Patient Selection and Risk:Benefit Considerations: A Surgeon's Perspective

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#MelanomaNeoadjuvant

Disclosures

- Stock Ownership: Pfizer (spouse)

What are the surgical *risks* with neoadjuvant therapy?

1) Will patients loose opportunity to undergo surgery?
   a) Does drug inhibit wound healing?
   b) Side effect which delays surgery
   c) Progression of disease

2) Neoadjuvant treatment change surgical approach?
   a) Major tumor shrinkage- less morbid surgery
   b) Adhesions/fibrosis- ?increased morbidity

3) Do patients with all patients with radiologic response need surgery?

Neoadjuvant targeted therapy

ELSEVIER

UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 31 (2013) 379–385

Original article

Surgical outcomes and complications associated with presurgical tyrosine kinase inhibition for advanced renal cell carcinoma (RCC)

Lauren C. Harshman, M.D.[a,*], R. James Yu, M.D.[b], Genevera I. Allen, Ph.D.[c], Sandy Srinivas, M.D.[a], Harcharan S. Gill, M.D.[b], Benjamin I. Chung, M.D.[b]

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Received 9 November 2010; received in revised form 2 January 2011; accepted 4 January 2011

Comparison of patients received neoadjuvant TKI- surgery versus Surgery

- Stopped medicines two weeks prior to surgery
- Intraop/postop complications similar
- Increased adhesions in neoadjuvant group

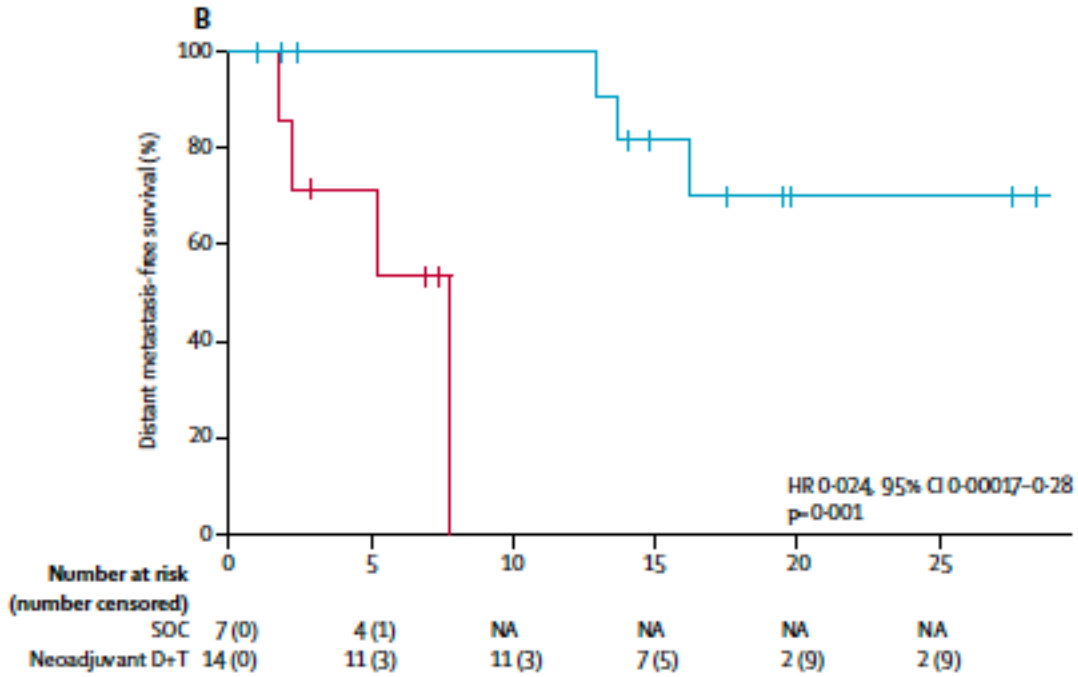
Neoadjuvant targeted therapy melanoma

Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial

Rodabe N Amaria, Peter A Prieto*, Michael T Tetzlaff, Alexandre Reuben, Miles C Andrews, Merrick I Ross, Isabella C Glitza, Wen-Jen Hwu, Hussein A Tawbi, Sapna P Patel, Jeffrey E Lee, Jeffrey E Gershenwald, Christine N Spencer, Vancheswaran Gopa Roland Bassett, Lauren Simpson, Rosalind Mouton, Courtney W Hudgens, Li Zhao, Haifeng Zhu, Zachary A Cooper, Khalida W Patrick Hwu, Adi Diab, Michael K Wong, Jennifer L McQuade, Richard Royal, Anthony Lucci, Elizabeth M Burton, Sangeetha I Padmanee Sharma, James Allison, Phillip A Futreal, Scott E Woodman, Michael A Davies†, Jennifer A Wargo†*

Summary

Background Dual BRAF and MEK inhibition produces a response in a large number of pa



Drug stopped 48 hours prior to surgery
Restarted within a week
Surgical complications similar

First Trial Immunotherapy and Surgery: Bladder Cancer

Preoperative CTLA-4 Blockade: Tolerability and Immune Monitoring in the Setting of a Presurgical Clinical Trial

Bradley C. Carthon[1], Jedd D. Wolchok[5,6], Jianda Yuan[6], Ashish Kamat[2], Derek S. Ng Tang[1], Jingjing Sun[1], Geoffrey Ku[6], Patricia Troncoso[3], Christopher J. Logothetis[1], James P. Allison[6,7,8], and Padmanee Sharma[1,4,6]

12 patients urothelial bladder cancer

- **6 Ipilimunab 3mg/kg**
- **6 Ipilimumab 10mg/kg**

4 week after last dose- surgical resection

No severe complications related to therapy

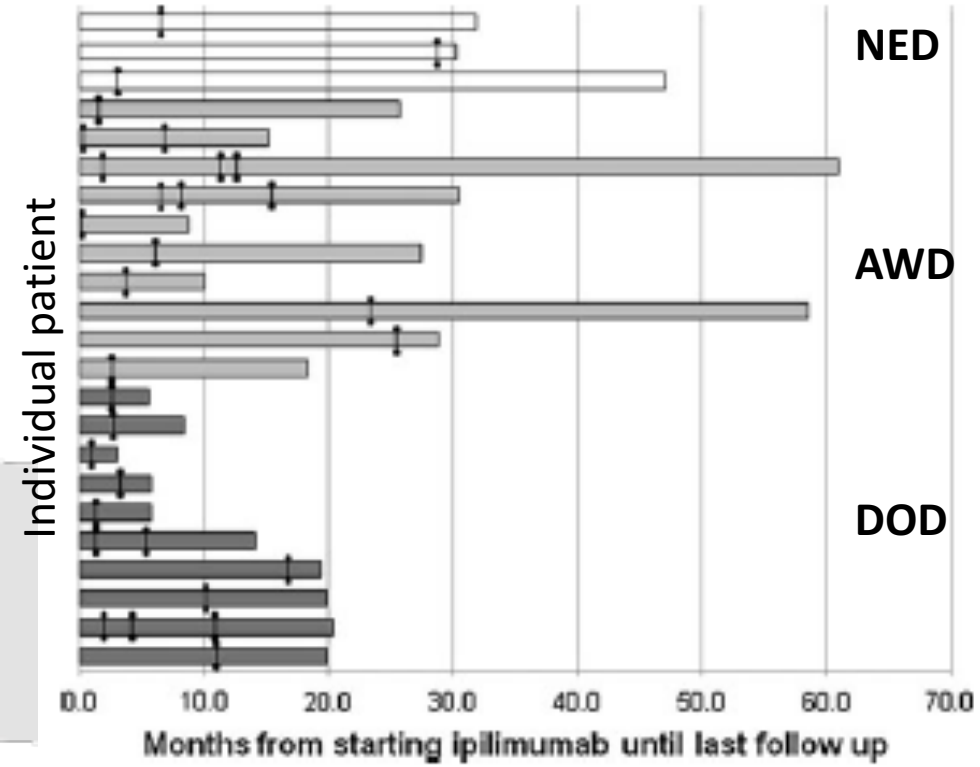
- **1) wound dehiscence/fistula**
- **2) UTI x 5**

Safety of Preoperative Immunotherapy in Bladder Cancer

Table 1. Clinical characteristics of patients with localized urothelial carcinoma who received anti–CTLA-4

Patient	Sex	Age (y)	Prior therapy	Adjuvant therapy	Drug-related irAEs	Surgery delay (wk)	Follow-up (mo)	Status
1	M	66	BCG	None	Rash, Gr 1; Diarrhea, Gr 1	None	33.37	NED Alive
2	M	75	None	Cis, Gem, Ifos chemo	None	5.1 (due to cardiac eval)	32.67	NED Alive
3	M	71	BCG	None	Amylase and lipase increased, Gr 2 Uveitis, Gr 2; diarrhea, Gr 1 ischemic papillitis, Gr 3;	None	28.83	NED Alive
4	M	60	None	MVAC chemo	Rash, Gr 1	None	27.3	NED Alive
5	M	55	None	None	Rash, Gr 1; Pruritis, Gr 1	None	24.9	NED Alive
6	M	75	BCG	None	Rash, Gr 2; Pruritis, Gr 2	None	23.1	NED Alive
7	M	76	None	None	Rash, Gr 1 Testicular swelling/ Epididymitis, Gr 2	None	7.7	NED Deceased
8	F	69	None	None	Rash, Gr 1 Transaminitis, Gr 3 Diarrhea, Gr 2	4.0 (due to irAE)	17.5	NED Alive
9	M	63	None	None	Diarrhea, Gr 2	None	17.03	NED Alive
10	F	68	None	None	Diarrhea, Gr 3 (received only one dose of antibody)	10.3 (due to irAE and cardiac and GI eval)	12.23	NED Alive
11	M	71	BCG	Ifos-Adria-Gem chemo	Rash, Gr 1; Pruritis, Gr 1; Elavated AST, Gr 1; Diarrhea, Gr 3	N/A*	9.27	Metastatic disease Alive
12	M	66	None	Gem-Cis chemo	Diarrhea, Gr 2	None	8.33	Metastatic disease Alive

Safety surgery and Immunotherapy: Melanoma



Retrospective look at patients operated on after Immunotherapy (n=23)

Surgery performed median 25 days after last dose

- **earliest 1 week after dose**
- **included bowel resections**

No grade 3-5 complications

Gyorki et al *Annals of Surg Onc*, 2013

Immune Monitoring of the Circulation and the Tumor Microenvironment in Patients with Regionally Advanced Melanoma Receiving Neoadjuvant Ipilimumab

Ahmad A. Tarhini[1]*, Howard Edington[2], Lisa H. Butterfield[1], Yan Lin[3], Yongli Shuai[3], Hussein Tawbi[1], Cindy Sander[1], Yan Yin[1], Matthew Holtzman[4], Jonas Johnson[5], Uma N. M. Rao[6], John M. Kirkwood[1]

Plos one, 2014

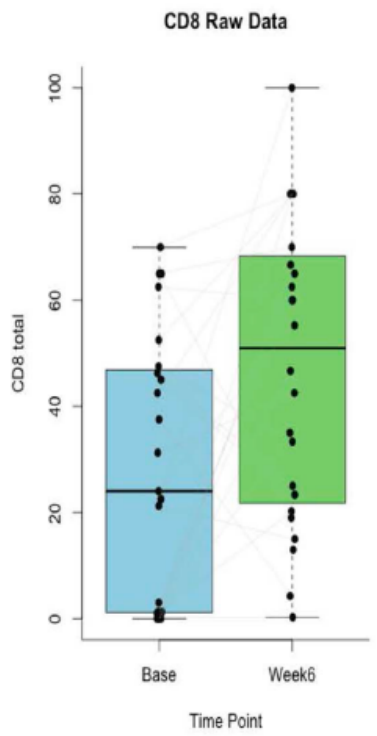
2 doses of Ipilimumab 10 mg/kg (q 3 weeks)

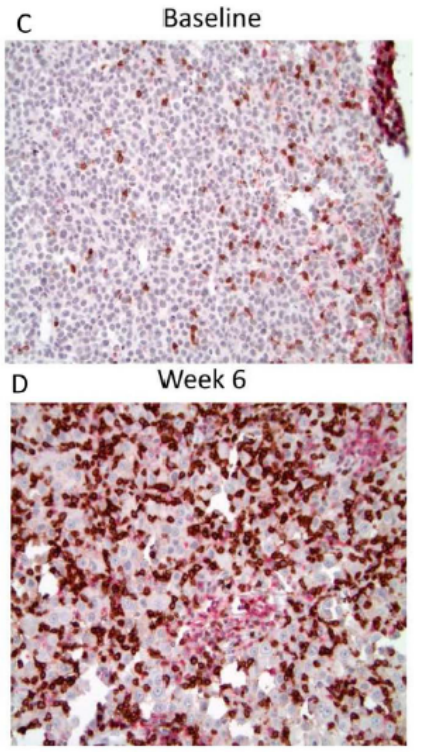
Surgery 6-8 weeks

No reported toxicity

Increased CD8 cells at week 6

Lack of B cells correlated with poor outcome





Neoadjuvant Immunotherapy: Bladder

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JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study

Andrea Necchi, Andrea Anichini, Daniele Raggi, Alberto Briganti, Simona Massa, Roberta Lucianò, Maurizio Colecchia, Patrizia Giannatempo, Roberta Mortarini, Marco Bianchi, Elena Farè, Francesco Monopoli, Renzo Colombo, Andrea Gallina, Andrea Salonia, Antonella Messina, Siraj M. Ali, Russell Madison, Jeffrey S. Ross, Jon H. Chung, Roberto Salvioni, Luigi Mariani, and Francesco Montorsi

50 patients, cT3, cT2, or cT2-3N1
3 doses of anti-PD1

All patients made it to surgery

42% **pT0**

Table 2. Postcystectomy Complications (N = 50)

Characteristic	No. (%)
Median length of hospital stay, days (IQR)	
Total patients	16 (12-20)
RARC	15 (10.8-18.3)
ORC	17 (15-20)
Neobladder	18.5 (15-24)
Ileal conduit	13 (9-17)
Median intraoperative blood loss, mL (IQR)	300 (150-500)
30-day readmission	11 (22)
30-day surgical reintervention	5 (10)
Postoperative complications (Clavien Dindo) within 90 days	
0	25 (50)
II	10 (20)
IIIa	9 (18)
IIIb	5 (10)
IV	1 (2)
Type of postoperative complications	
Fever of unknown origin	4 (8)
Sepsis	10 (16)
Subocclusion	8 (20)
Ureteral anastomosis dehiscence	2 (4)
Ileal anastomosis dehiscence/fistula	3 (6)
Median No. of removed lymph nodes (IQR)	
Total patients	27 (22-31)
RARC	30 (26-39.3)
ORC	20.5 (18.3-25)
Positive margin status	0 (0)

Neoadjuvant Immunotherapy: Lung

TRIAL	Treatment	STAGE (n)	Surgical Resection (%)
Forde et al NEJM 2018	PD1 x 2	I- IIIa (n=21)	95%
Shu et al ASCO 2018	PDL1 + chemo	IB-IIIa (n=14)	78%
Neostar ASCO 2019	Nivo IPI Nivo	I-IIIa (n=44)	95%
LCM3 ASCO 2019	PDL1	IIIa-b (*mostly) (n=101)	89%

Neoadjuvant/Adjuvant Checkpoint Blockade: Increased Surgical Morbidity?

Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non–small cell lung cancer

Matthew J. Bott, MD,[a] Stephen C. Yang, MD,[b] Bernard J. Park, MD,[a] Prasad S. Adusumilli, MD,[a] Valerie W. Rusch, MD,[a] James M. Isbell, MD,[a] Robert J. Downey, MD,[a] Julie R. Brahmer, MD,[c] Richard Battafarano, MD, PhD,[b] Errol Bush, MD,[b] Jamie Chaft, MD,[d] Patrick M. Forde, MD,[c] David R. Jones, MD,[a] and Stephen R. Broderick, MD, MPHS[b]

50% of all minimally invasive approaches converted because of fibrosis/inflammation

Bott et al, *J Thorac Cardiovasc Surg*. 2019

Will patients loose opportunity to undergo surgery?

Targeted Therapy

Good Selection: Limited to patients with known mutation, BRAF V600E/K (melanoma)

Most responses rapid

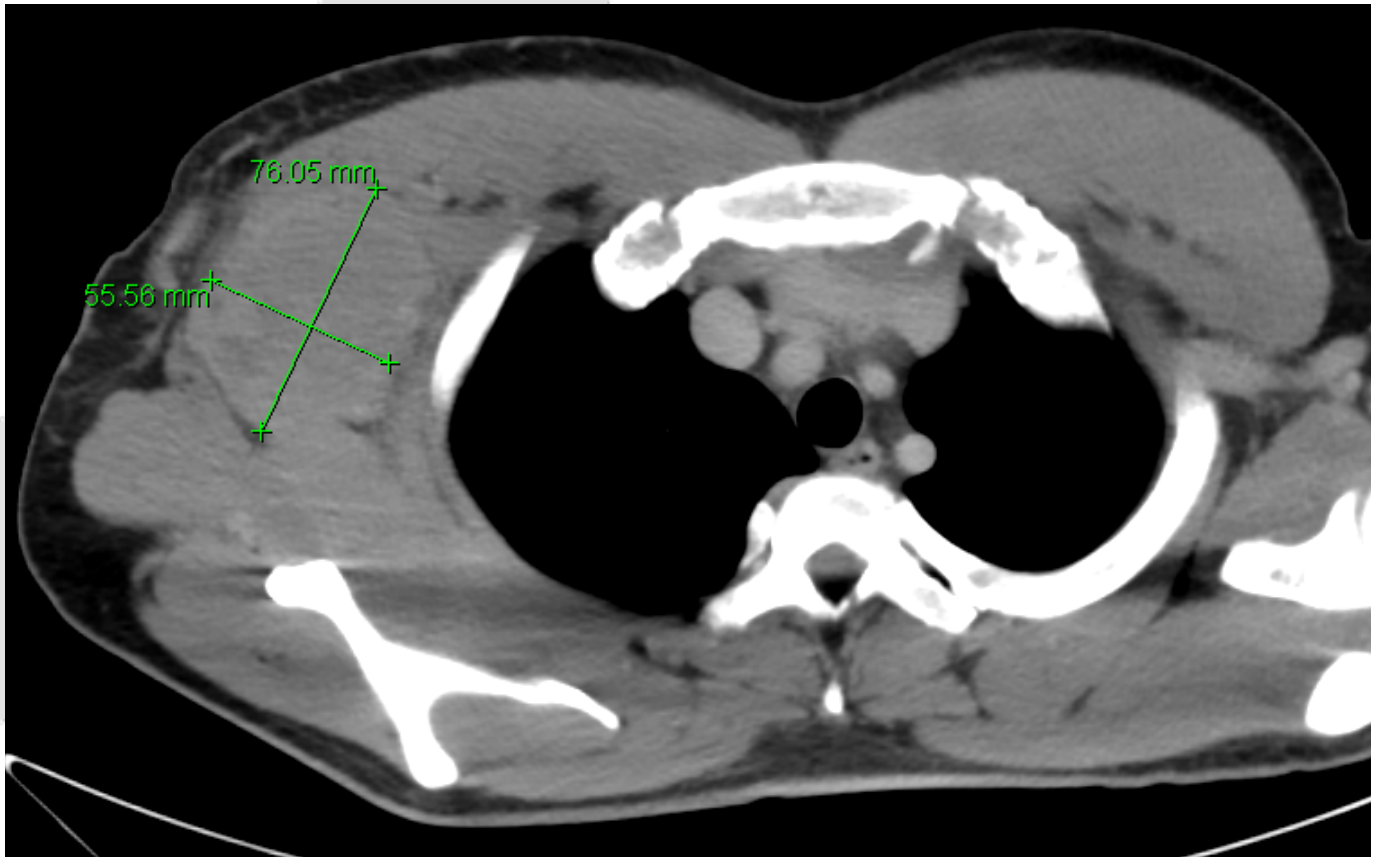
Immune Therapy

No selection criteria? PDL1

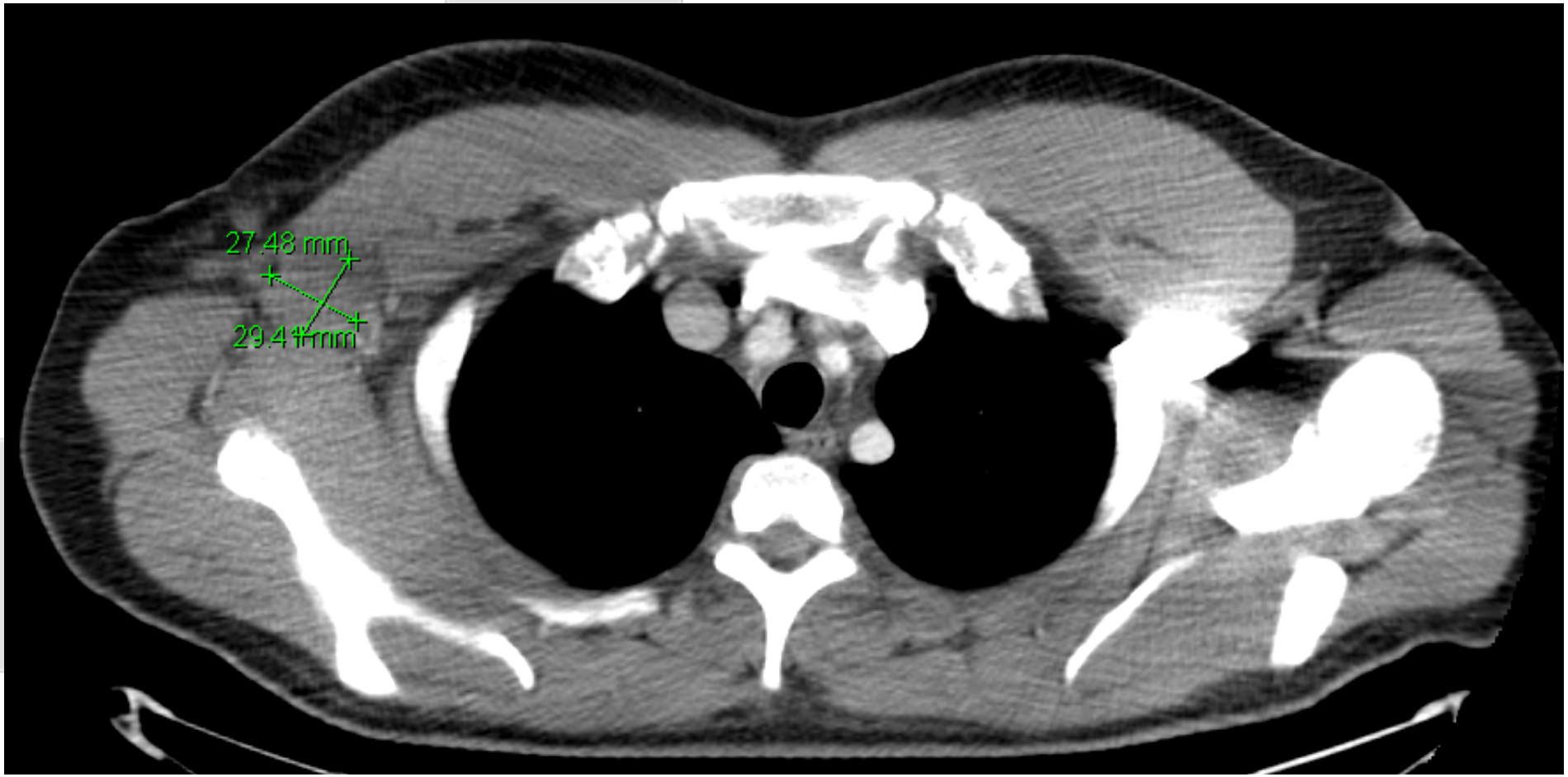
Responses can be rapid or slow with pseudoprogression

Toxicity can be long lasting and interfere with surgery

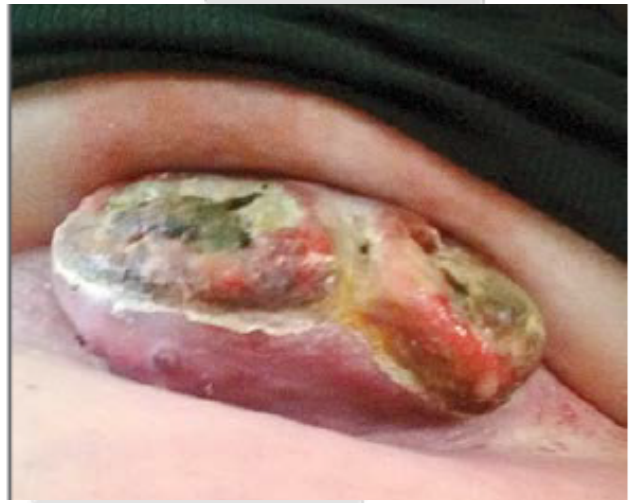
25 year old with unknown primary and biopsy proven melanoma in axilla
Imaging without evidence of distant disease
On pain meds for terrible neuropathic pain in axilla
BRAF V600E mutation



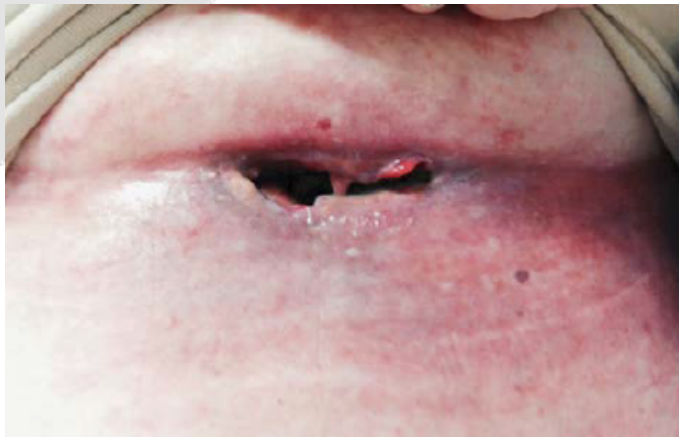
s/p 6 months of BRAF, followed by surgical resection

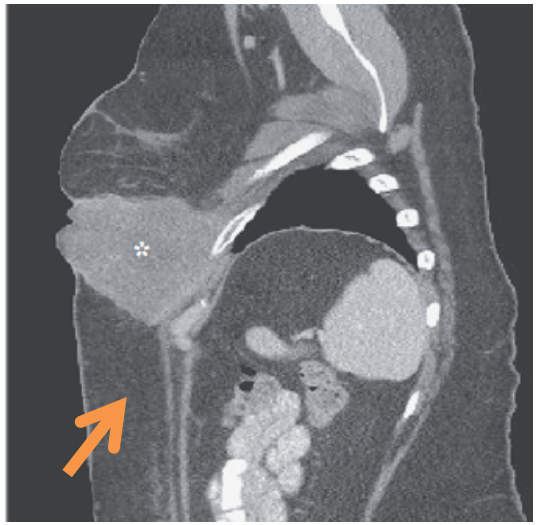


Rapid Responses CTLA-4/PD1

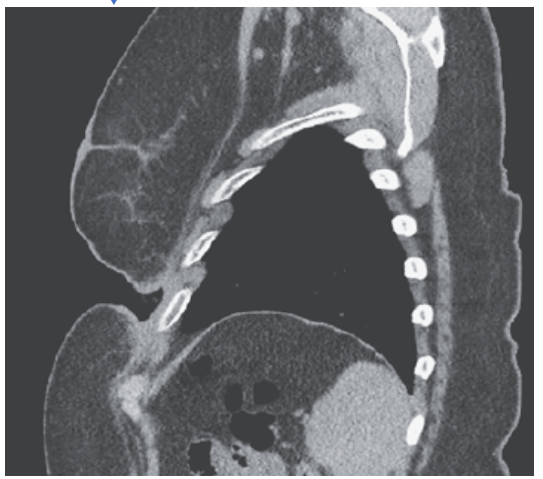


s/p one dose(3 weeks)





s/p one dose(6 weeks)



Chapman et al, *NEJM*, 2015

Neoadjuvant/Adjuvant Checkpoint Blockade: Melanoma

MDACC: Stage IIIB and IIIC and oligometastatic Stage IV

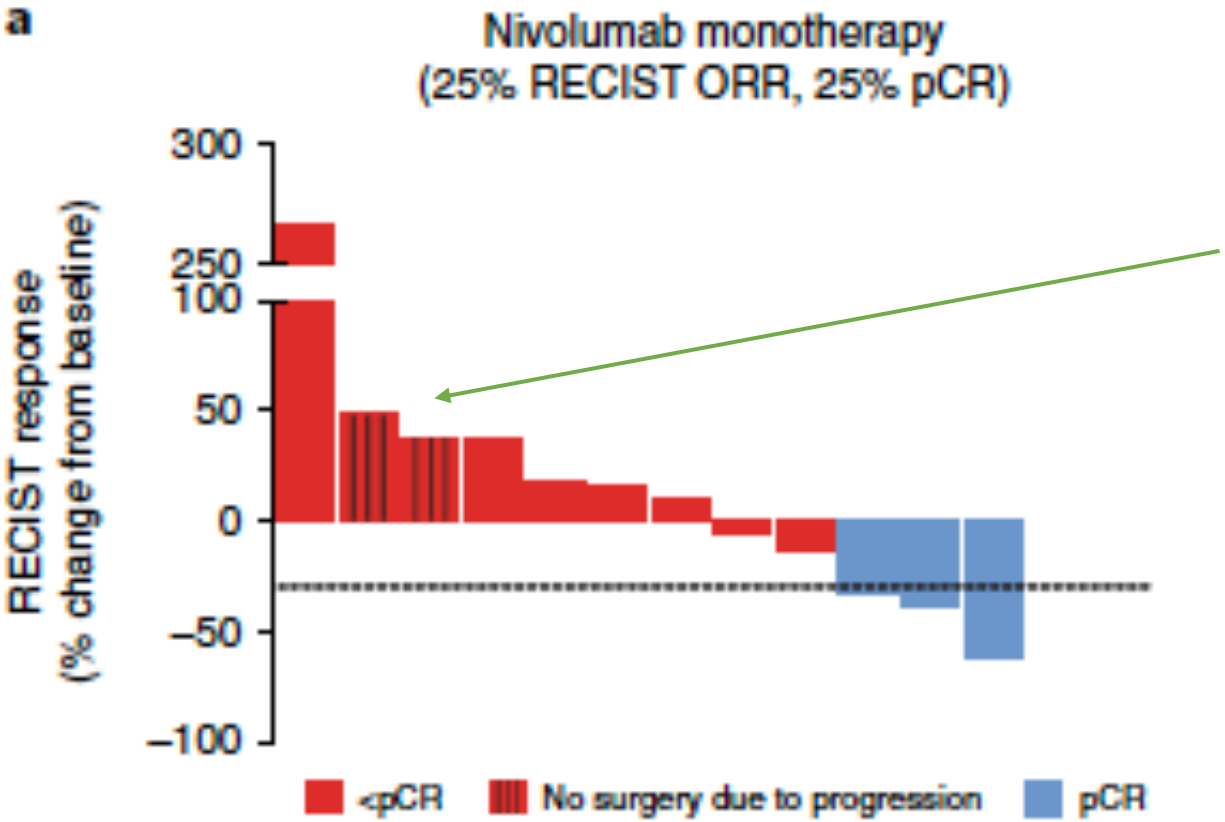
Amaria, Wargo et al *Nature Medicine* 2018

Neoadjuvant/Adjuvant Checkpoint Blockade: Melanoma

MDACC: Stage IIIB and IIIC and oligometastatic Stage IV

Amaria, Wargo et al *Nature Medicine* 2018

Neoadjuvant Checkpoint Blockade Melanoma: Failure to get to surgery with anti-PD1

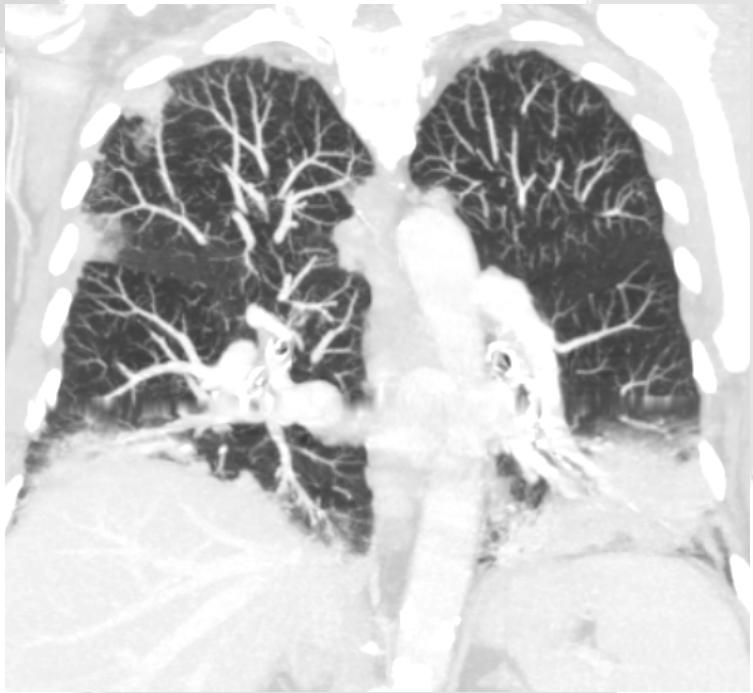


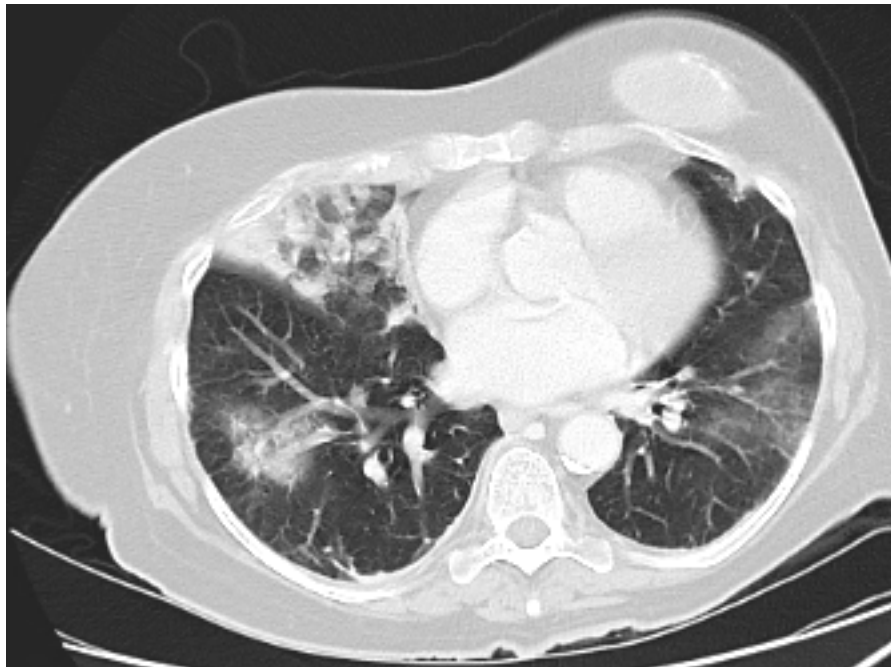
PROGRESSON AND NO SURGERY

2/11 patient progressed and surgery not performed

Amaria, Wargo et al *Nature Medicine* 2018

Immunotherapy Side Effects and Delay Surgery





74 yo female s/p resection of 8mm buttock(skin) melanoma and 2 positive nodes from superficial groin

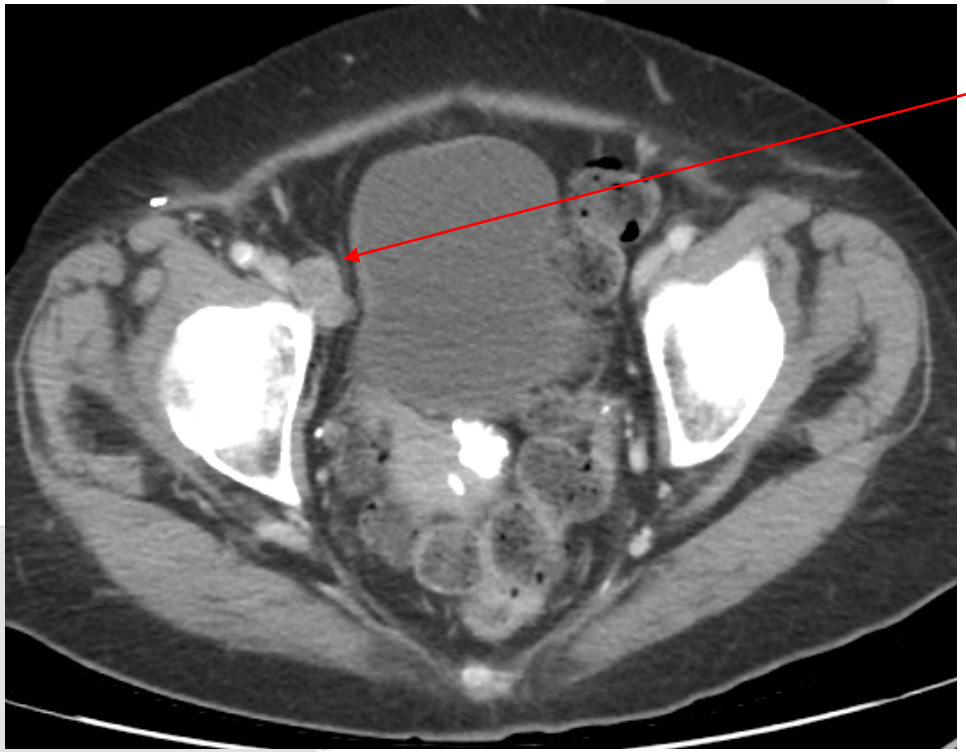
relapsed metastatic melanoma pelvic lymph nodes 3 months later

Treated with anti-PD1

Severe pneumonitis- ICU admission

- home o2
- several courses of steroids, relapse when steroid dose decreased

Balancing surgery and Immunotherapy Side Effects



pelvic nodes with metastatic melanoma

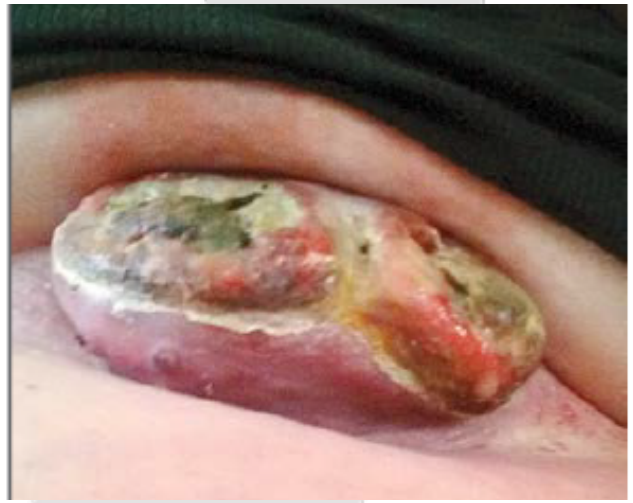
To get to surgery

SLOW prednisone taper and off home O2

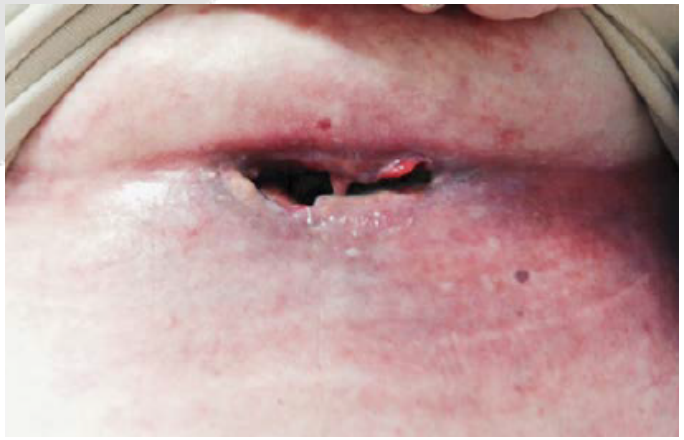
Robotic- barotrauma

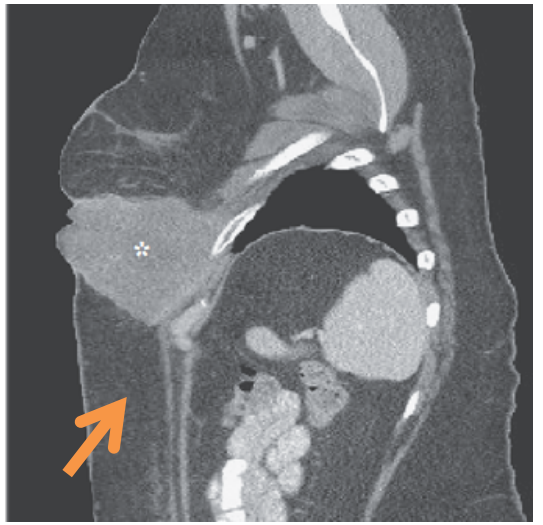
Open- wound healing

Rapid Responses CTLA-4/PD1

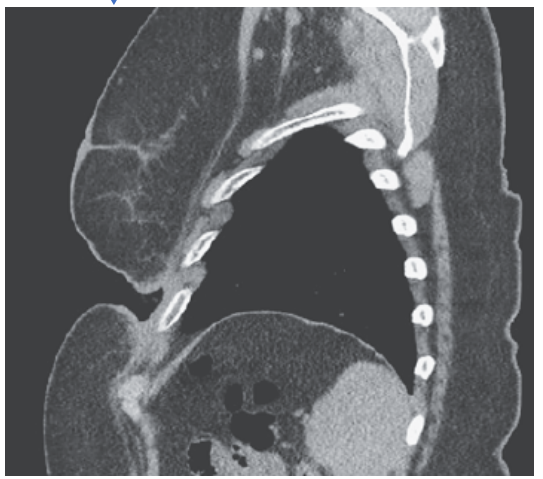


s/p one dose(3 weeks)





s/p one dose(6 weeks)

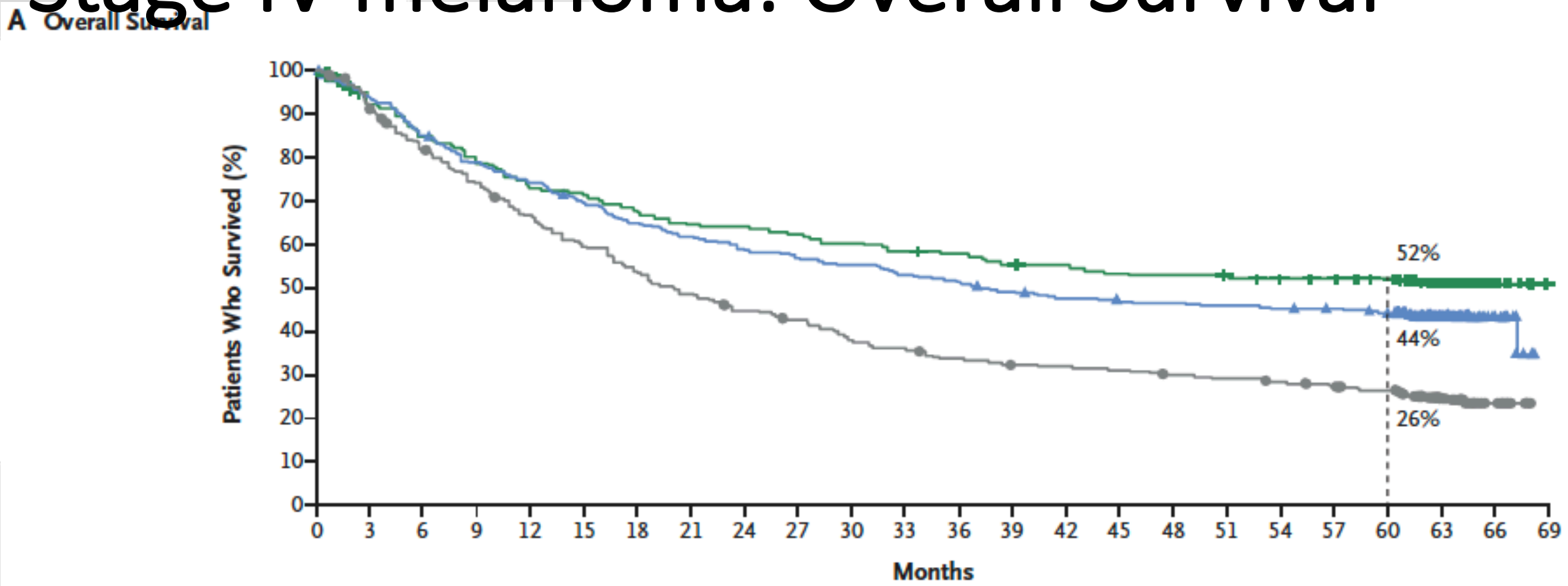


Does this patient need surgery?

Is there a correlation with radiologic CR and pCR?

Chapman et al, *NEJM*, 2015

Stage IV melanoma: Overall Survival

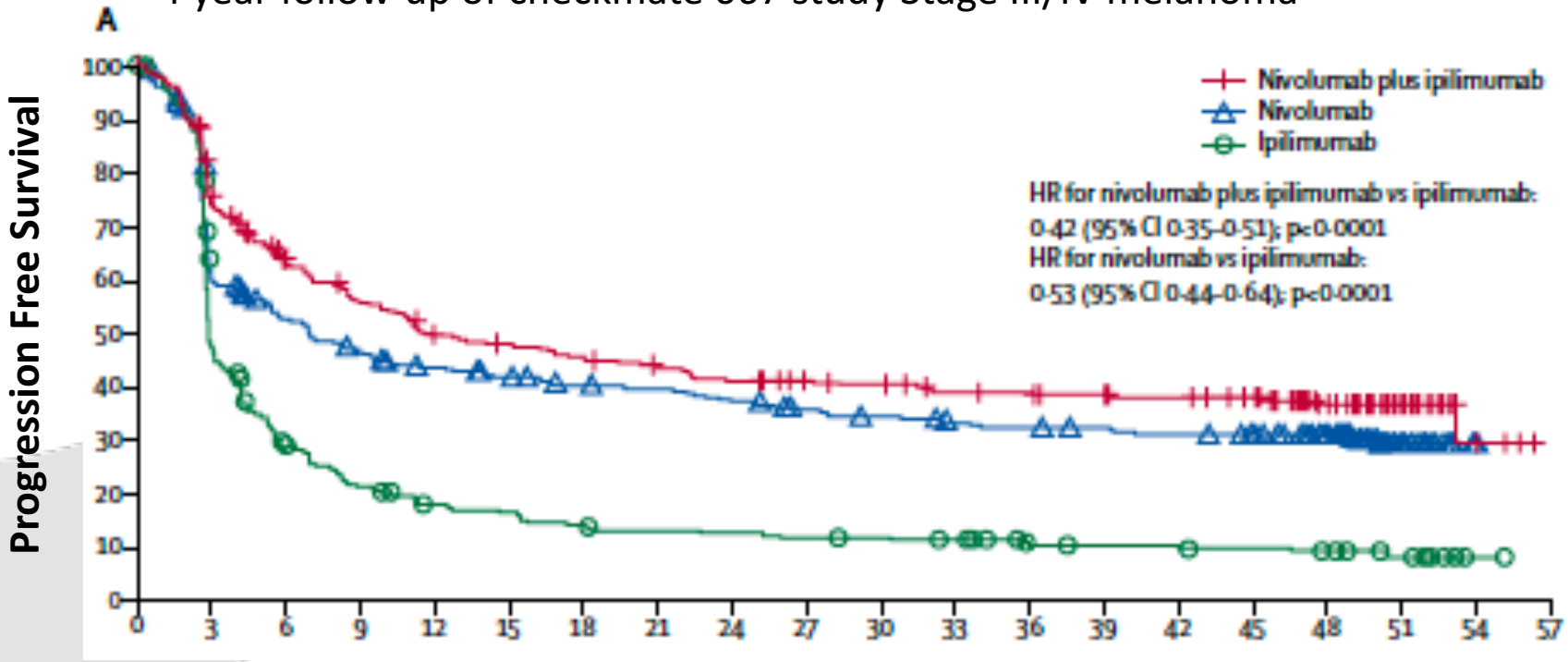


No. at Risk																								
Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

Larkin et al, NEJM 2019

Stage IV melanoma: Many patients progress after Immunotherapy

4 year follow-up of checkmate 067 study Stage III/IV melanoma



<u>Median PFS</u>

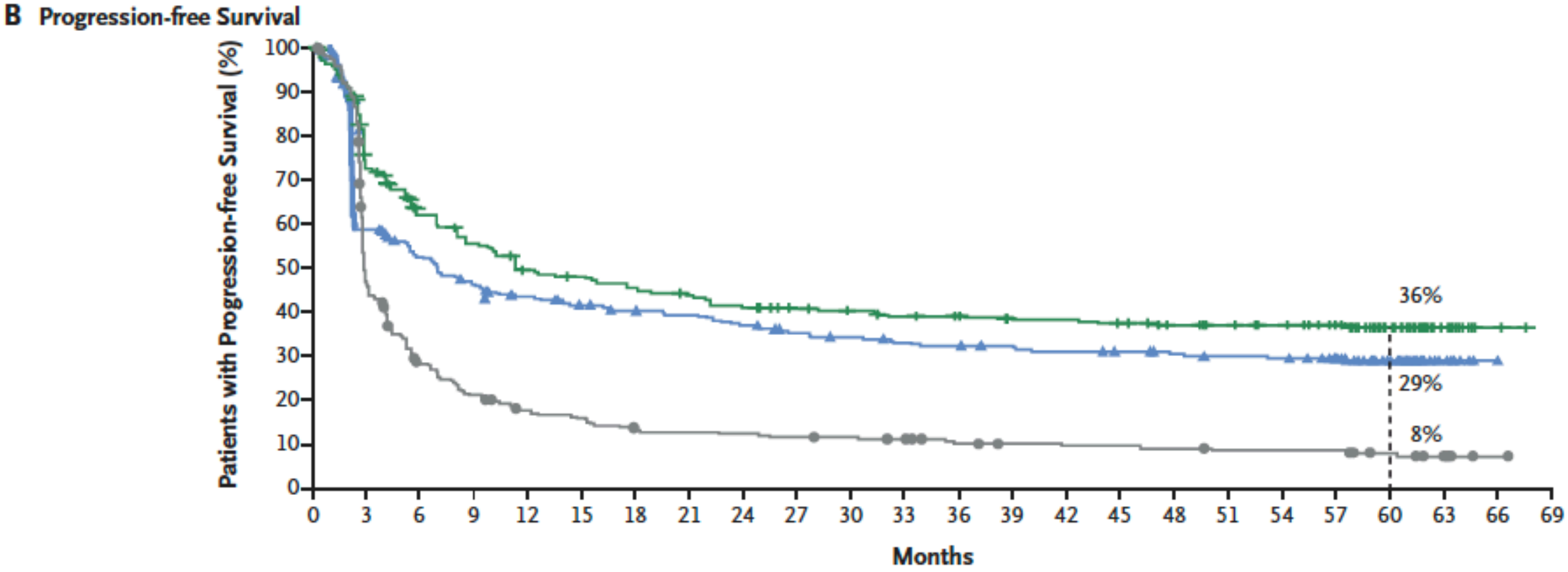
IPI/NIVO 11.5 months

Nivo 6.9 months

Ipi 2.9 months

Hodi et al *Lancet Oncology*, 2018

Stage IV melanoma: Progression Free Survival



Larkin et al, NEJM 2019

Treatment after Systemic Immunotherapy

	Nivolumab Plus Ipilimumab (n=314)	Nivolumab (n=316)	Ipilimumab (n=315)
Any subsequent therapy, n (%)	135 (43)	182 (58)	236 (75)
Subsequent systemic therapy	104 (33)	150 (48)	206 (65)
Subsequent immunotherapy	53 (17)	103 (33)	148 (47)
Anti-PD-1 agents	36 (12)	47 (15)	143 (45)
Anti-CTLA-4 agents	19 (6)	91 (29)	17 (5)
Other immunotherapy	7 (2)	12 (4)	11 (4)
BRAF inhibitor	42 (13)	60 (19)	72 (23)
MEK/NRAS inhibitor	32 (10)	43 (14)	42 (13)
Other approved agents	45 (14)	63 (20)	75 (24)
Other investigational agent	8 (3)	9 (3)	15 (5)
Subsequent radiotherapy	61 (19)	92 (29)	123 (39)
Subsequent surgery	60 (19)	69 (22)	95 (30)
Median time from randomisation to subsequent systemic therapy, months (95% CI)*	NR	25·2 (16·0–43·2)	8·1 (6·5–8·7)

Hodi et al *Lancet Oncology*, 2018

What is the outcome of patients (initially not resectable) selected for surgery after systemic immunotherapy?

ADJUVANT SURGERY

Neoadjuvant Therapy Prior to Surgery

Targeted Therapy

Good Selection: Limited to patients with known mutation, BRAF V600E/K (melanoma)

Most responses rapid

=Ideal group for neoadjuvant therapy
- select for patients most likely to respond
- short window for assessment
- most toxicities reversible quickly

GREAT CANDIDATES FOR NEOADJUVANT

Immune Therapy

Selection criteria? PDL1

Responses can be rapid or slow with psuedoprogression

Toxicity can be long lasting and interfere with surgery

BALANCE THE DELAY WITH NEED FOR SURGICAL PALLIATION

Conclusions

Surgery safe in combination with immunotherapy, targeted therapy

Neoadjuvant treatment

- High response rate
- Toxicity manageable- requires multi-disciplinary approach
- Loss of surgical window- what is acceptable amount?
- Do patients with radiologic CR need to have surgery?

Favorable outcomes in advanced patients undergoing surgery with response to immunotherapy consistent with favorable outcomes in neoadjuvant trials

Should surgery become the “Adjuvant?”

LONG TERM OUTCOMES AND BIOMARKERS NEEDED