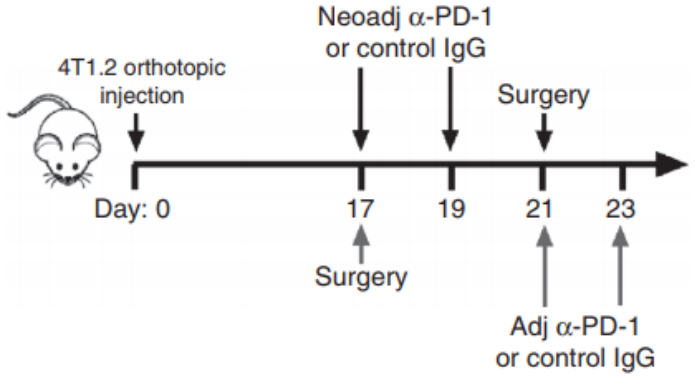
- Single arm or randomized trials where all get neoadjuvant therapy; surgery at a specified time (3-9 weeks)- RR (path CR), RFS, safety, biomarkers are major endpoints
- Randomized trials where patients get same therapy in either the neoadjuvant or adjuvant setting - RFS, OS, and safety are principal endpoints

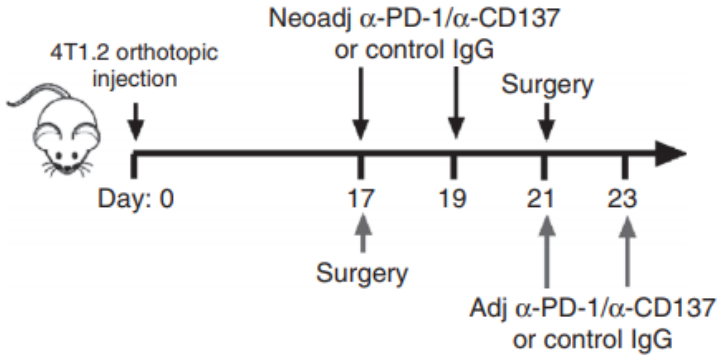
- Eligibility criteria might be different for these distinct trials

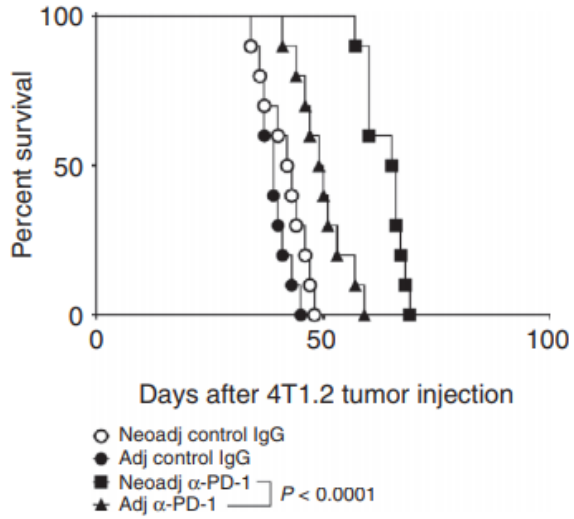
Potential Benefits of Neoadjuvant Treatment

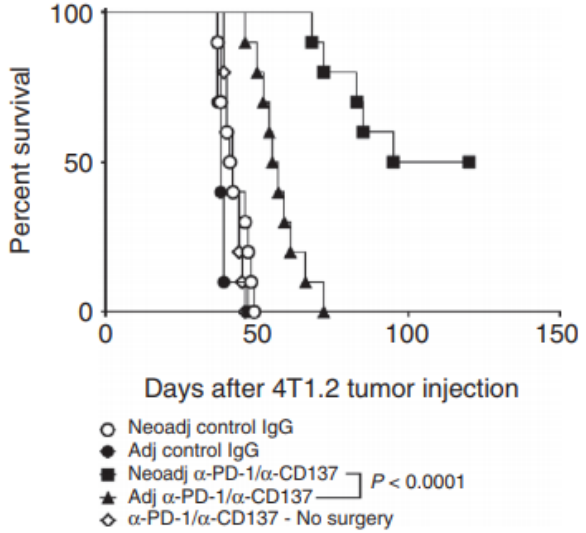
- Tumor shrinkage → decreased surgical morbidity
  - Potentially decreased need for surgery
- Destruction of micrometastases → prevention of distant disease spread
  - May be superior to adjuvant treatment (S1801 Trial)
- Objective measure of response to therapy → personalization of subsequent adjuvant therapy
- Opportunity to collect high-quality serial biospecimens to facilitate understanding of drug response and resistance; identify surrogate markers
- Potential pathway for new drug evaluation/registration
  - Expedite, rationalize combination drug regimen development
  - Ability to study intralesional therapies

Preclinical Data Suggest Neoadjuvant Checkpoint Inhibition Is Superior to Adjuvant Checkpoint Inhibition



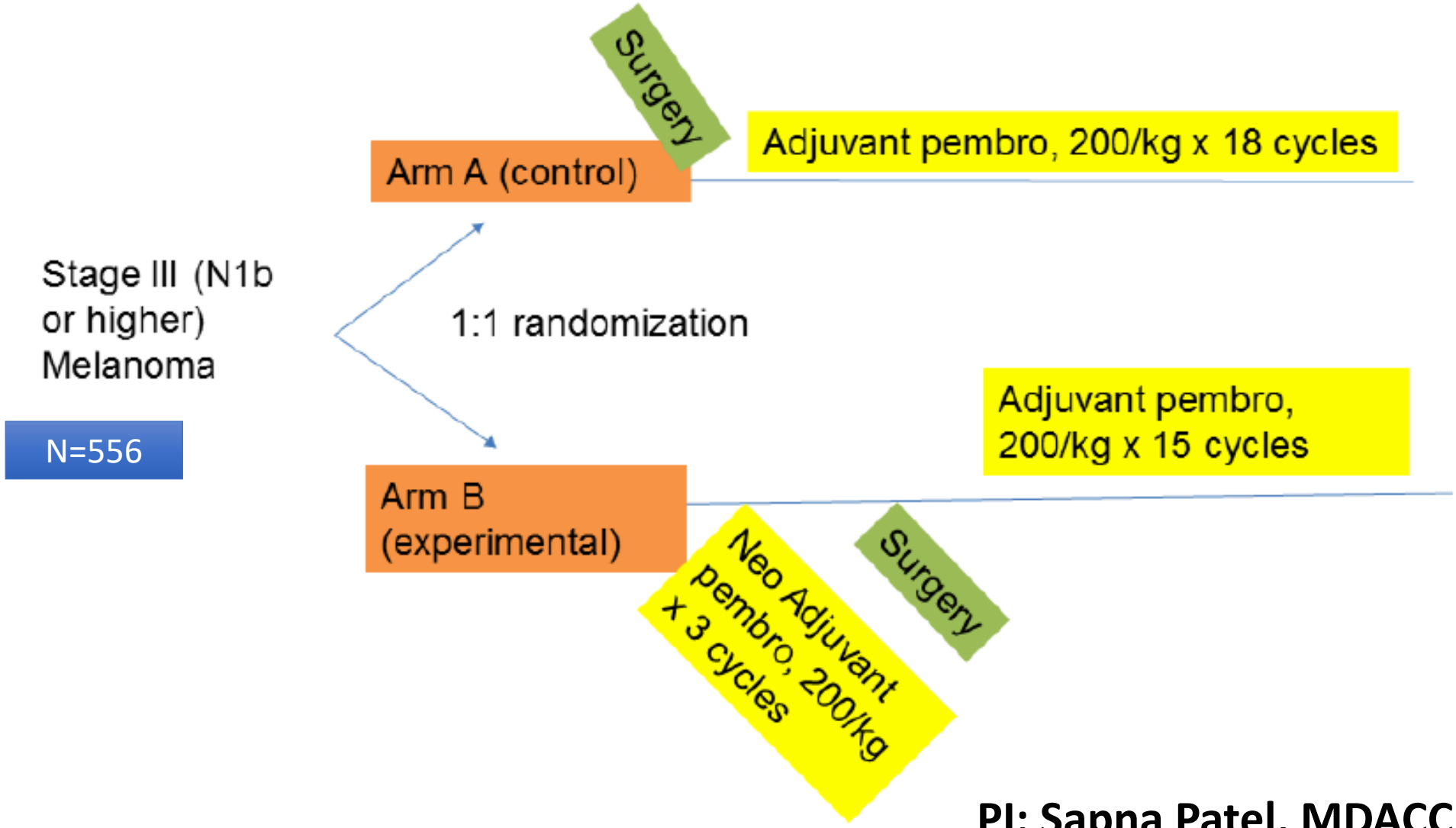






Liu. Cancer Discovery. 2016;6:1382.

S1801 Schema



PI: Sapna Patel, MDACC

Data cut-off date July 2nd, 2019
Median follow-up time: 28.4 months (n=167)

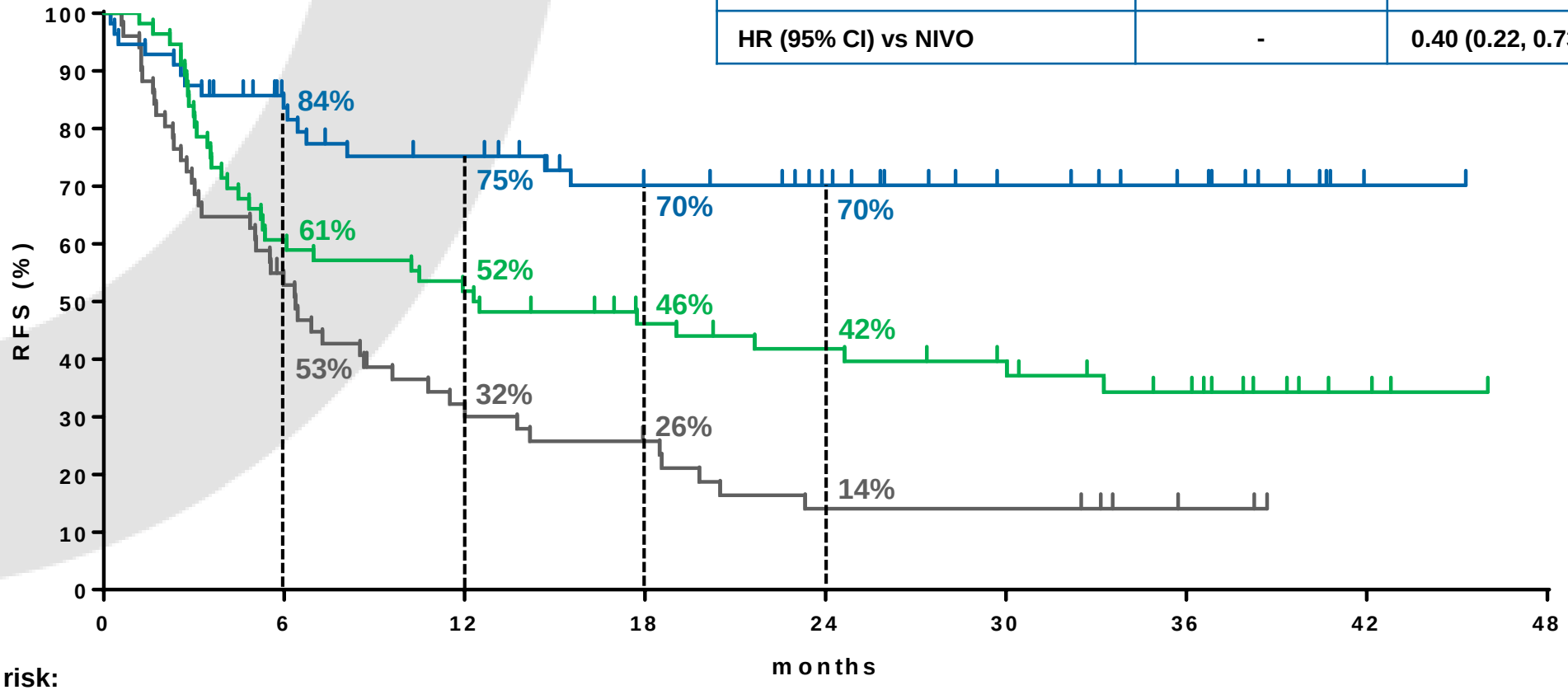
THE IMMUNED STUDY- STAGE IV NED

RFS in all patients

Schadendorf et al ESMO 2019

	NIVO (n=59)	NIVO+IPI (n=56)	Placebo (n=52)
Median RFS, mo (95% CI)	12.4 (5.30, 33.26)	NR[1]	6.4 (3.26, 9.61)
HR (95% CI) vs placebo	0.56 (0.36, 0.88)	0.23 (0.13, 0.41)	-
HR (95% CI) vs NIVO	-	0.40 (0.22, 0.73)	-

[1]NR: not reached



Patients at risk:

NIVO	59	34	29	22	19	16	11	3	-
NIVO + IPI	56	40	34	26	21	14	10	1	-
Placebo	52	26	15	11	6	6	2	-	-

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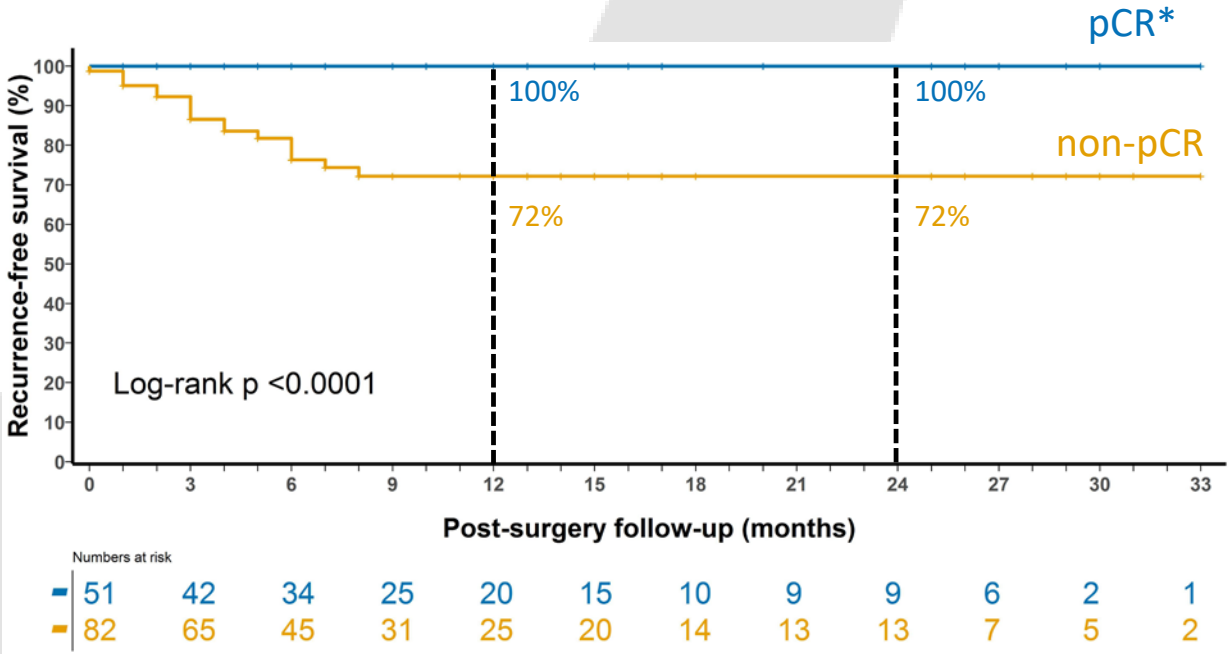
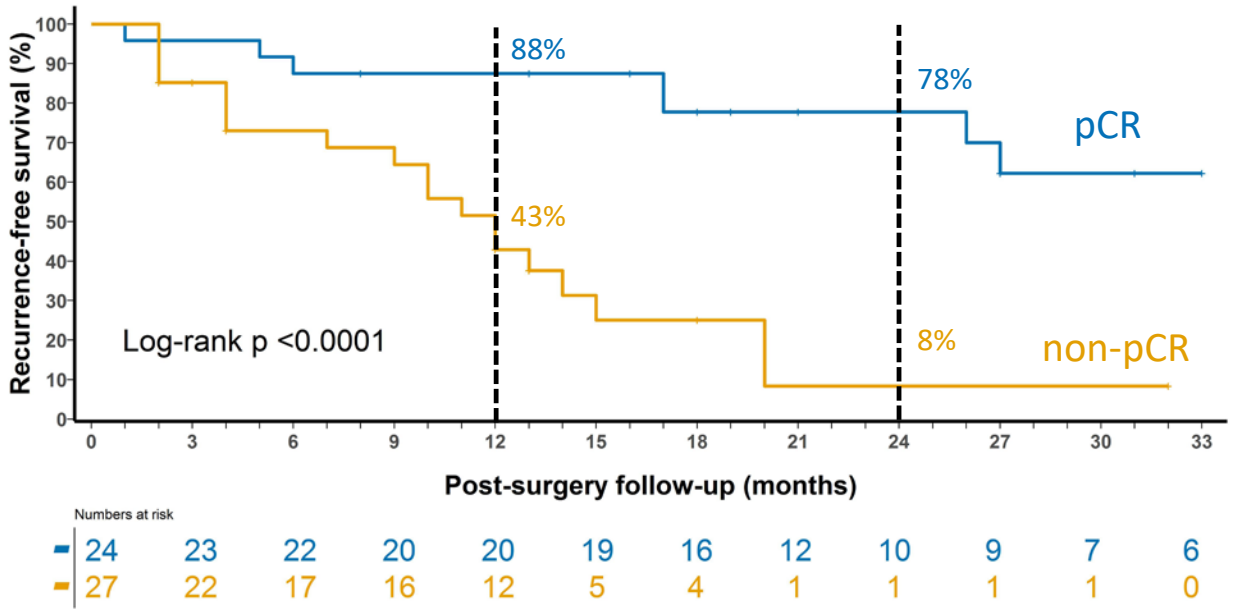
INMC Pooled Analysis of Neoadjuvant Trials: RFS by pathological response and drug

Immunotherapy



Med f/u 10 mo

Targeted Therapy



Med f/u 22 mo

Menzes Et al ASCO 2019

1 pt died from toxicity without recurrence, censored at time of death

Potential Benefits of Neoadjuvant Treatment

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Potential Risks of Neoadjuvant Therapy: Factors favoring Adjuvant Therapy

- Possible loss of some standard prognostic factors: LN #, tumor volume, etc
- Treatment toxicity may limit ability to undergo surgery at scheduled time (may be more than in Stage IV disease)
- Disease growth might make surgery more complicated/impossible
- Disease might spread to distant sites during delay in surgical therapy

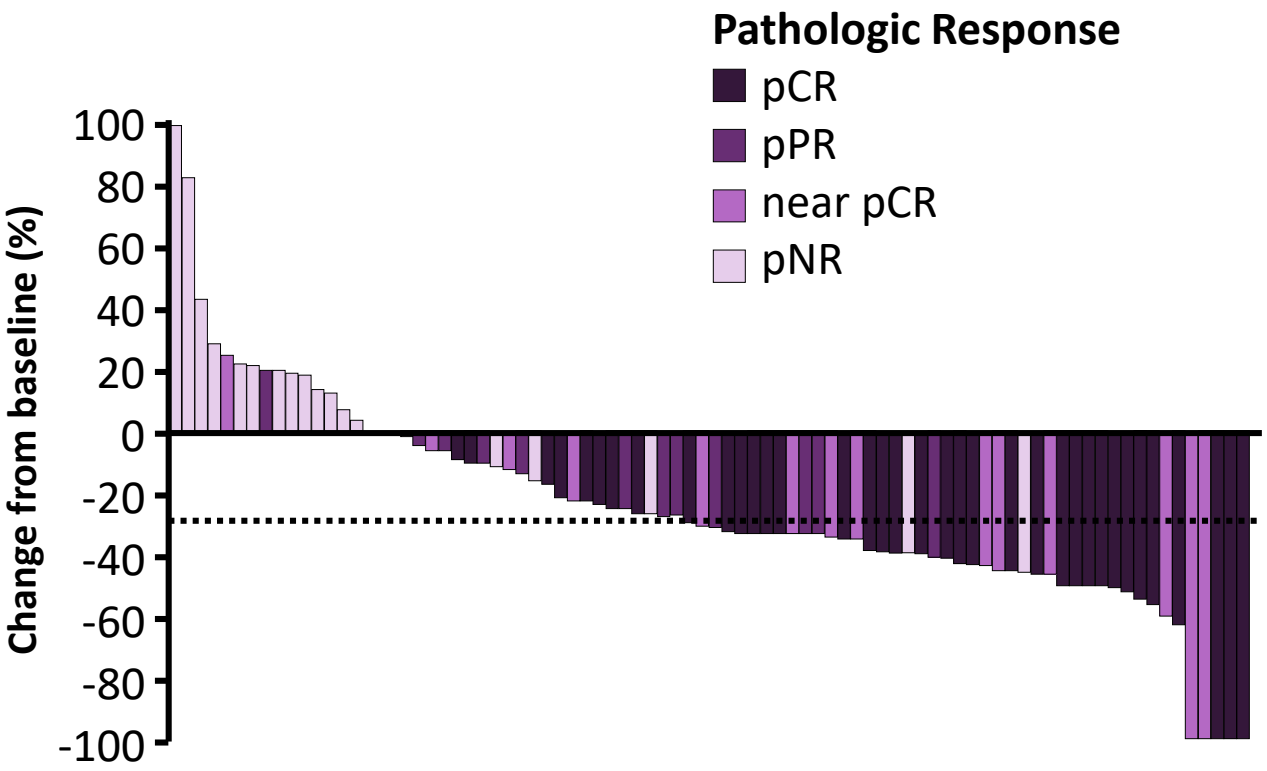
OpACIN-Neo: irAEs in First 12 Weeks

AE, n (%)	Nivo 1 mg/kg + Ipi 3 mg/kg (n=30)		Nivo 3 mg/kg + Ipi 1 mg/kg (n=30)		Ipi 3 mg/kg then Nivo 3 mg/kg (n = 26)	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
Any	**29 (97)**	**12 (40)**	**29 (97)**	**6 (20)**	**26 (100)**	**13 (50)**
Fatigue	19 (63)		17 (57)		14 (54)	
Rash	18 (60)	2 (7)	11 (37)	1 (3)	18 (69)	3 (12)
Pruritus	12 (40)		10 (33)		10 (38)	
ALT increased	12 (40)	6 (20)	6 (20)	1 (3)	9 (35)	2 (8)
Hyperthyroidism	12 (40)		2 (7)		9 (35)	1 (4)
Diarrhea	7 (23)	1 (3)	4 (13)	1 (3)	11 (42	3 (12)
Headache	8 (27)	1 (3)	5 (17)		4 (15)	
Fever	4 (13)		4 (13)	1 (3)	7 (27)	
Dry mouth	6 (20)		3 (10)		3 (12)	
Colitis	2 (7)	2 (7)	1 (3)		7 (27)	5 (19)
Hypothyroidism	5 (17)		2 (7)		3 (12)	
Nausea	4 (13)		1 (3)		4 (15)	1 (4)
Arthralgia	2 (7)		3 (10)		4 (15)	
Dry eye	2 (7)		3 (10)		2 (8)	
Flu-like symptoms	1 (3)		4 (13)		2 (8)	
Infusion related reaction			5 (17)		2 (8)	
Serum amylase increased	3 (10)	1 (3)	2 (7)	1 (3)	1 (4)	

AEs that occurred in ≥ 10% of patients.

Rozeman. ESMO 2018. Abstr LBA42.

OpACIN-Neo: Pathologic Responses



Pathologic Response: Central Review

Response, n (%)	Nivo 1 mg/kg + Ipi 3 mg/kg (n = 30)	Nivo 3 mg/kg + Ipi 1 mg/kg (n = 30)	Ipi 3 mg/kg Then Nivo 3 mg/kg (n = 26)
Overall	24 (80)	23 (77)	17 (65)
▪ pCR	14 (47)	17 (57)	6 (23)
▪ Near pCR	7 (23)	2 (7)	6 (23)
▪ pPR	3 (10)	4 (13)	5 (19)
▪ pNR	6 (20)	7 (23)*	8 (31)
▪ NE	-	-	1 (4)†

*n = 1, only palliative resection of largest lymph node. †Surgery not performed due to toxicity; patient had a radiologic CR.

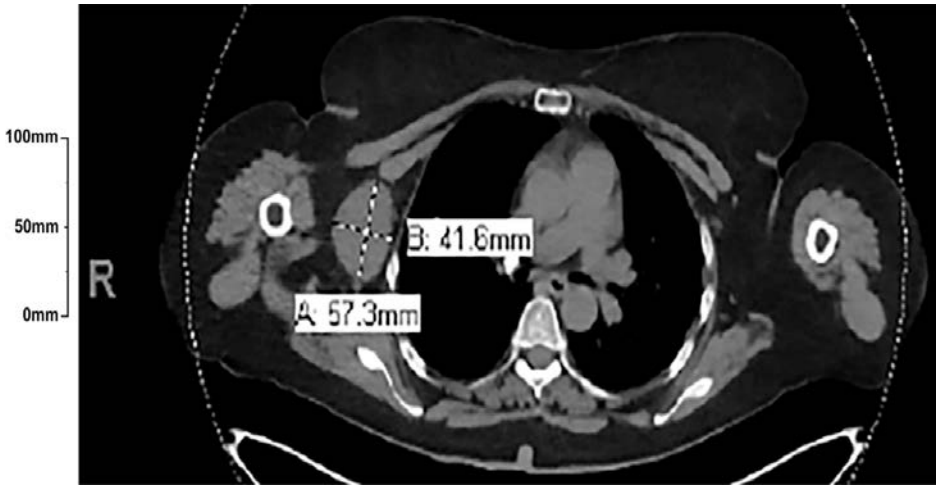
Rozeman. ESMO 2018. Abstr LBA42.

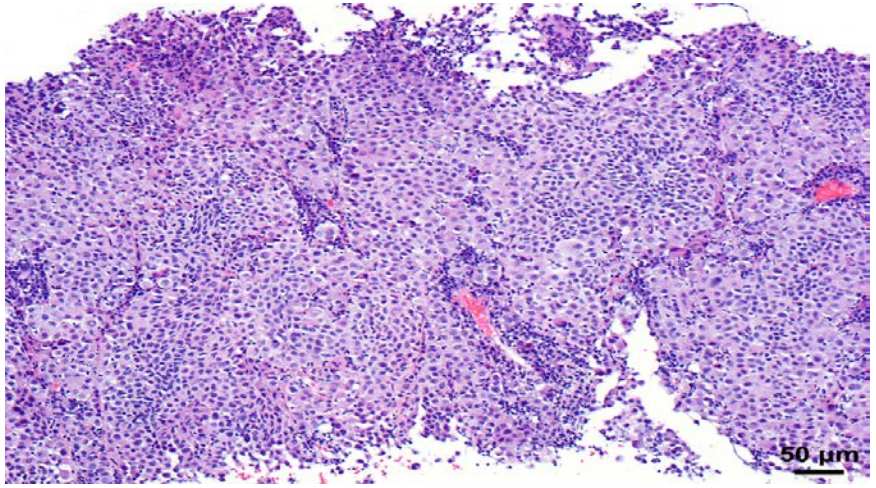
Eligibility for Neoadjuvant Trials

- Palpable or radiographically detectable (RECIST measurable) disease (Stage IIIB-Stage IV)
  - Biopsy proven
  - Surgically “resectable” with acceptable morbidity (Stage III incl. in transits, some Stage IV)
  - Medically resectable – pace of disease
    - Normal range LDH
    - “Stable stage”
  - No co-morbidities relevant to surgery, ECOG PS < 2
- No other metastatic sites
- No prior relevant systemic therapies
- Eligible for specific systemic therapies
  - No h/o autoimmune conditions, requirement for immunosuppressive drugs, etc
  - A targetable mutation (if a targeted therapy trial); no CHF, other cancers, etc
- Compliant- willing to follow protocol

Ideal Patient for Neoadjuvant Clinical Trial

- 39-year-old woman with history of T2aN0M0 melanoma of the right upper arm (excised 5/2009)
- Current presentation:
  - Palpated a right axillary mass 5/2016
  - Imaging showed solitary right axillary node
  - Core biopsy revealed melanoma that is BRAF, NRAS, KIT wild type

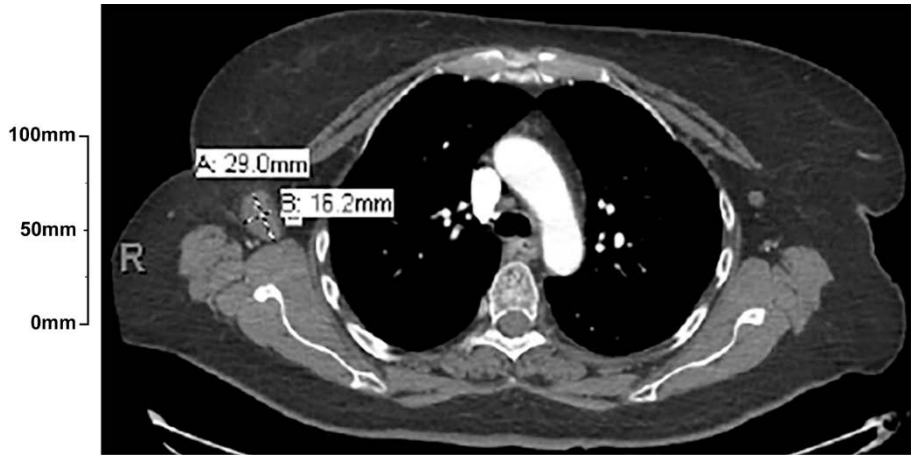


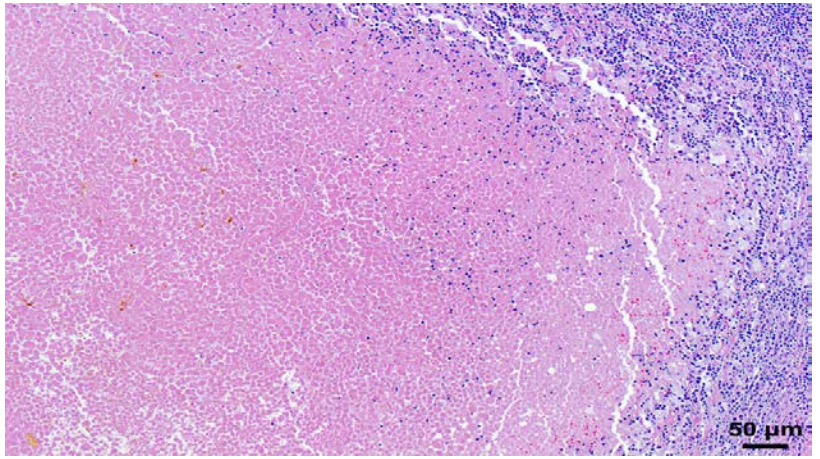


Slides courtesy of Rodabe Amaria, MD
MD Anderson Cancer Center

Ideal Patient for NeoAdjuvant Clinical Trial

- Patient entered neoadjuvant combination immunotherapy clinical trial
- Randomized to nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for up to 3 doses
- Able to receive all planned neoadjuvant doses
  - Grade 1 diarrhea, grade 2 fevers, grade 2 fatigue
- Scans prior to surgery showed PR (45% reduction); pathology review at surgery shows pCR
- Remains without evidence of disease 31 months after surgery





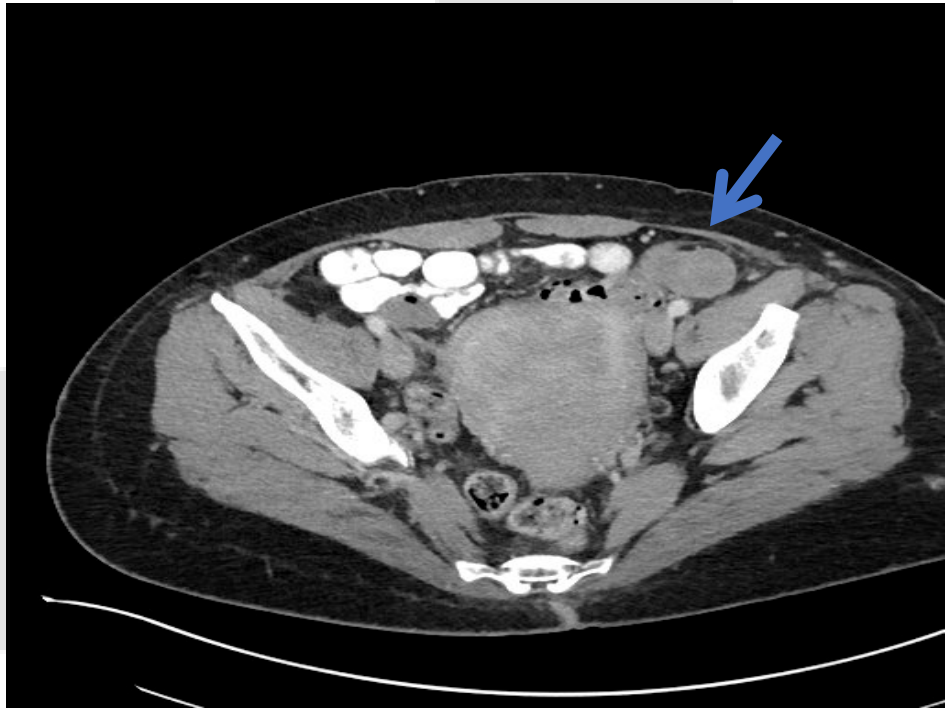
- 39-year-old woman with history of excised T2aN0M0 melanoma of the right upper arm
- Current presentation: solitary right axillary node mass; core biopsy revealed melanoma that is BRAF, NRAS, KIT wild type

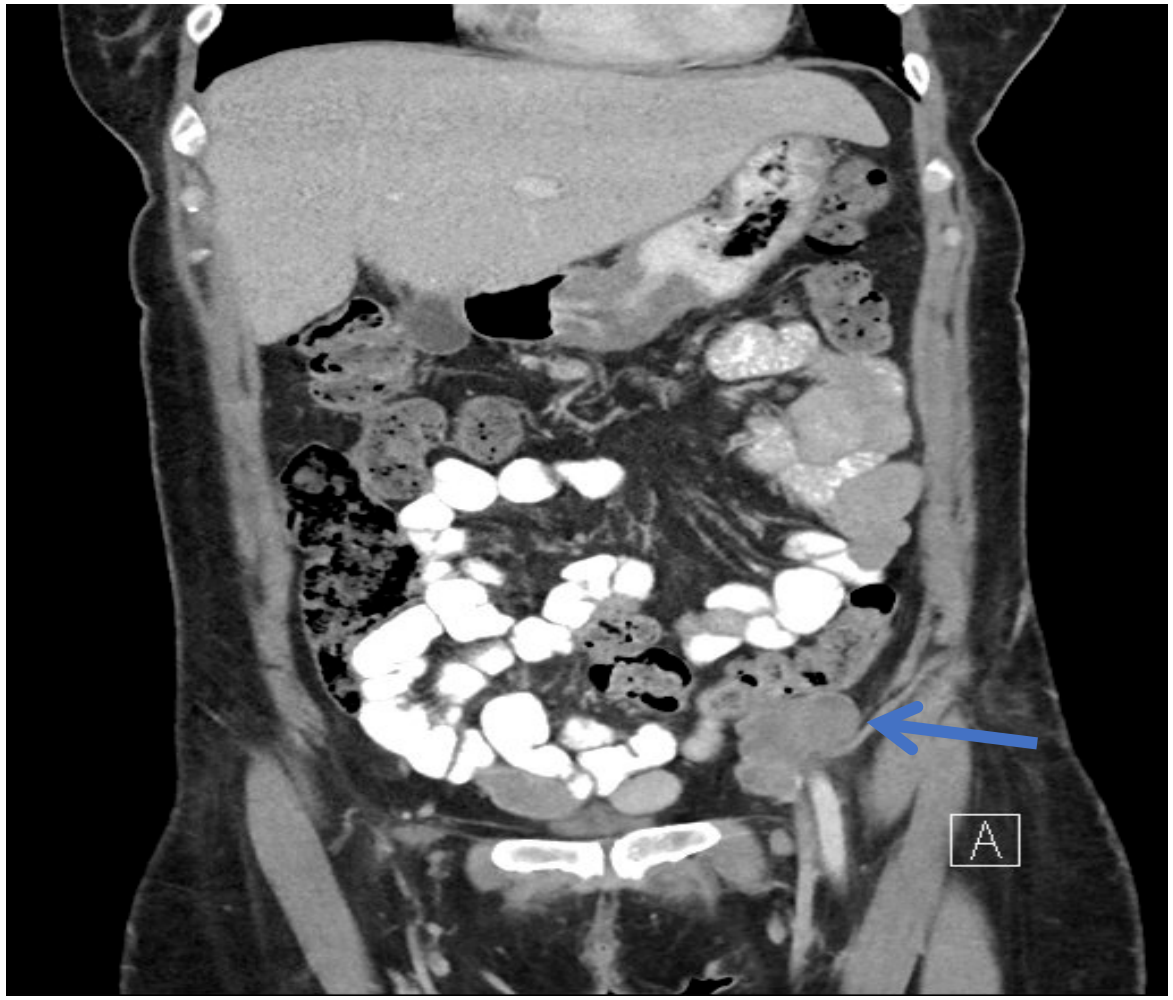
Not Ideal Patient for Some Neoadjuvant Clinical Trials

- 52 yo woman presented 7/2018 with a raised, nodular, bleeding lesion on her left thigh that had been present for over a year
  - Shave bx- at least 1.4 mm thick melanoma transected at base with ulceration and MR of 17/mm2
  - Excisional bx showed 5.35 mm thick lesion with negative margins.
  - PET-CT showed no foci of distant disease
- 2 months later- Underwent WLE and SLN biopsy at MSKCC.
  - Pathology showed 0.5 mm satellite in SQ tissue and 0/2 SLNs involved.
  - Tumor is BRAF V600E and NRASQ61R negative
- 1 month later- presents to MGUH for discussion of subsequent therapy:
  - Adjuvant IO recommended
- 2 months later- presents to begin adjuvant therapy
  - LDH elevated – (278)
  - Imaging shows large PET+ pelvic mass; No other active disease

CT Scan - baseline

Left external iliac node



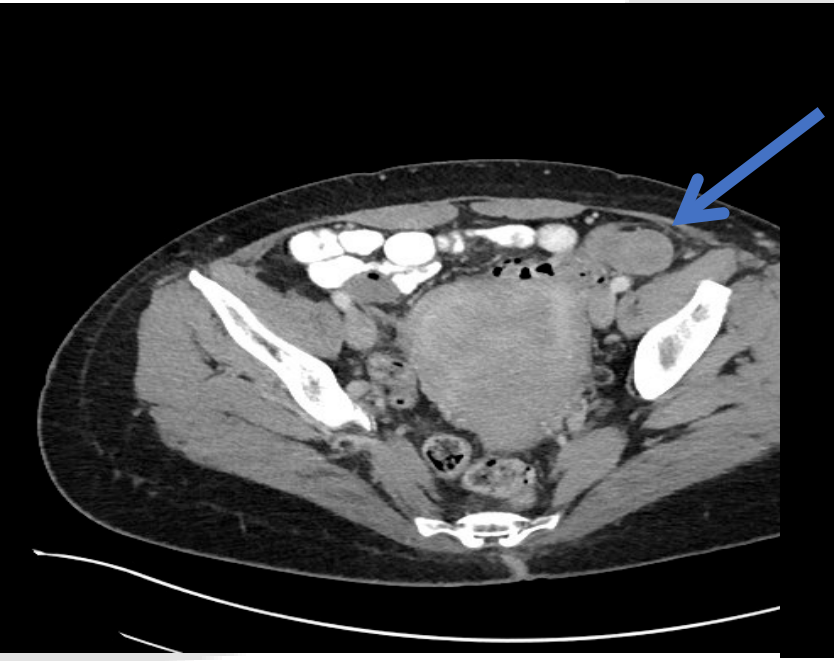


Not Ideal Candidate for Some Neoadjuvant Trials (cont)

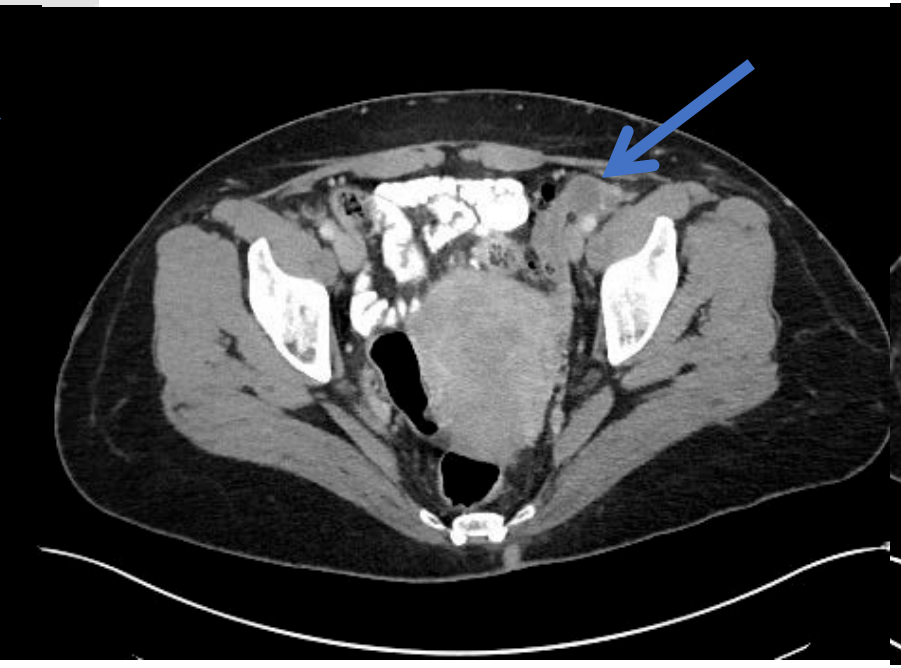
- Patient case was discussed at Multidisciplinary Conference
  - Concern raised about extent of surgery; pace of disease
  - upfront treatment with nivo/ipi
- She began nivo 3 mg/kg + ipi 1 mg/kg IV q 3 weeks.
- She presented after dose 2 (4 weeks) with acute onset cough and dyspnea (O2 sat 92%)
- Diagnosed with bronchospasm- received HD steroids with improvement in breathing; IO therapy held
- Taper required 8 weeks because recurrent symptoms
- Repeat CT scan at 6 weeks showed major tumor shrinkage.
- Repeat scan at 12 weeks showed additional shrinkage Metabolic-CR

Serial Images

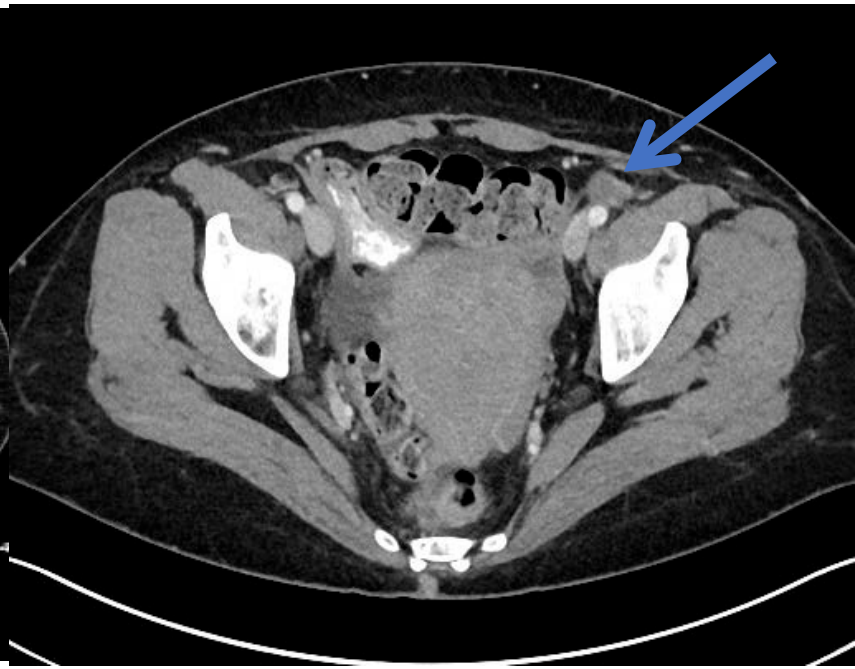
Baseline



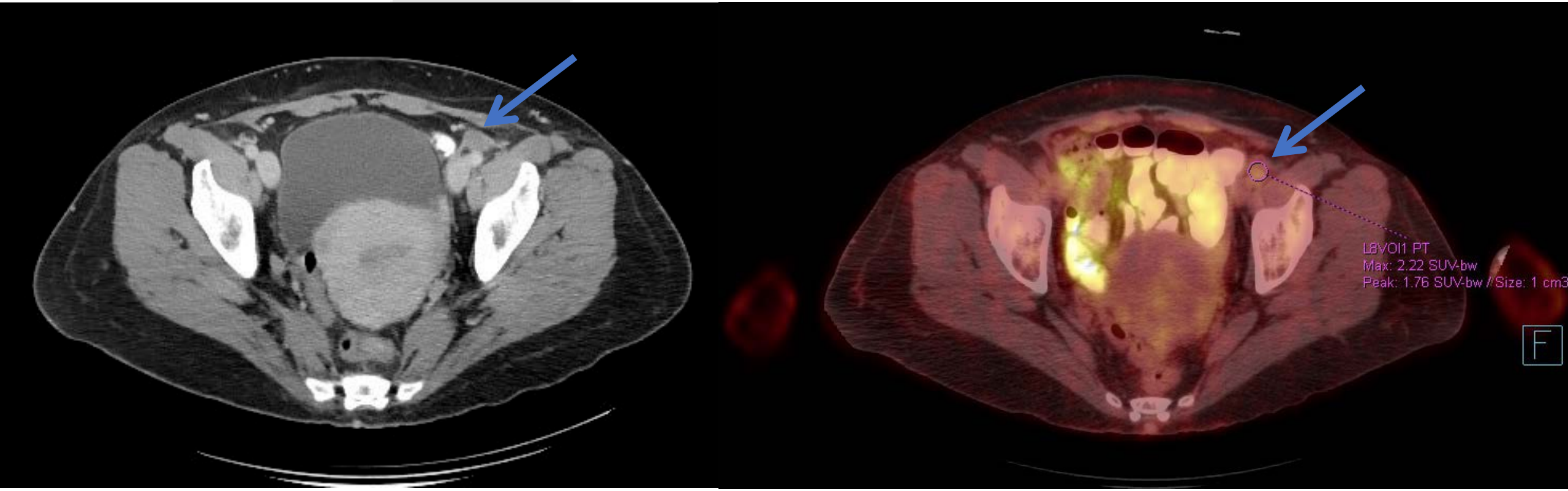
Week 6



Week 12



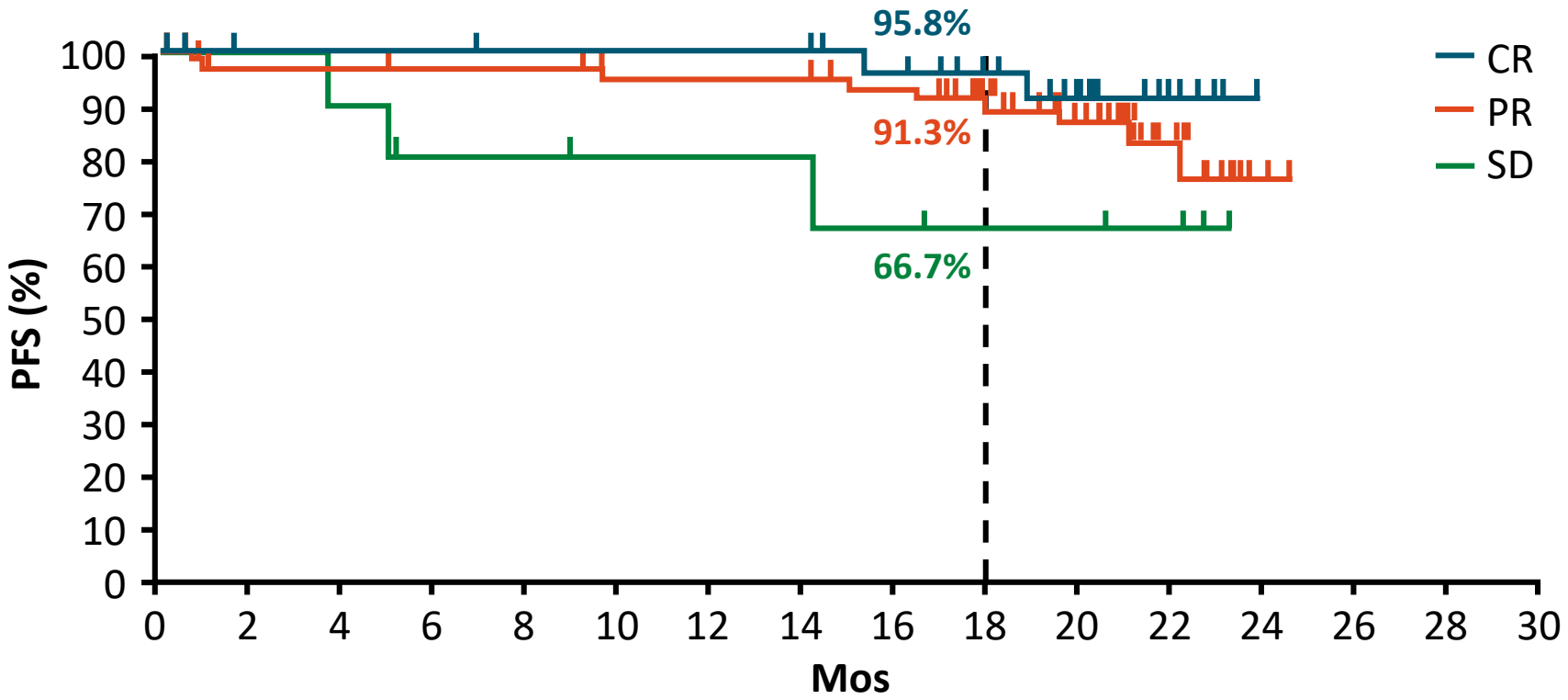
Pet-CT Scan findings



What is the value of subjecting this patient to surgery?

KEYNOTE-006: PFS With Pembrolizumab in Patients Who Completed Protocol

- Randomized, open-label phase III trial of **pembrolizumab** (Q2W or Q3W) vs **ipilimumab** for patients with unresectable stage III/IV melanoma (N = 834); current analysis assessed population of patients who completed protocol-specified 2 yrs of **pembrolizumab** (n = 103)

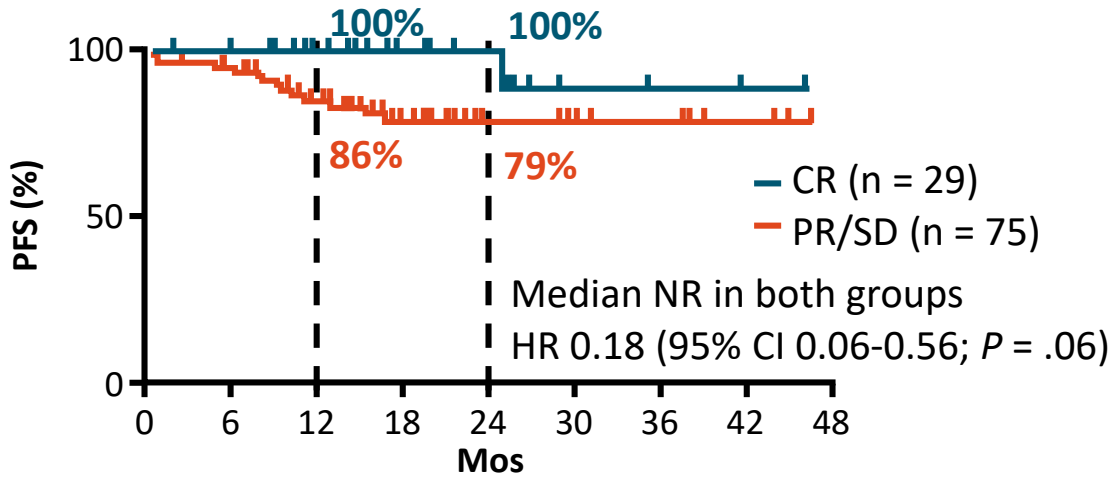


Long. ASCO 2018. Abstr 9503.

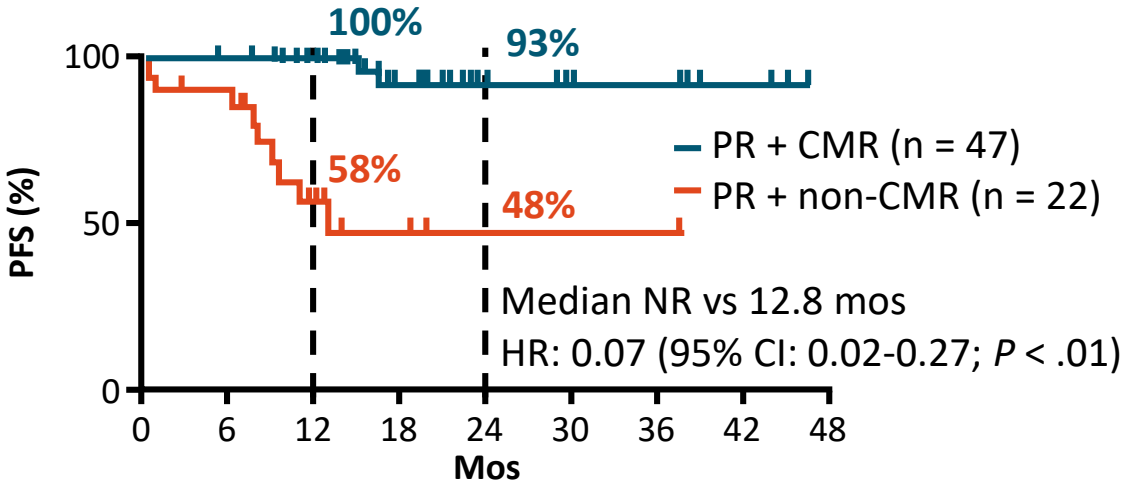
Imaging Biomarkers and Response Durability Predictions

- Prospective single center cohort of patients with metastatic melanoma treated with PD-1–based therapy who underwent baseline and 1-yr PET (N = 118)

PFS After 1 Yr by CT Response



PFS After 1 Yr by PET/CT Response in Patients With CT-Based PR

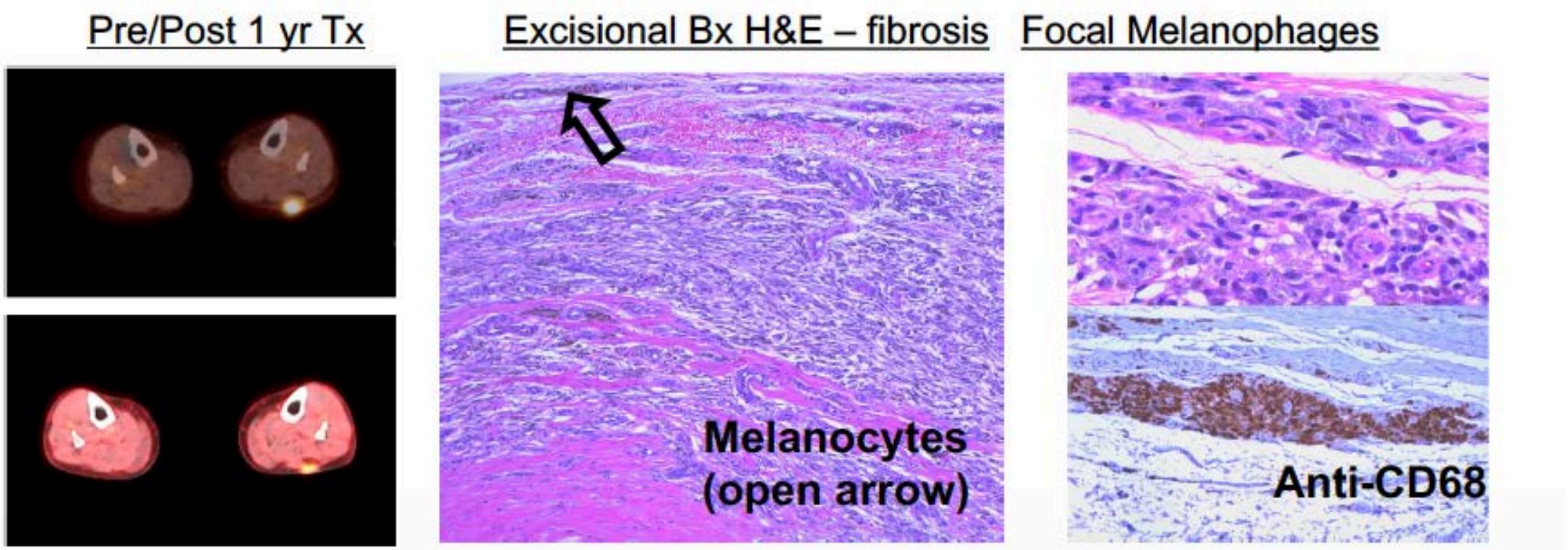


- Many “remission” patients do not reach CR by CT scan
- CMR by PET likely better at predicting long-term PFS than CT in patients with PR
- CMR by PET might guide treatment discontinuation—needs prospective validation

Tan. ASCO 2018. Abstr 9517.

MedStar Georgetown Approach: Create TFS

- Patient example: PET/CT scan with near CR except for residual hypermetabolic disease site negative on excisional biopsy

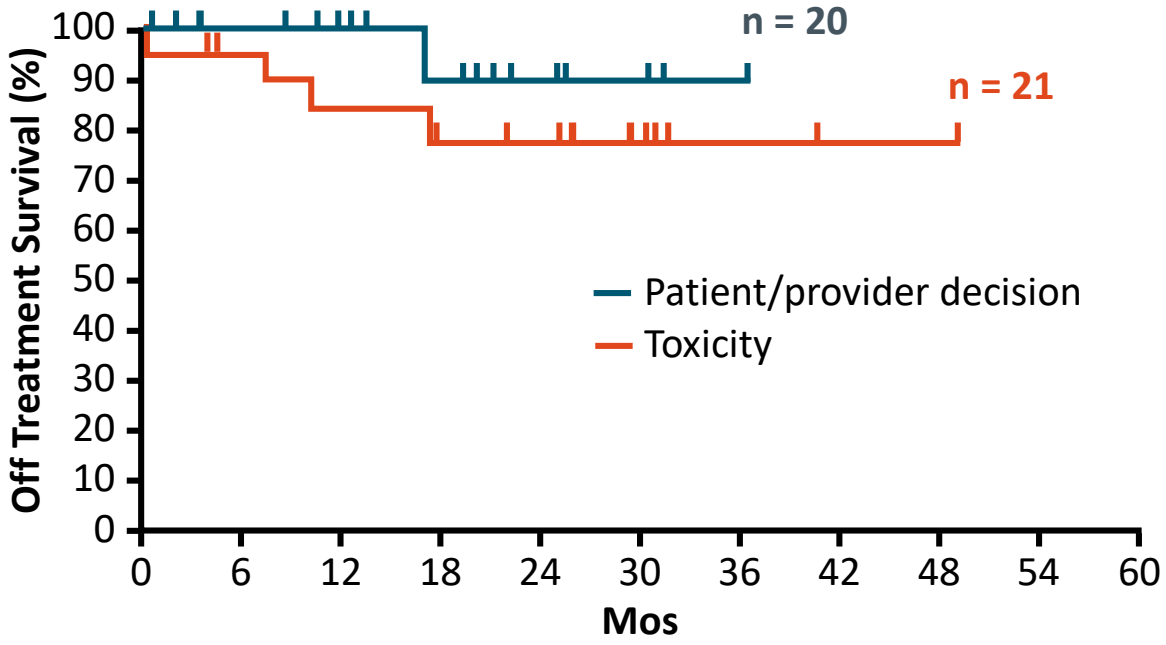


Christiansen. ASCO 2018. Abstr 9554.

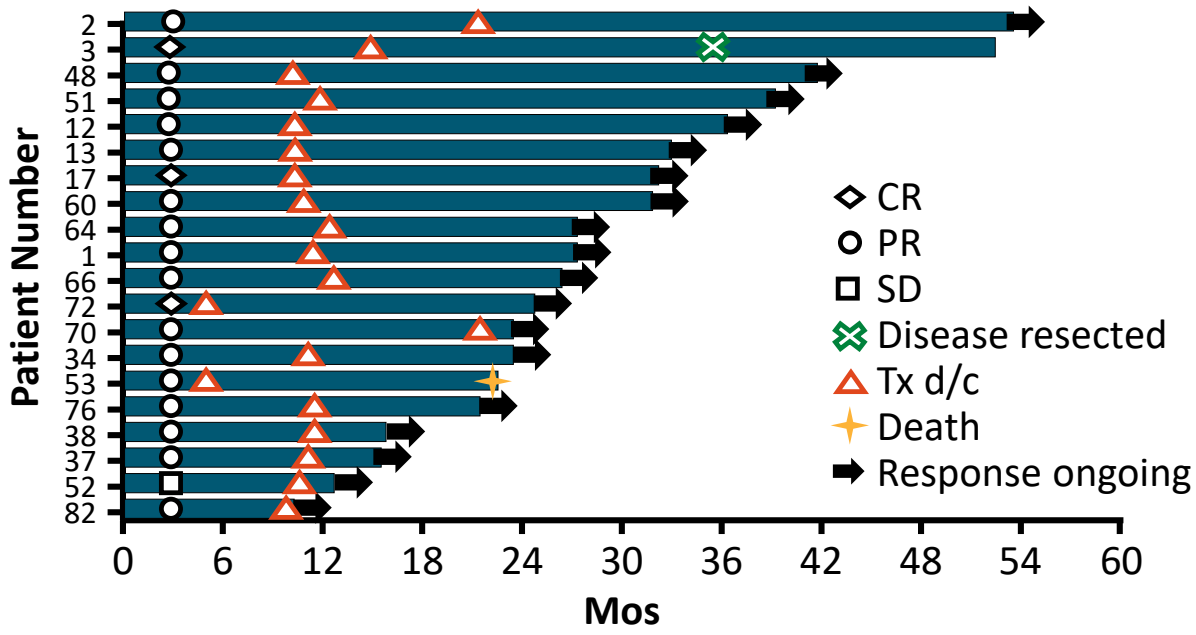
MedStar Georgetown Approach in Stage IV: Create TFS

- Single institution review of patients with advanced melanoma treated with PD-1–based therapy (pembrolizumab or nivolumab monotherapy or combination therapy with ipilimumab) (N = 96)

Off Treatment Survival Following Tx D/c by Reason



OS for Patients With Tx D/c for Patient/Provider Decision (n = 20)*



*1 PD, 1 death (nonmelanoma related).

Christiansen/Gibney. ASCO 2018. Abstr 9554.

Take Home Messages

- Neoadjuvant therapy is currently a research tool in melanoma
  - Useful for understanding biology and potentially expediting drug development
  - Its clinical utility over adjuvant therapy remains to be determined
  - Toxicities might interfere with proposed surgery
  - Risk/benefits need to be discussed with all patients
  - pCR may be more important for immunotherapy/than tumor targeted therapy

- Upfront therapy with surgical salvage is an future alternative
  - Current immunotherapies create sufficient durable responses to make this an option for patients with stage IV or difficult to resect stage III melanoma
    - Improvement in imaging, blood based biomarkers may ultimately guide salvage surgery decision
  - Targeted therapies for patients with BRAF mutant melanoma are reliably effective in making surgery easier; impact on other efficacy outcomes uncertain