NASDC
NCI Awardee Skills Development Consortium

Integrating Surgery and Local Regional Therapy into Immunotherapy(IO) Treatment

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Memorial Sloan Kettering Cancer Center

Disclosures

» Stock: Pfizer (spouse)

Cancer Care is More Integrated

Historically

- Aggressive surgery used in early stage disease
- Chemotherapy later disease
- Surgery isolated distant disease

Current Era: Effective systemic therapy (immunotherapy) Renewed interest for local therapies

- remove tumors developed under treatment
- augment a systemic immune response

Why is this important?

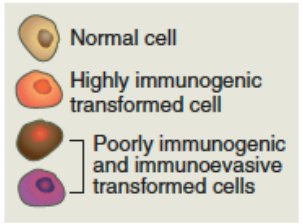
- Many patients who respond to immunotherapy will have recurrence
  - opportunity for combination therapy or surgical resection
- Many patients will not respond at all
  - opportunity for combination therapy to increase response rates

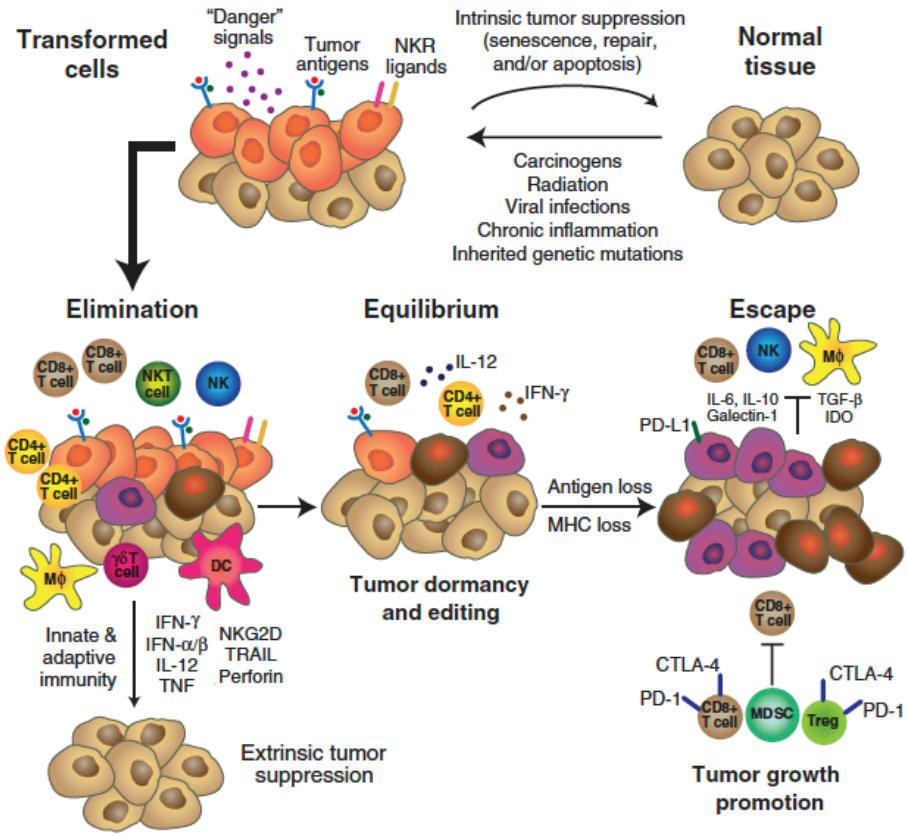
Cancer Immunoediting

» Elimination

» Equilibrium

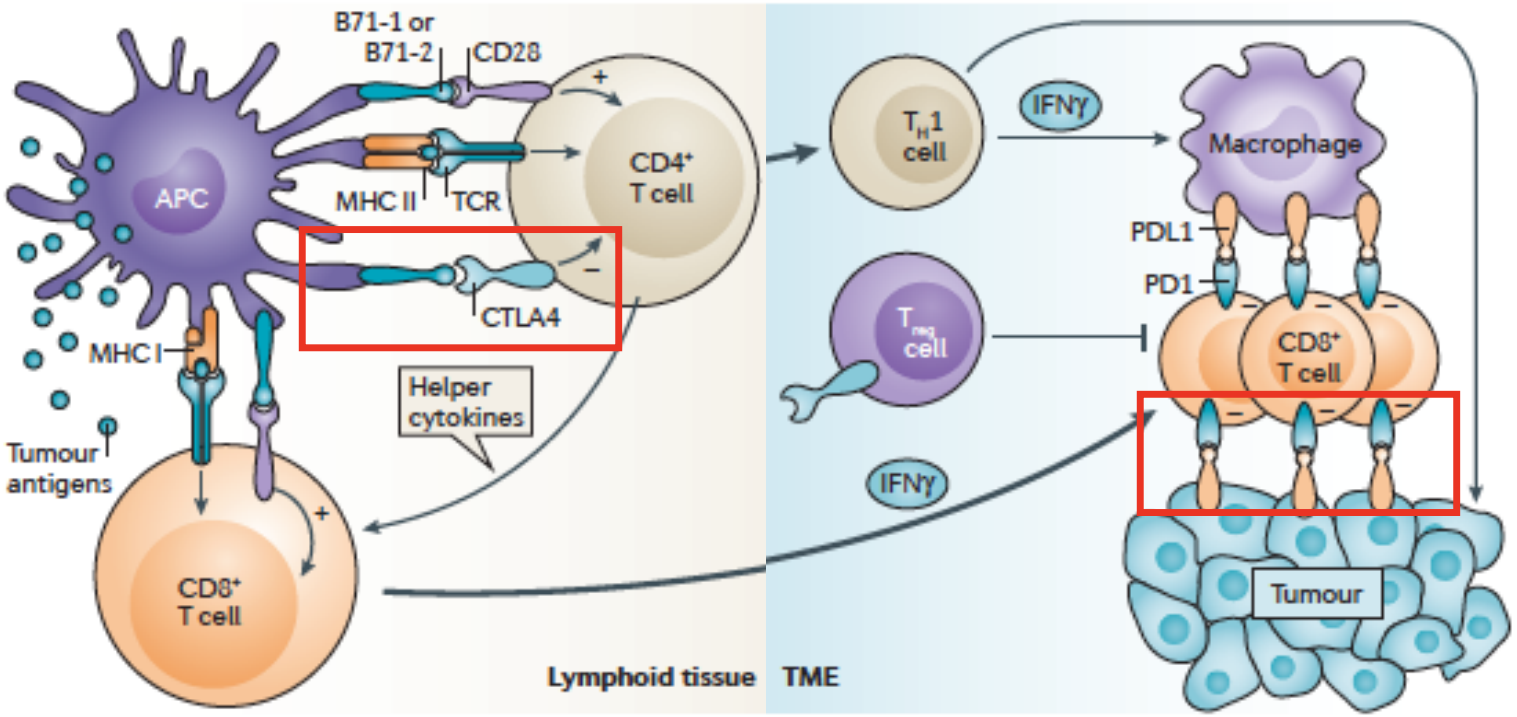
» Escape





Schreiber et al Science 2011

Checkpoint Blockade



Topalian et al
Nature Review
Cancer, 2016

Stage IV melanoma: Many patients progress after Immunotherapy

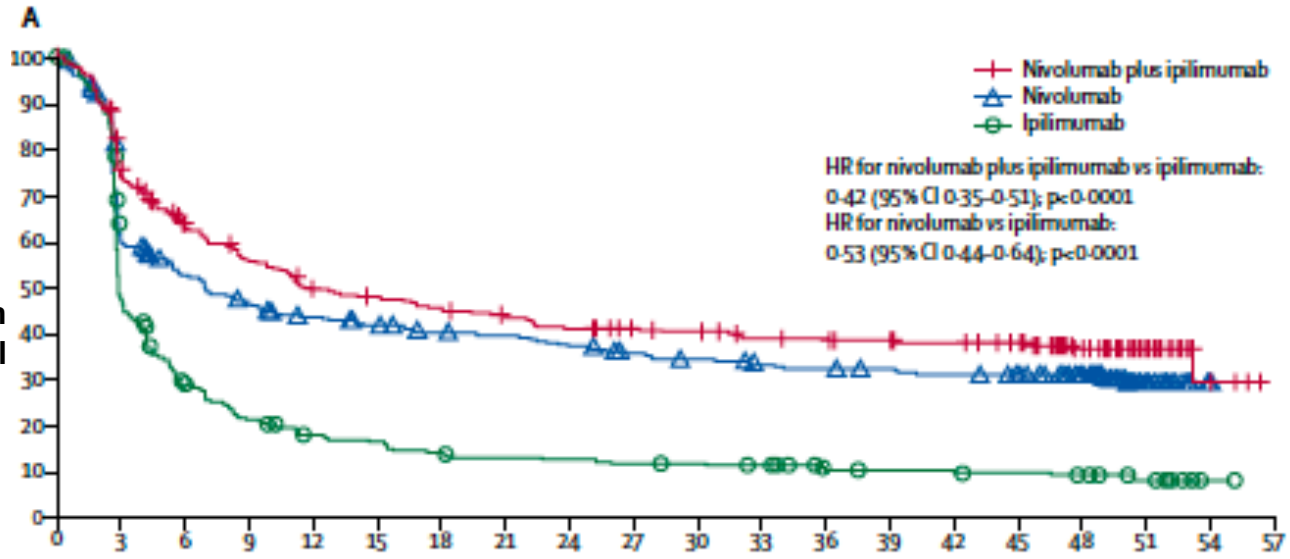
Median PFS

IPI/NIVO - 11.5 months

Nivo - 6.9 months

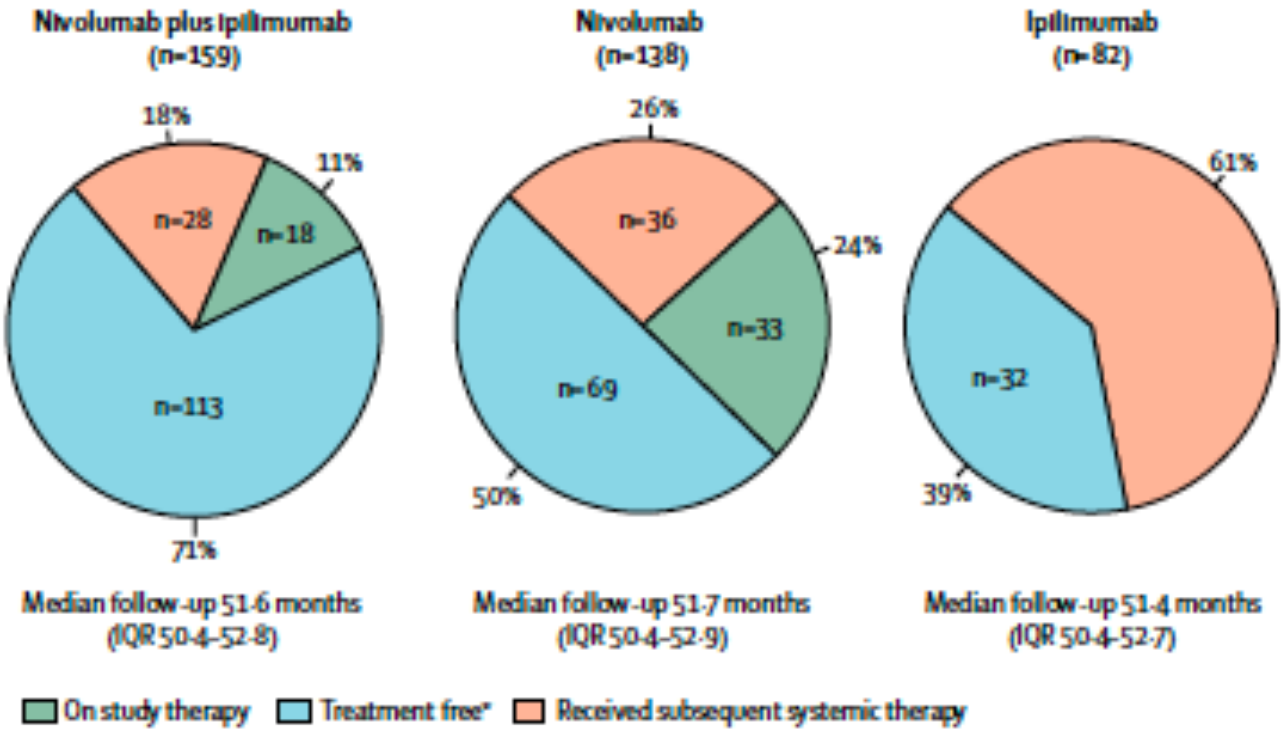
Ipi - 2.9 months

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



Hodi et al Lancet Oncology, 2018

Treatment after Systemic Immunotherapy



Hodi et al Lancet Oncology, 2018

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

Prior to Checkpoint Blockade: Surgery for recurrent disease modest benefit

- Patients recurrence on MSLT-1
- 397 (20%) patients developed distant melanoma recurrence

Characteristic (N=291)	N (%)
Breslow Thickness	
<1.2mm	15 (5)
1.2-3.5mm	189 (65)
>3.5mm	87 (30)
Treatment for Stage IV Recurrence	
Surgery Only	43 (15)
Surgery Then Systemic Medical Therapy (SMT)	85 (29)
Systemic Medical Therapy (SMT) Then Surgery	33 (11)
Systemic Medical Therapy Only	130 (45)

Howard JH, Thompson JF,…Morton DL.
Ann Surg Oncol. 2012; 19(8):2547-55.

Prior to Checkpoint Blockade: Surgery for recurrent disease modest benefit

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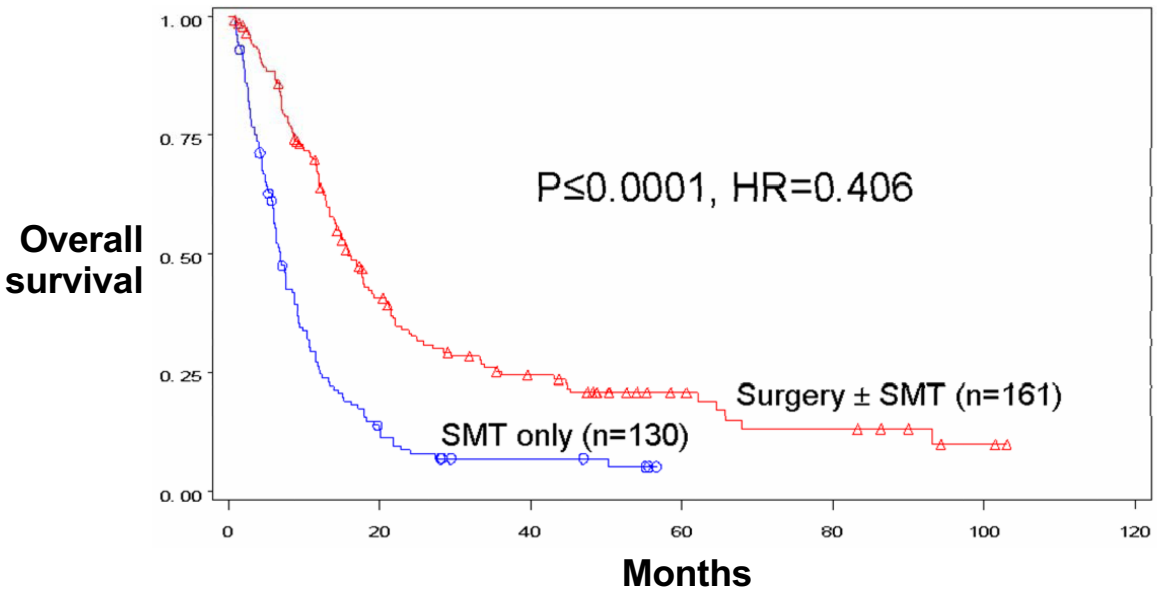

Median Survival:

Surgery +/- SMT: 15.8months

SMT Alone: 6.9 months

4 year-OS:

Surgery +/- SMT: 21%

SMT Alone: 7%

Howard JH, Thompson JF,…Morton DL.
Ann Surg Oncol. 2012; 19(8):2547-55.

What is the outcome of patients selected for surgery after systemic immunotherapy?

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Metastatectomy after IO is safe

- 23 Patients Stage IIIB/C, Stage IV Patients
- 34 operations within 30 days of Ipilimumab or on maintenance Ipilimumab- NO INCREASED COMPLICATIONS

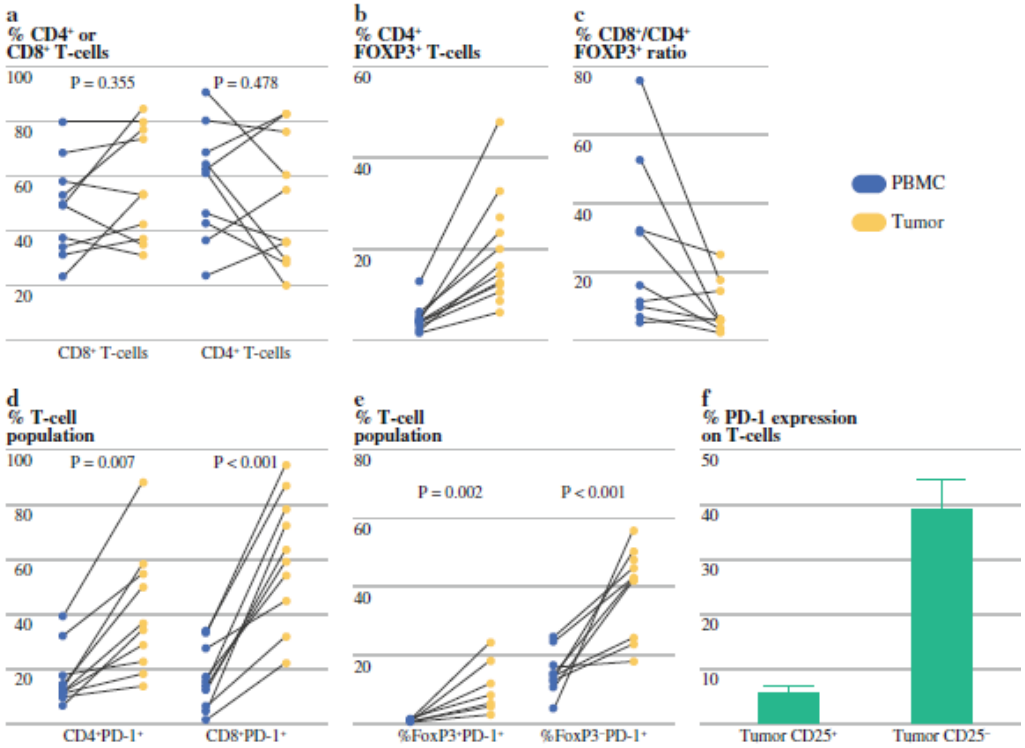
Metastasectomy Site	n(%)	Isolated Disease	Progressive Disease	Symptomatic Disease
Subcutaneous	12 (35)	2	5	5
Intra-abdominal	11 (32)	0	7	4
Brain	5 (15)	0	0	5
Nodal	3 (9)	1	2	0
Other	3 (9)	0	0	3

- Improved Median survival (9 months) in patients resected to NED, or with a single progressing lesion versus palliative resection (5 months)

Gyorki DE,…Wolchok JD, Ariyan CE. Ann Surg Onc. 2013; 20: 3106-3111.

Metastasectomy provides insights into lack of response

- Matched PB and Tumor Samples in 10 patients
- Most tumors have more “suppressive” phenotype compared to matched blood
  - Foxp3, PD1
- Low numbers precluded correlation



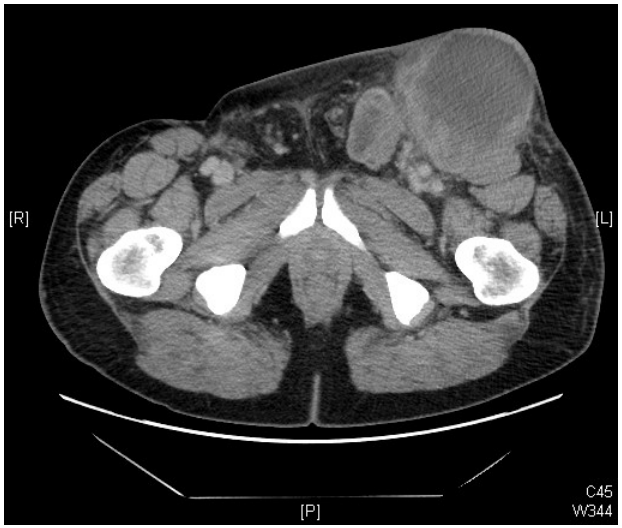
Gyorki DE,…Wolchok JD, Ariyan CE. Ann Surg Onc. 2013; 20: 3106-3111.

Case Presentation

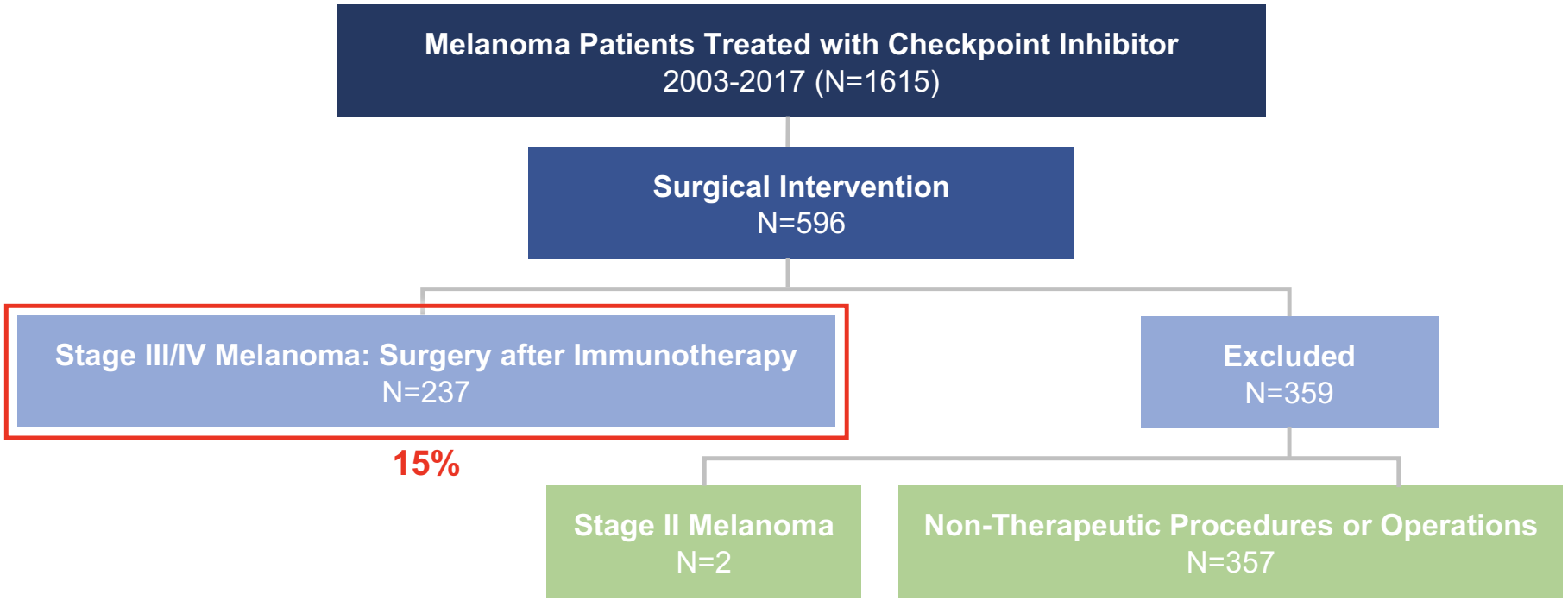
- **2012 –** resection of primary melanoma and nodes
- **2013 –** recurrence on observation with lung mets, recurrent groin and pelvic nodes
  - Ipilimumab (CTLA-4)- lung and pelvic nodes resolve, groin increases
  - Pembrolizumab (PD-1)- groin nodes increase
  - Radiation- progression
  - Referral Surgery

Recurrent groin disease with systemic response to immunotherapy

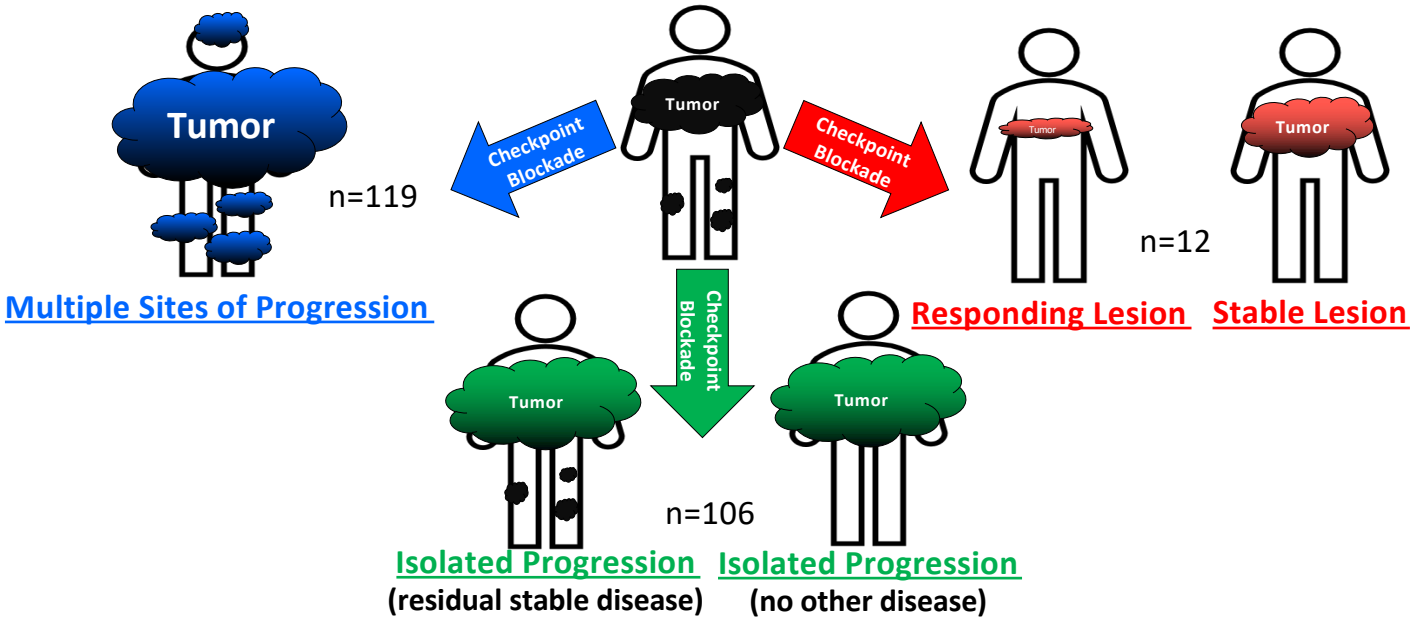
» Patient undergoes surgery, no further treatment, NED 7 years



MSKCC Melanoma Database: Surgery after immunotherapy



Adjuvant Surgery: Patients Stratified by Radiologically Assessed Response to Immunotherapy



Surgery After Checkpoint Blockade

Clinical Characteristics	Number of Patients (%) N=237
Median Age, years (Range)	63 (19-92)
Gender	
Female	91 (38)
Male	146 (62)
Stage III	29 (12)
Stage III (unknown primary)	2 (1)
Stage IIIB	6 (3)
Stage IIIC	21 (9)
Stage IV	208 (88)

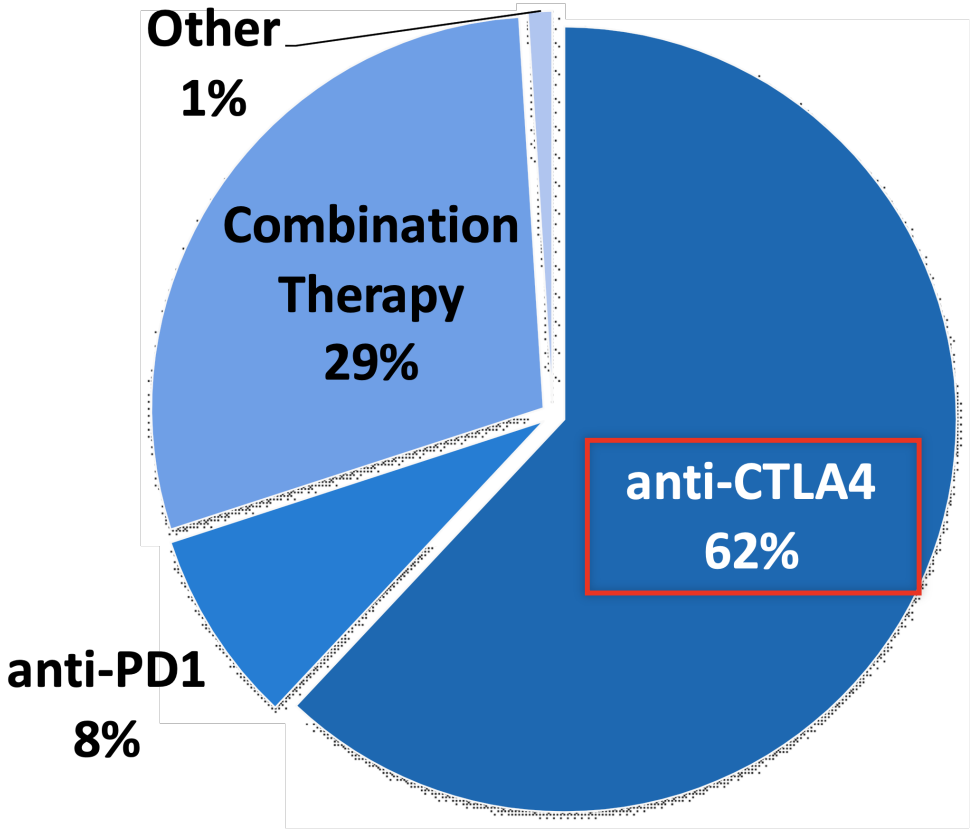
Bello et al, ASO 2019

Surgery After Checkpoint Blockade

Primary Site of Disease	Number of Patients N=237 (%)
Site of Primary Disease	
Cutaneous	162 (68.5)
Ocular/Uveal	3 (1)
Mucosal	16 (7)
Acral	17 (7)
Unknown Primary	39 (16.5

Bello et al, ASO 2019

Checkpoint Blockade Prior to Surgery



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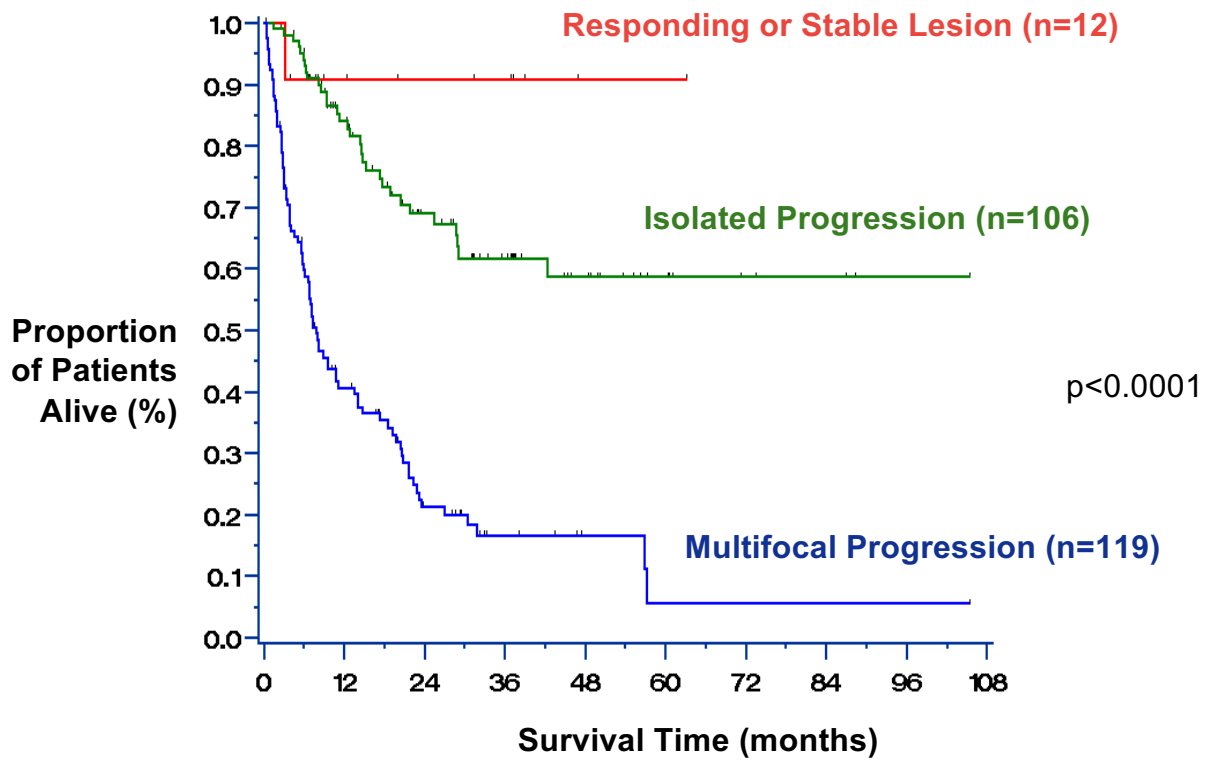
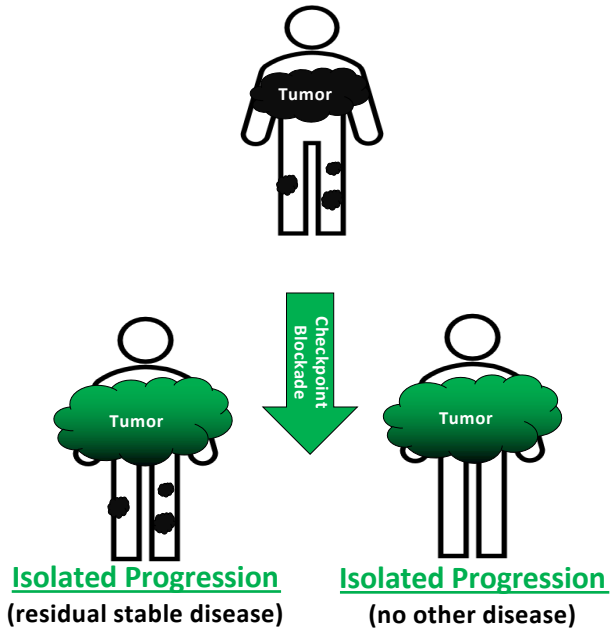
Bello et al, ASO 2019

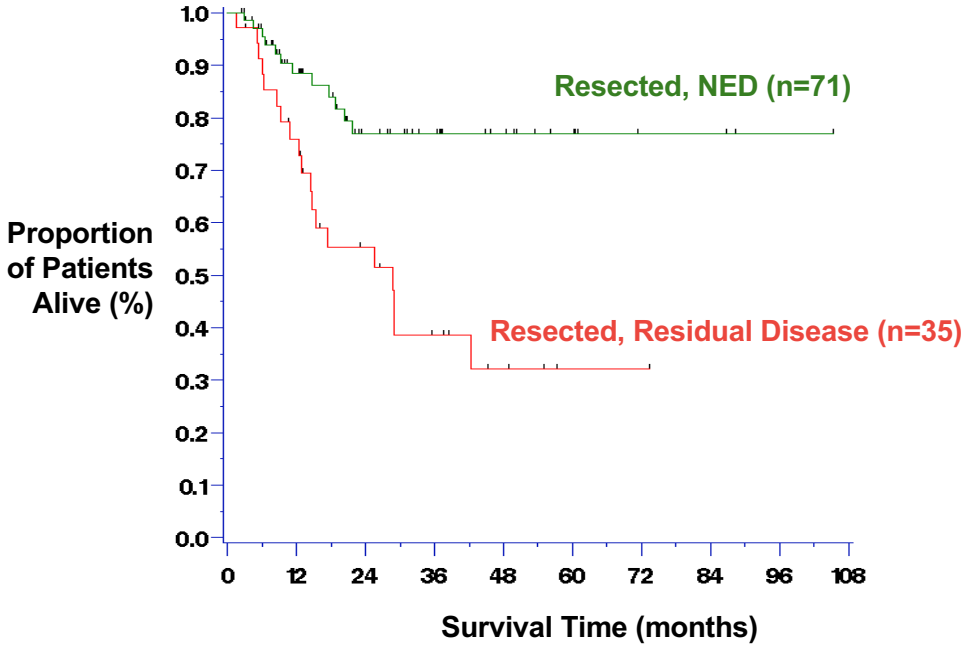
Adjuvant Surgery: Selected by systemic response to immunotherapy



Bello et al, ASO 2019

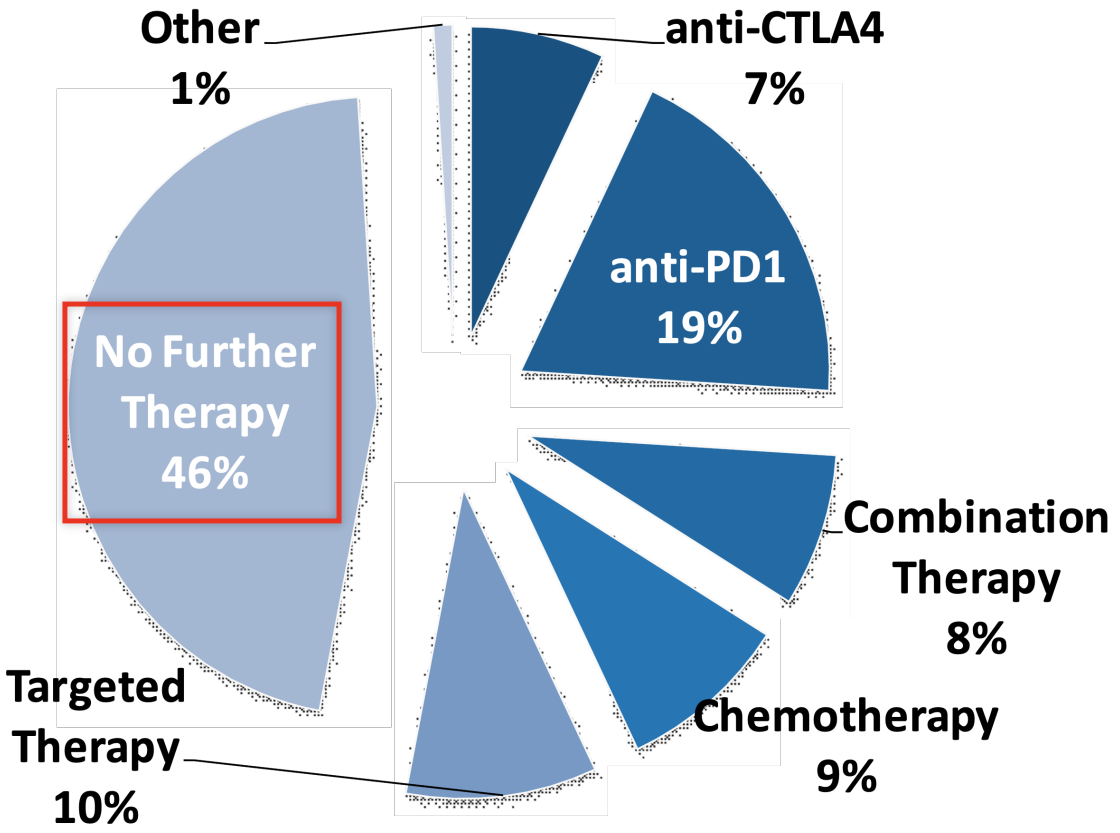
Adjuvant Surgery for Escape Lesions After Immunotherapy





Bello et al,
ASO 2019

Adjuvant Surgery: Many patients have not required further treatment



Bello et al, ASO 2019

Can Responses to Immunotherapy be Improved with local therapy?

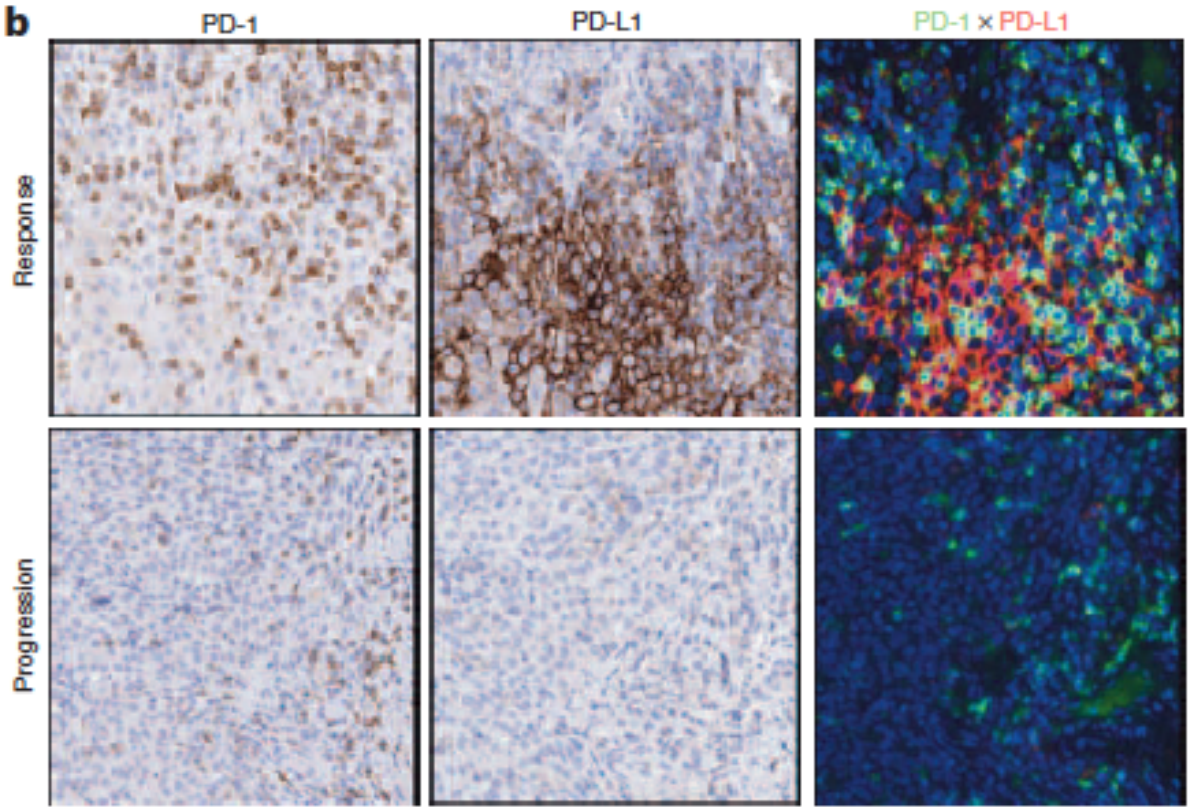
Primary Resistance

- » “COLD TUMORS”
- » B catenin/WNT-exclude immune cells
- » TGF-beta
- » Few mutations

Acquired Resistance

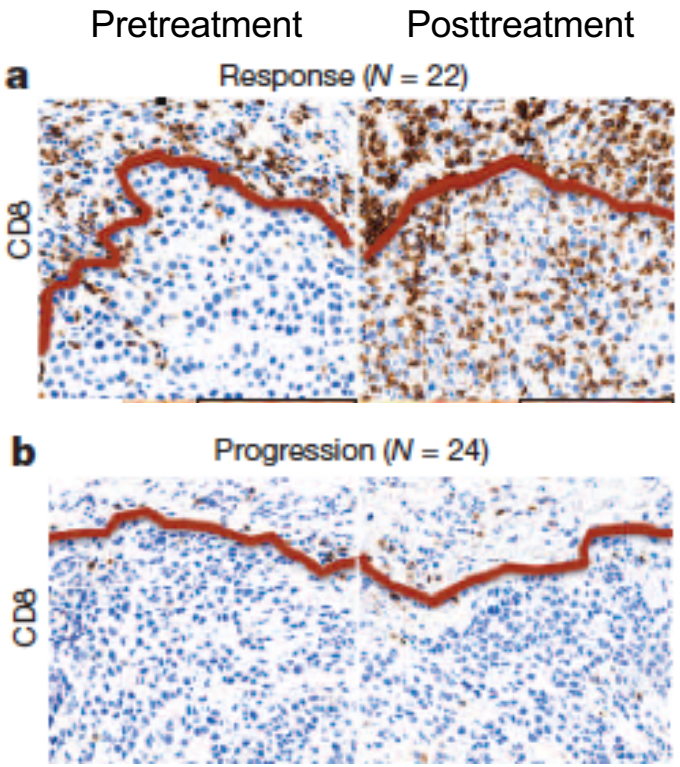
- » IFN induced resistance
  - › Upregulation of inhibitory ligands on cancer cells
- » Acquire loss of function mutation
  - › JAK 1, JAK2, HLA
- » Increased tumor burden

Pre-Treatment PD-1/PD-L1 Correlates with Response PD1



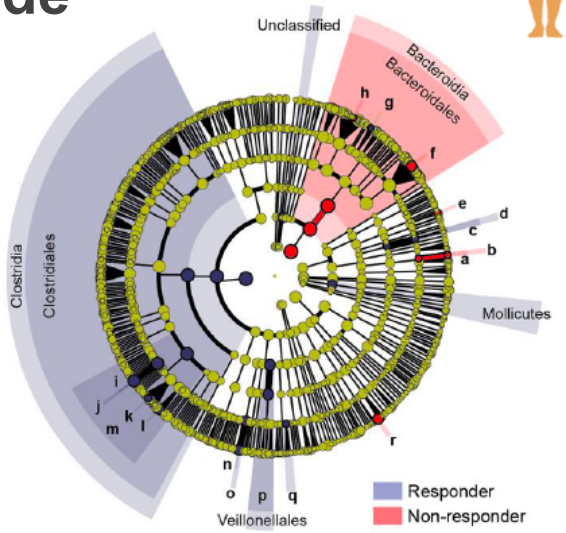
Tumeh et al, Nature 2015

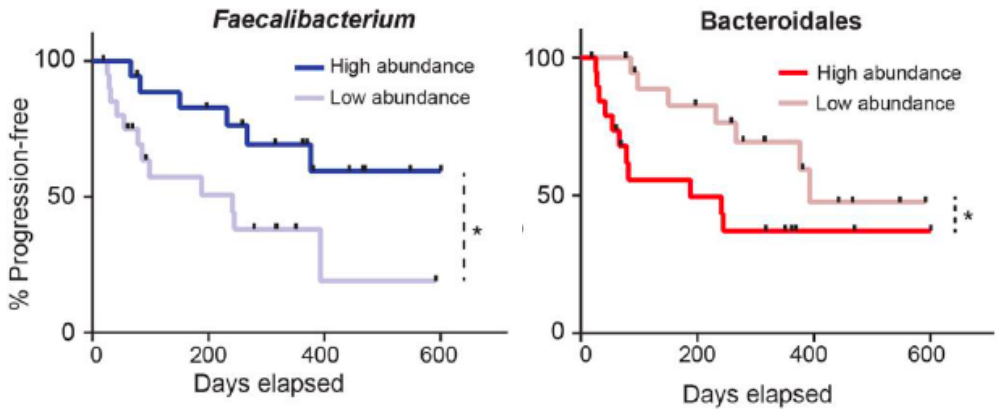
Responders to Immune Therapy(PD1) Have “Inflamed” Tumor



Tumeh et al, Nature 2015

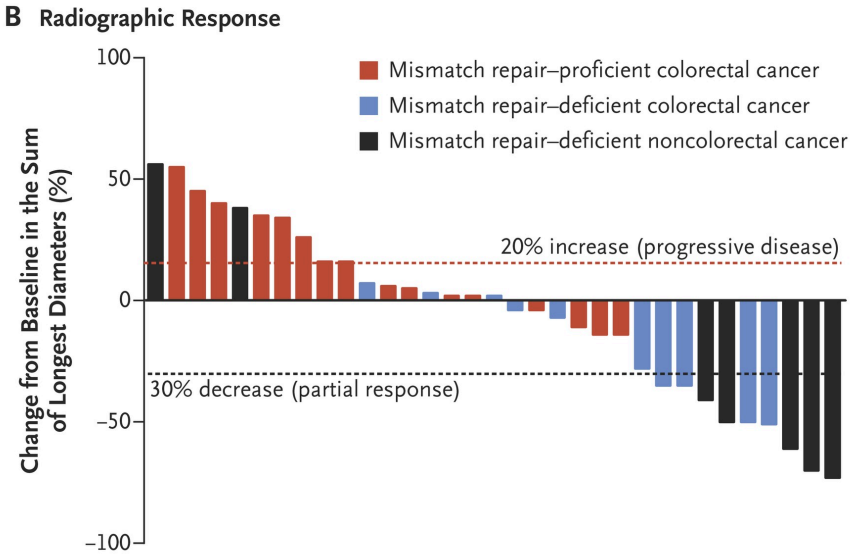
Gut Microbiome Associated with Response to PD-L1 Blockade

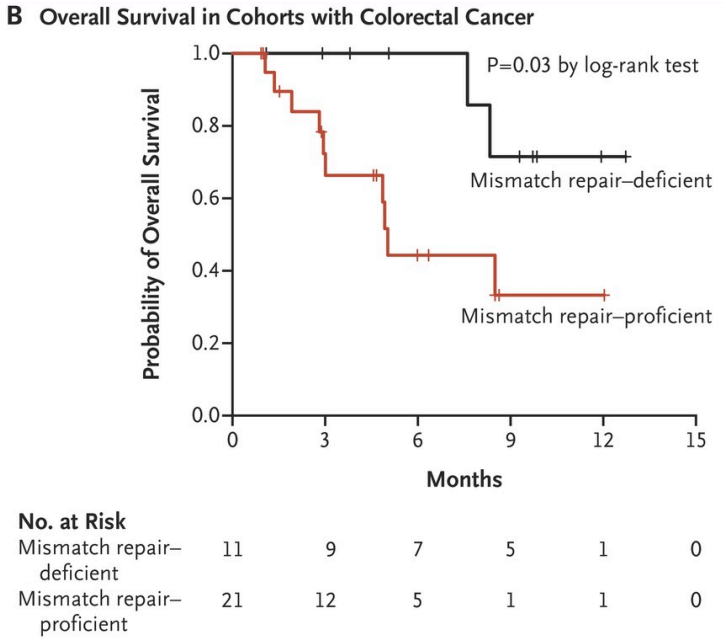




Gopalakrishnan et al Science 2017

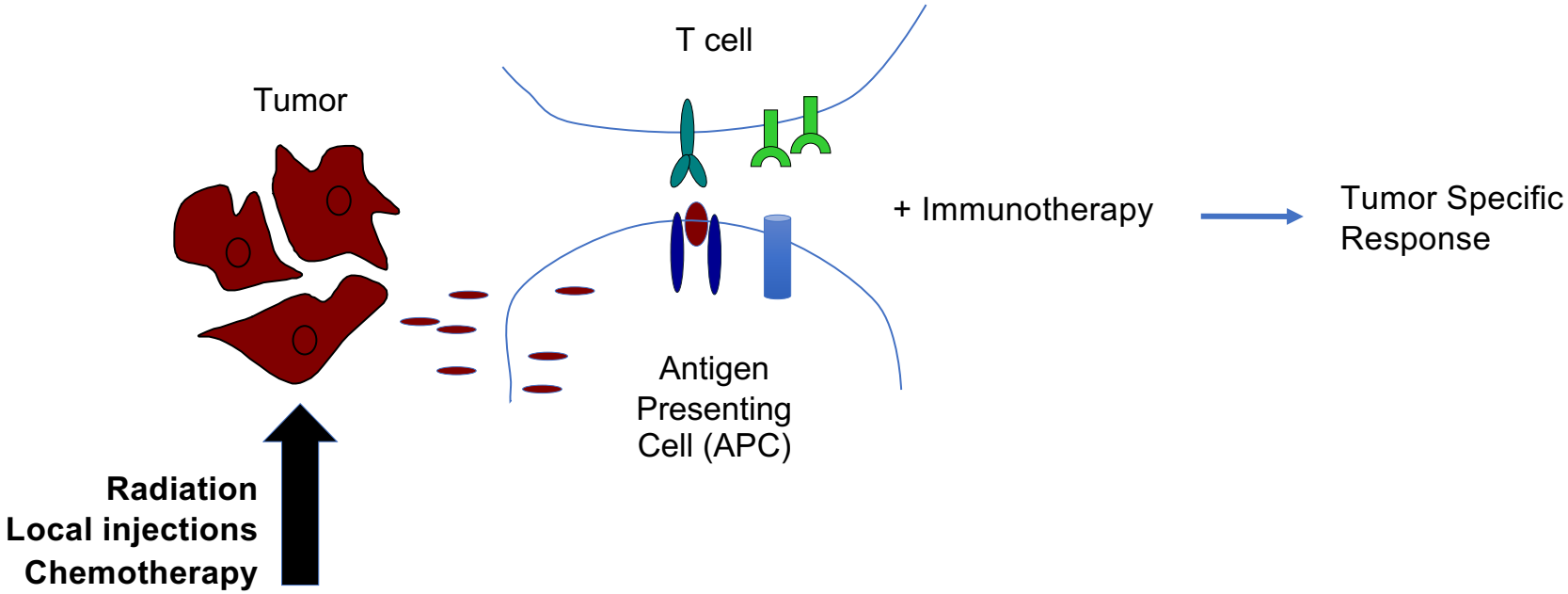
Mismatch Repair Deficient Tumors Respond to PD-1 Blockade



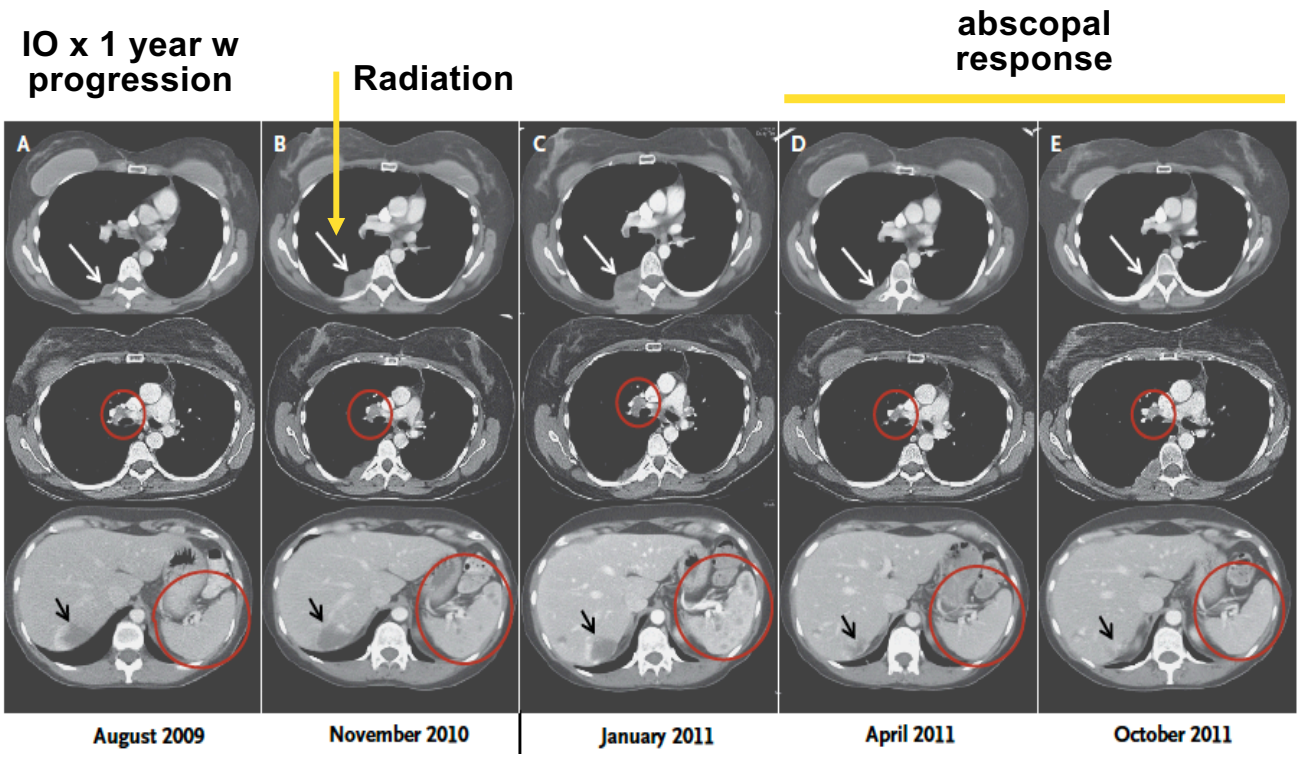


Le, DT et al NEJM 2015

Can Local Therapies Enhance Immunotherapy Response?



Abscopal response with Immunotherapy and radiation



Memorial Sloan Kettering Cancer Center

Postow NEJM 2012

Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Christina Twyman-Saint Victor[1,2]*, Andrew J. Rech[2]*, Amit Maity[3,4], Ramesh Rengan[3,4]†, Kristen E. Pauken[5,6], Erietta Stelekati[5,6], Joseph L. Benci[2,3], Bihui Xu[2,3], Hannah Dada[2,3], Pamela M. Odorizzi[5,6], Ramin S. Herati[1,6], Kathleen D. Mansfield[5,6], Dana Patsch[3], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Hemant Ishwaran[7], Rosemarie Mick[4,8], Daniel A. Pryma[4,9], Xiaowei Xu[4,10], Michael D. Feldman[4,10], Tara C. Gangadhar[1,4], Stephen M. Hahn[3,4]†, E. John Wherry[4,5,6]§, Robert H. Vonderheide[1,2,4,6]§ & Andy J. Minn[2,3,4,6]§

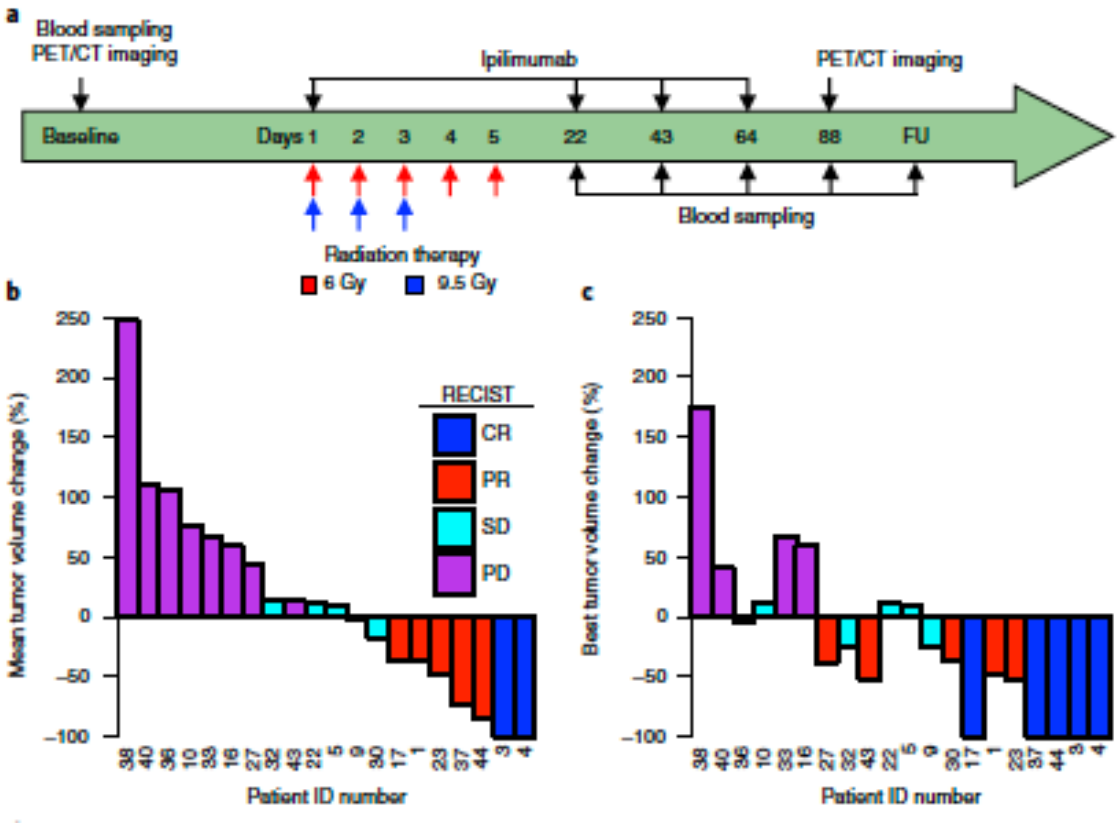
nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0232-2

Radiotherapy induces responses of lung cancer to CTLA-4 blockade

Silvia C. Formenti[1*], Nils-Petter Rudqvist[1,15], Encouse Golden[1,14,15], Benjamin Cooper[2], Erik Wennerberg[1], Claire Lhuillier[1], Claire Vanpouille-Box[1], Kent Friedman[3], Lucas Ferrari de Andrade[4,5], Kai W. Wucherpfennig[4,5], Adriana Heguy[6,7], Naoko Imai[8], Sacha Gnjatic[8], Ryan O. Emerson[9], Xi Kathy Zhou[10], Tuo Zhang[11], Abraham Chachoua[12] and Sandra Demaria[1,13*]



Chemo-refractory lung cancer

CTLA-4 not effective (historically

Addition of radiation + CTLA-4-responses

Increased IFN-beta

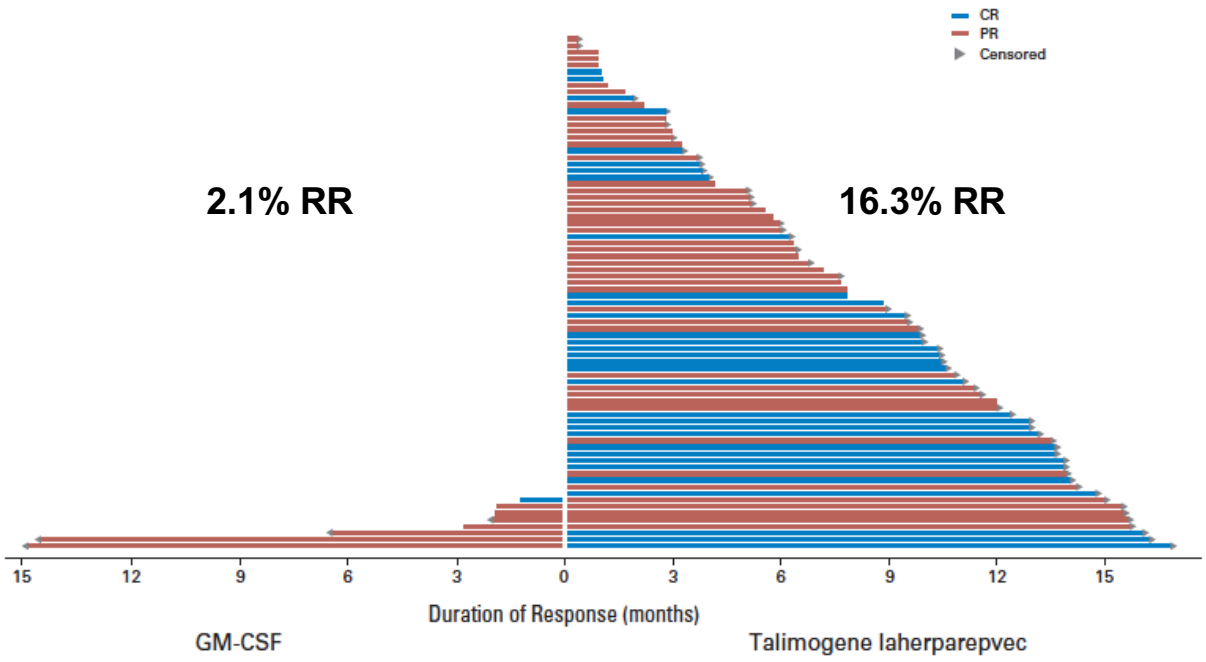
Increased CD8 cells

Increased T cell clones

Formenti et al Nature Medicine 2018

TVEC Response

- Enhanced oncolytic ability
- Deletion of ICP34.5
  - less neurovirulence
- Insertion GM-CSF
  - promotes antigen presentation cells/dendritic cells

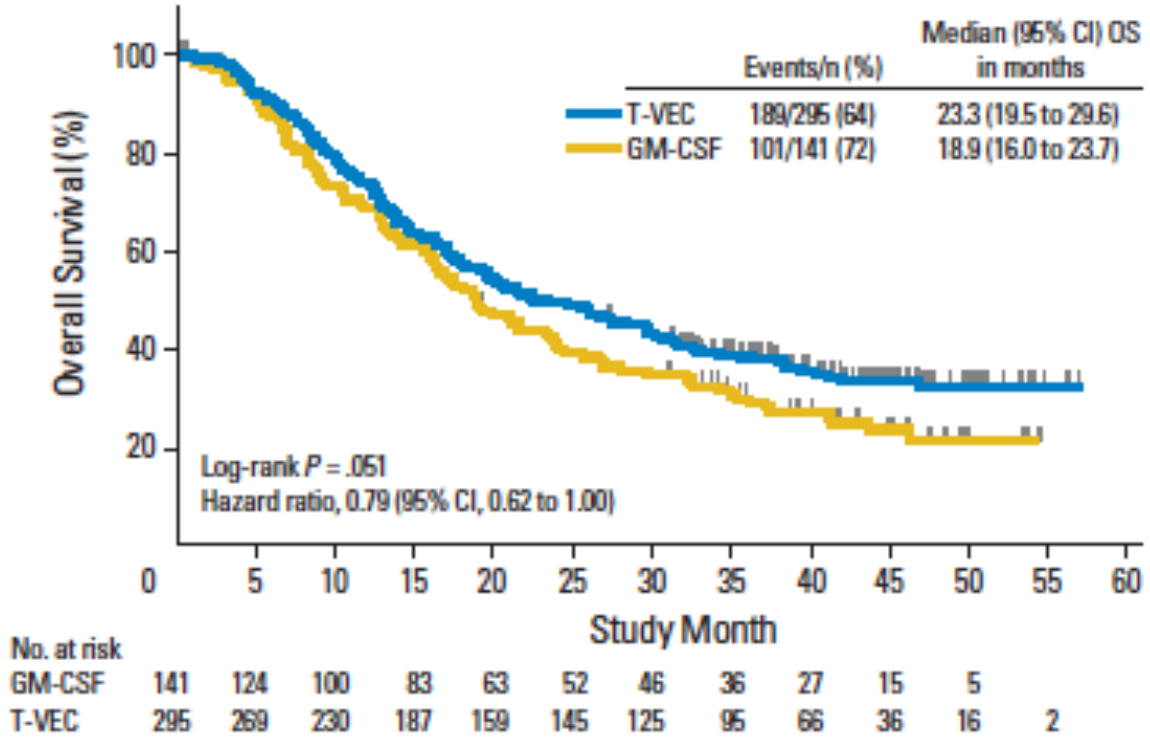


Overall response rate 5.6 % versus 26% (10.8% complete response) T-VEC

Andtbacka, et al JCO, 33:25 2015

Local TVEC Injections do not Improve Survival

- Prospective Randomized Control Trial
  - TVEC(GM-CSF) versus GM-CSF



Andtbacka, R et al JCO, 33:25 2015

TVEC Combination Therapy: TVEC + Ipilimumab

- 18 patients Stage III/IV melanoma
  - Overall response rate 50%, 22% complete response (n=4)

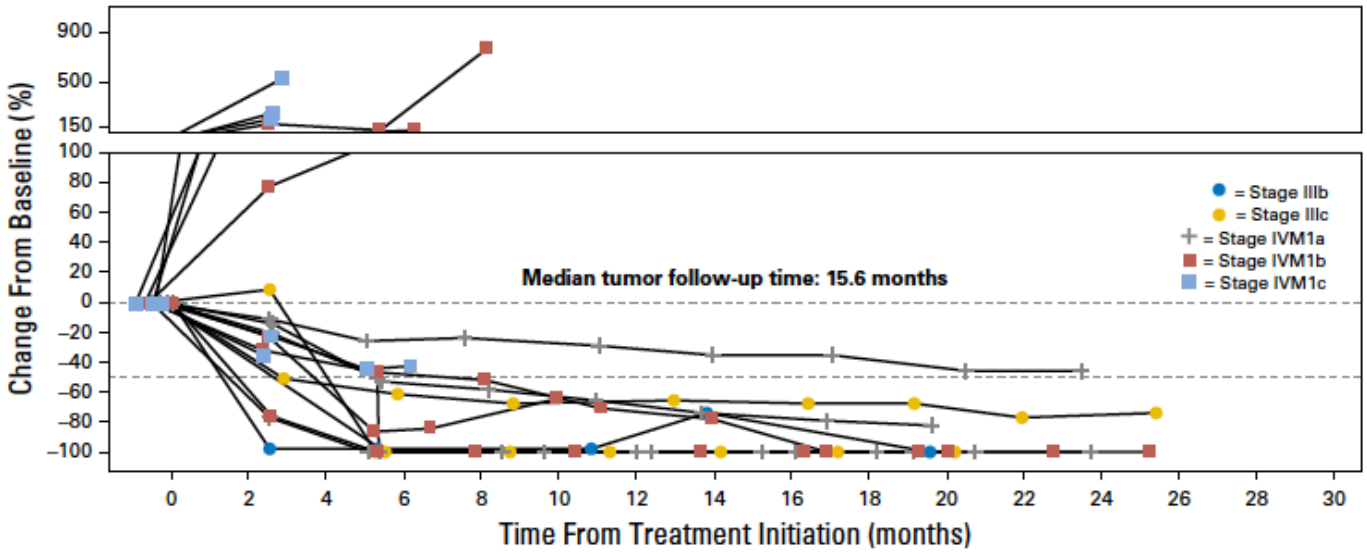
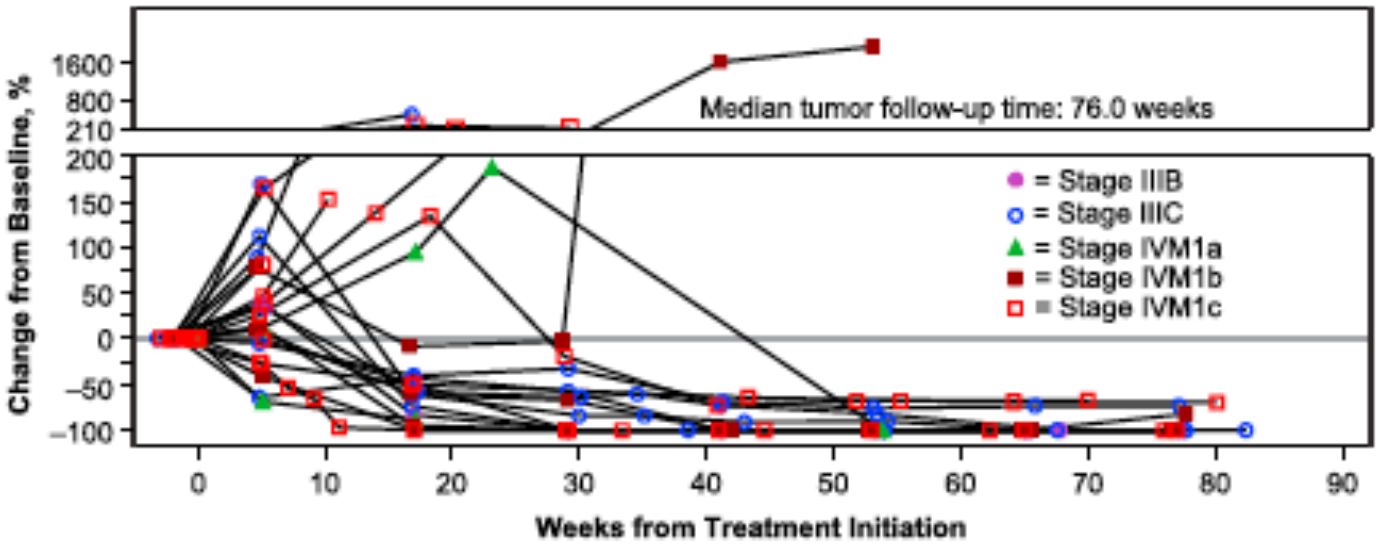


Fig 2. Changes in tumor burden by disease stage.

Andtbacka, R et al JCO, 34:22 2016

TVEC Combination Therapy: TVEC + anti-PD1

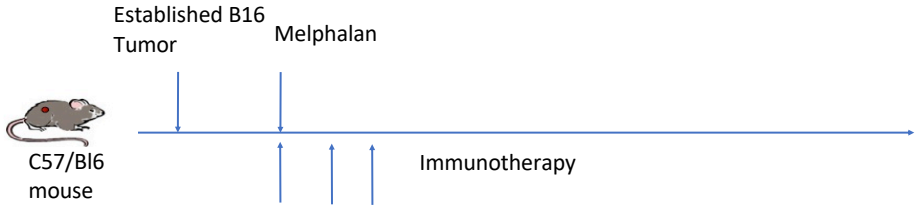
- 21 patients Stage III/IV melanoma
  - Overall response rate 62%, 33% complete response (n=8)

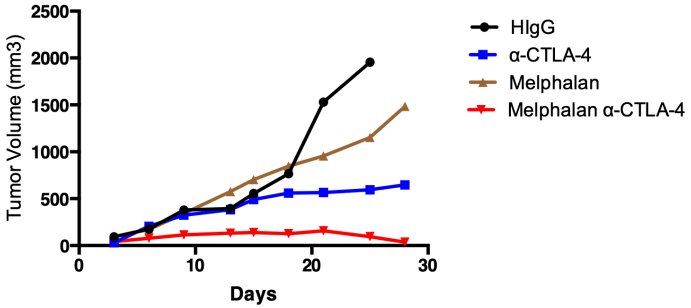


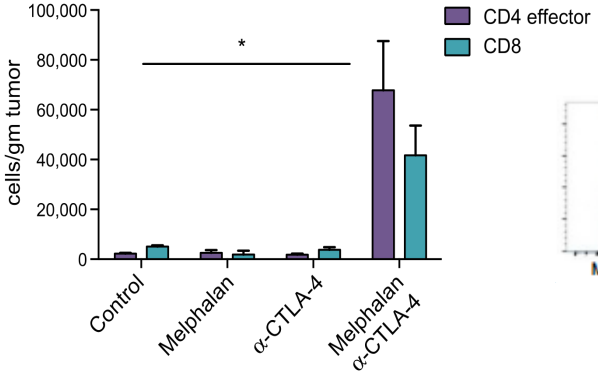
Phase 3 RCT trial of PD1/ TVEC versus PD1/ placebo accrued

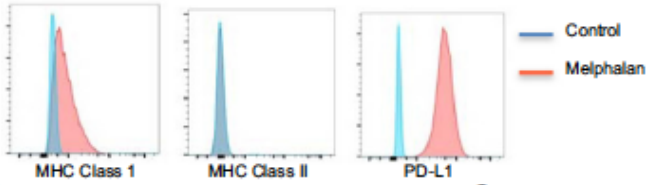
Andtbacka, R et al JCO, 34:22 2016

Local Chemotherapy Enhances responses to CTLA-4 Blockade

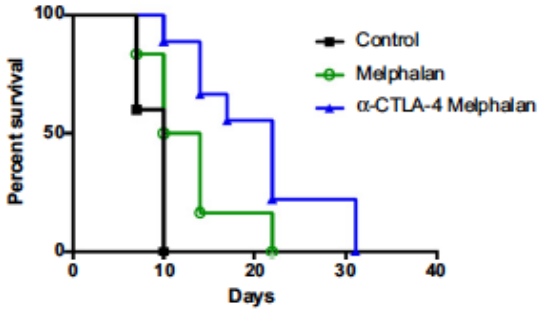








Tumor

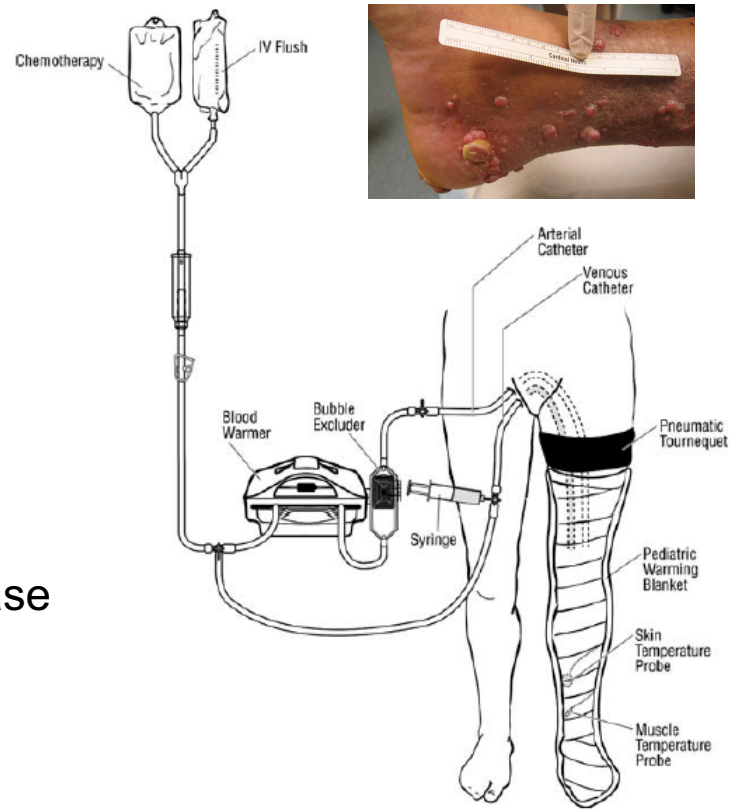


IFNR-/- mice

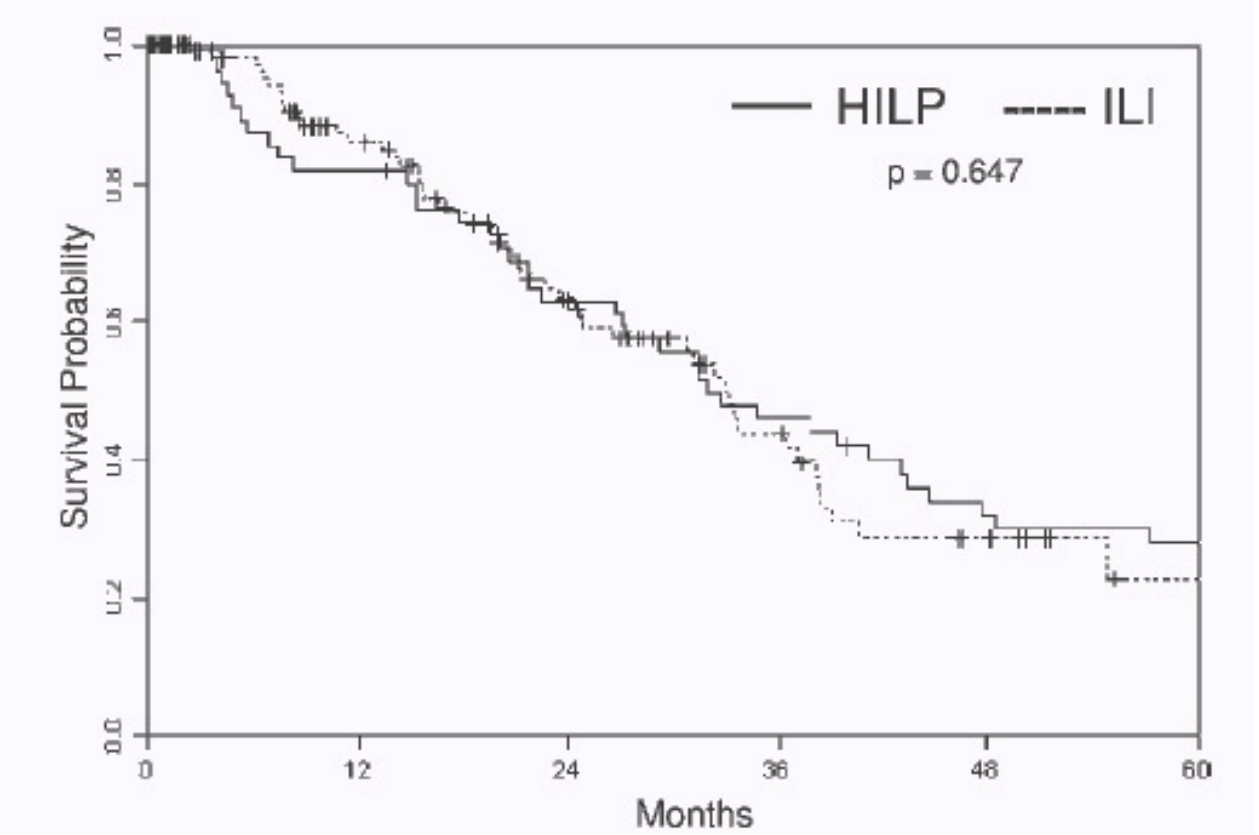
Local Chemothearpy: Isolated Limb Infusion

Treatment of advanced recurrent melanoma (in transit disease)

- 50% response rate
  - 25% partial response
  - 25% complete response
- Palliative, 80% patients will die of distant disease
- Most patients recur within a year
  - Progression free survival 8 months



Infusion Therapy is a Regional Treatment Most Patients Die of Distant Disease (Duke Experience)



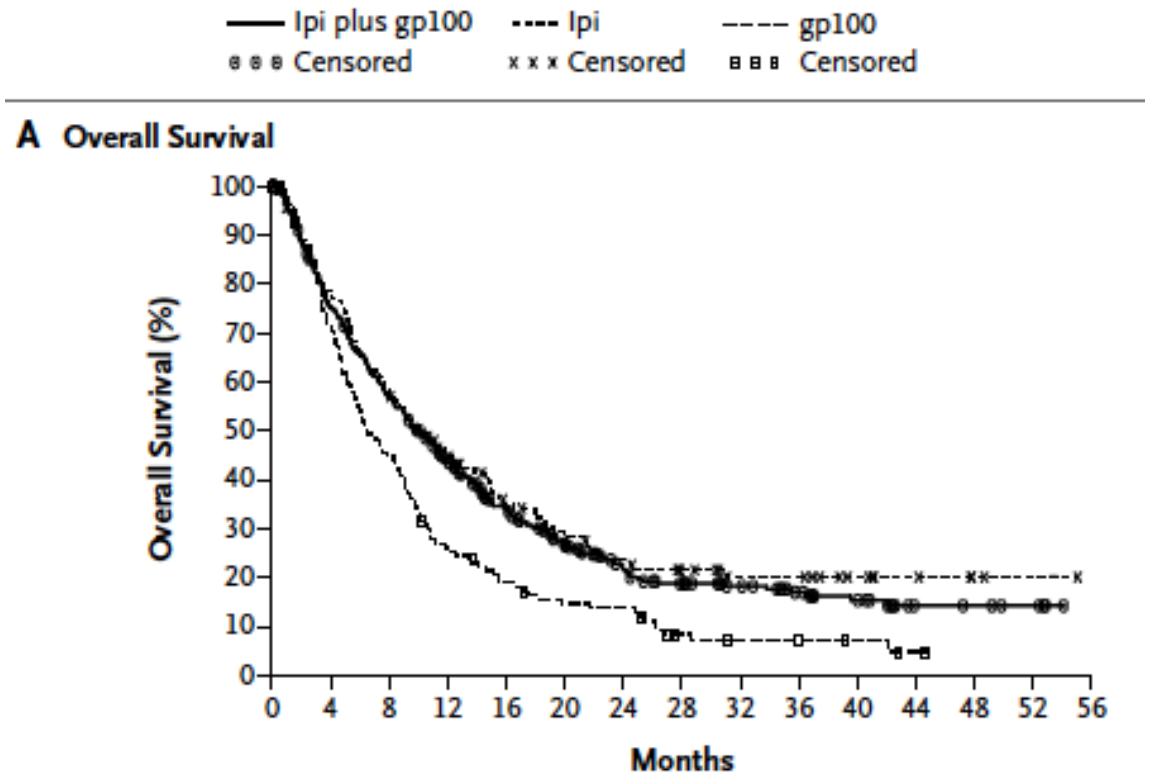
Memorial Sloan Kettering Cancer Center

Raymond et al JACS 2011

CTLA-4 Blockade (Ipilimumab) Alone (10mg/kg) Rarely Cures In-Transit Melanoma

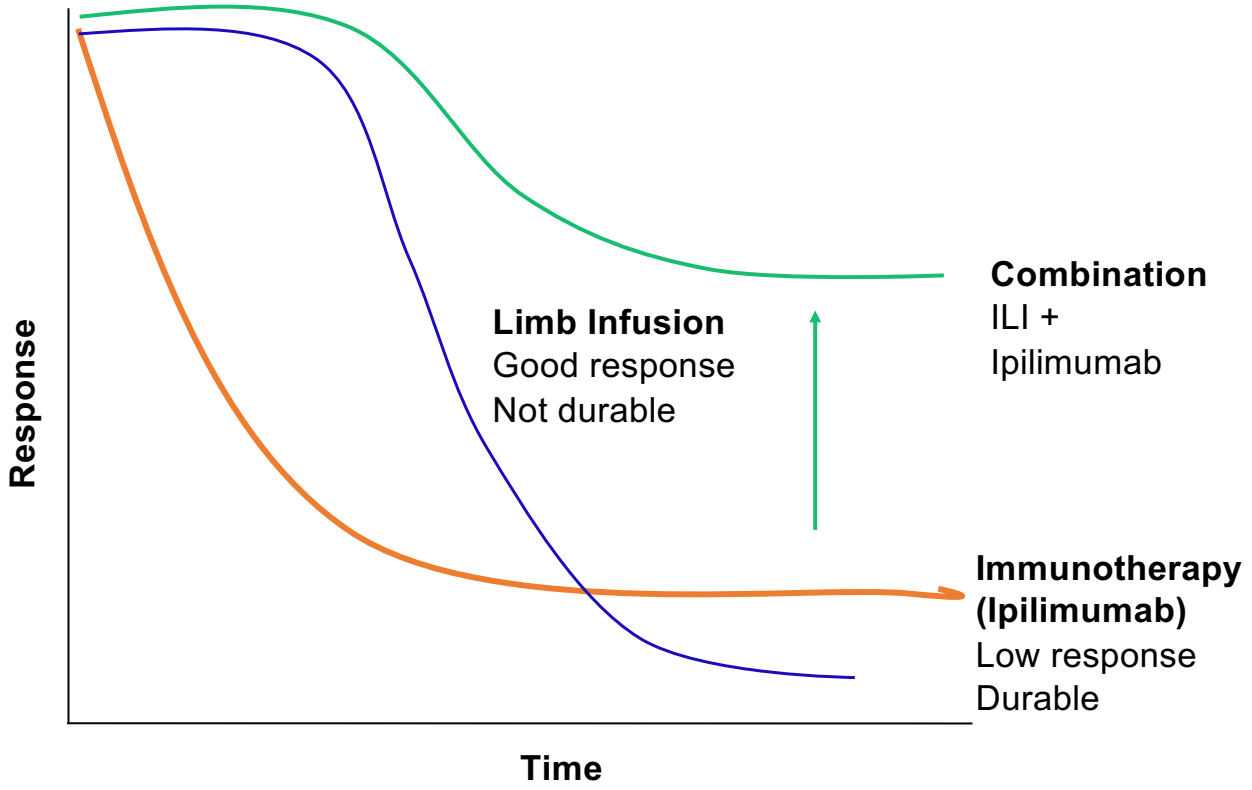
Response rate of patients with M0 disease is 8.3%

(95% CI 0.2-8.5)

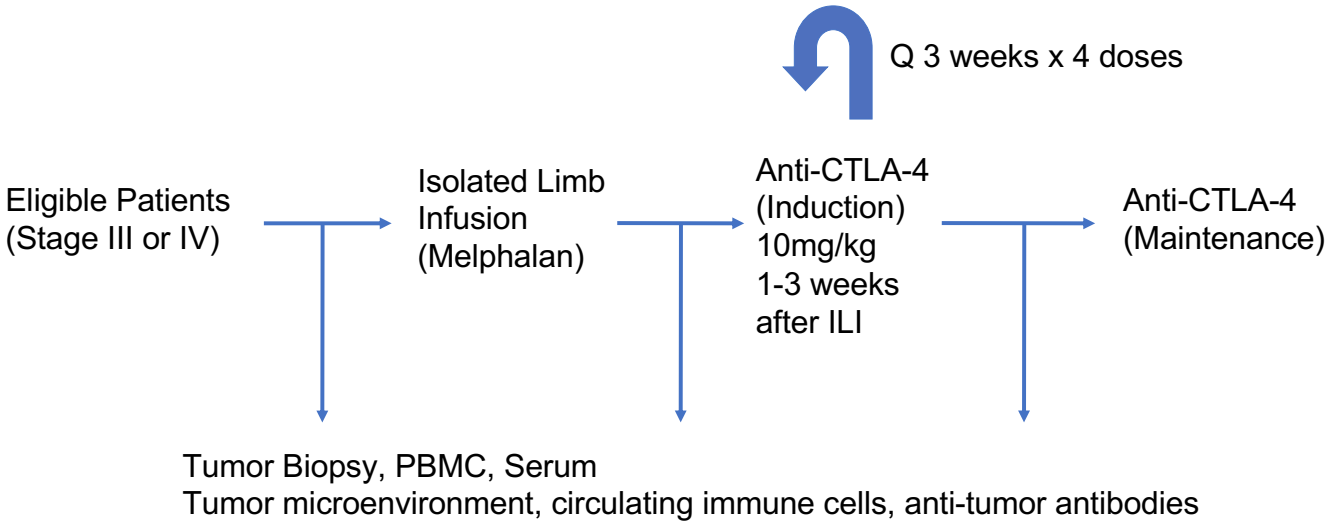


Hodi et al NEJM 2010

Can Chemotherapy Enhance Immunotherapy Response?



A Phase II trial of Systemic CTLA-4 blockade after Isolated Limb Infusion



Primary endpoint:
Progression Free Survival

Secondary endpoint:
Safety
Response
Immunological changes

Ariyan et al, CIR 2018

Patient Characteristics (26 patients)

	N(%)
Gender	Female n=10 (38) Male n=16 (62)
	IIIB n=11 (42) IIIC n=12 (46) IV n=3 (12)
Mutation Status	BRAF V600E n=4 (15) NRAS n=9 (35) WT n=9(35) Unknown n=4(15)
Melanoma Subtype	Acral n=3 (12) Cutaneous n=19 (73) Unknown Primary n=4 (15)
High Tumor Burden (>50 lesions or one > 3cm)	Yes n=7 (27) No n=19 (73)

Ariyan et al, CIR 2018

A Phase II trial of Systemic CTLA-4 blockade after Isolated Limb Infusion

» No Increased Limb Toxicity

Wiederbink Scale of Limb Toxicity

1 (no visible effect)	0%
2 (slight erythema/edema)	84%
3 (considerable erythema/edema)	16%
4 (extensive epidermolysis with threatened compartment syndrome)	0%
5 (needs amputation)	0%

Ariyan et al, CIR 2018

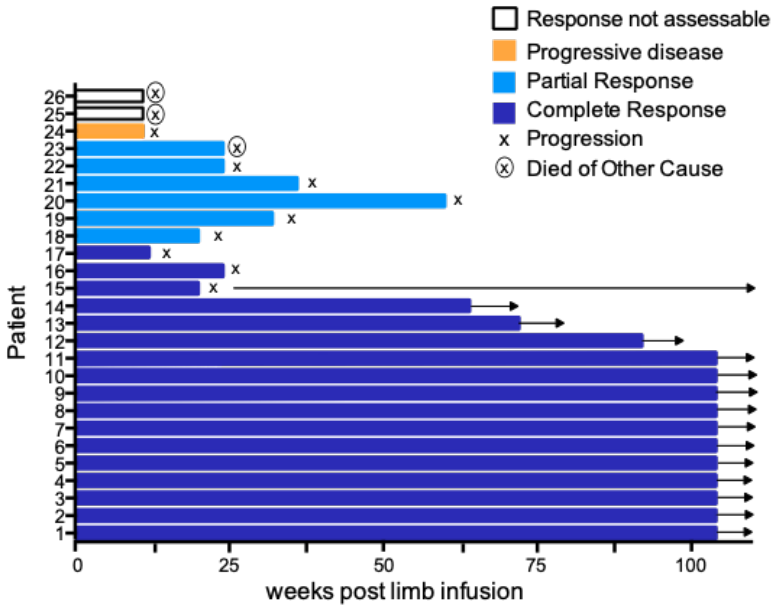
Ipilimumab Toxicity: Immune Mediated Adverse Events

	n	Steroids (PO)	Remicade or IV steroids	Replacement (hydrocortisone/thyroid)
Rash	10	2		
Diarrhea/Colitis	10	10	6	
Hypophysitis	5			5
Hepatitis	3	3		

Ariyan et al, CIR 2018

Local chemotherapy and CTLA-4 blockade creates an inflamed tumor microenvironment and robust therapeutic anti-tumor responses

C. E. Ariyan,*1 M. S. Brady1, R.H. Siegelbaum2, J. Hu1, D. M. Bello1, J. Green1, C. Fisher3, R. A. Lefkowitz4, K. S. Panageas5, M. Pulitzer7, O. Misholy1, M. Vignali10, R. Emerson10, C. Tipton10, H. Robins10, T. Merghoub6, J. Yuan6, A. Yungbluth7, J. Blando9, P. Sharma9, A. Y. Rudensky8, J. D. Wolchok6,8, J. P. Allison9



Response rate 85%

62% Complete response

23% Partial response

PFS at one year 58%

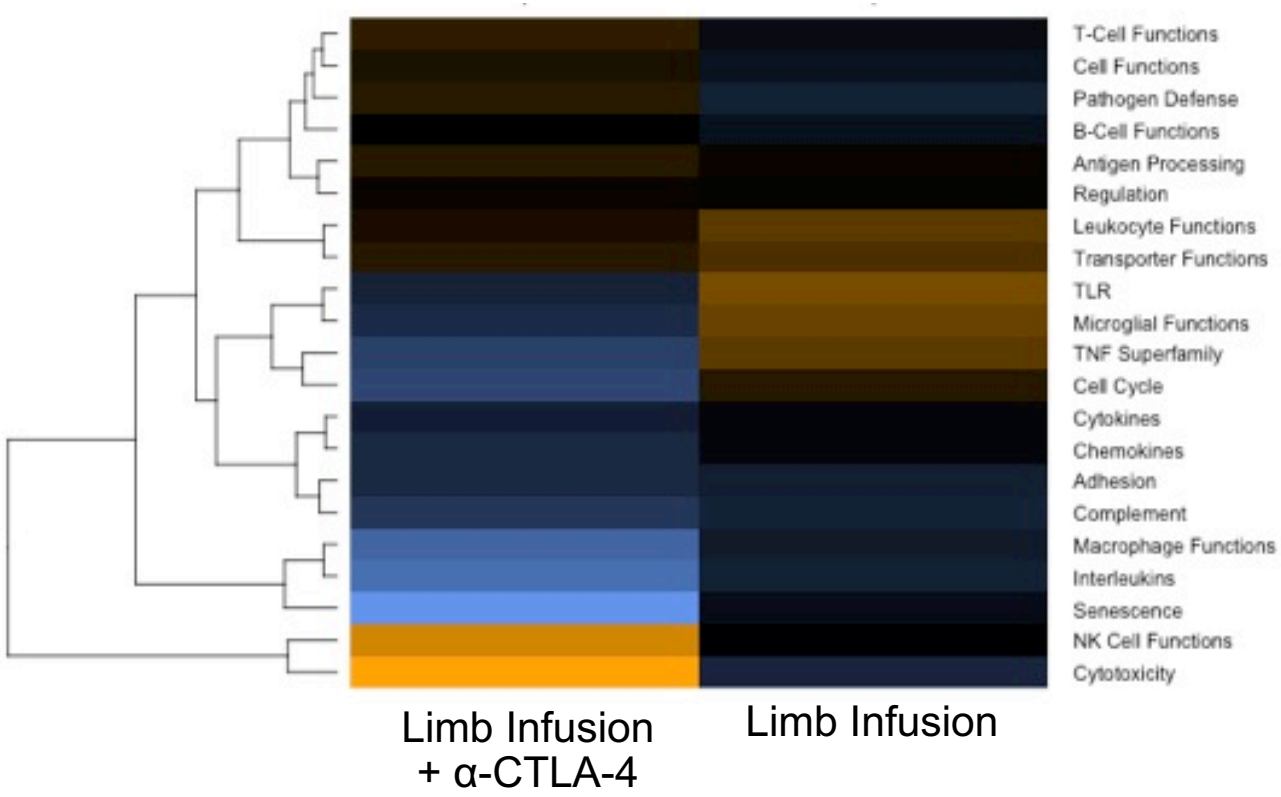
Most complete responses durable

Immune infiltration into tumors

Systemic responses

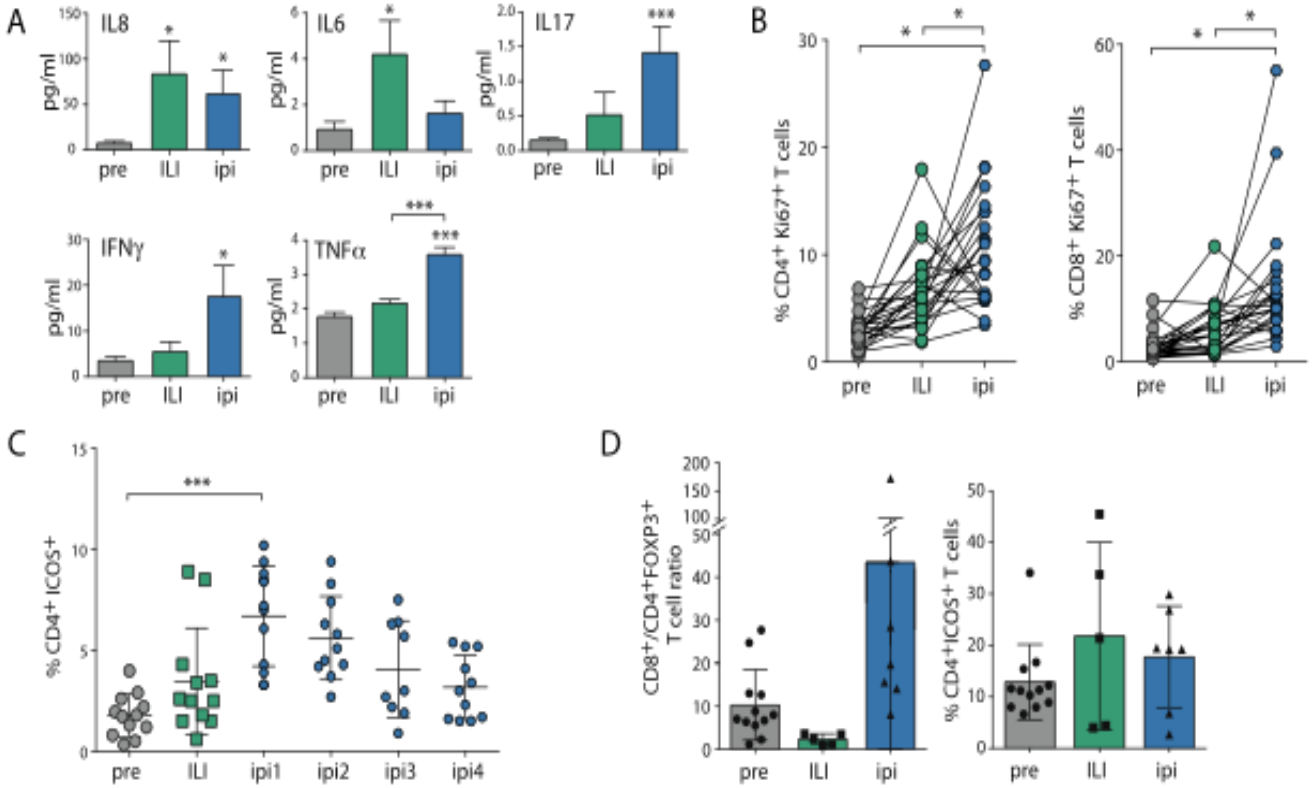
Ariyan et al, CIR 2018

Gene expression supports an inflammatory phenotype in tumors



Ariyan et al, CIR 2018

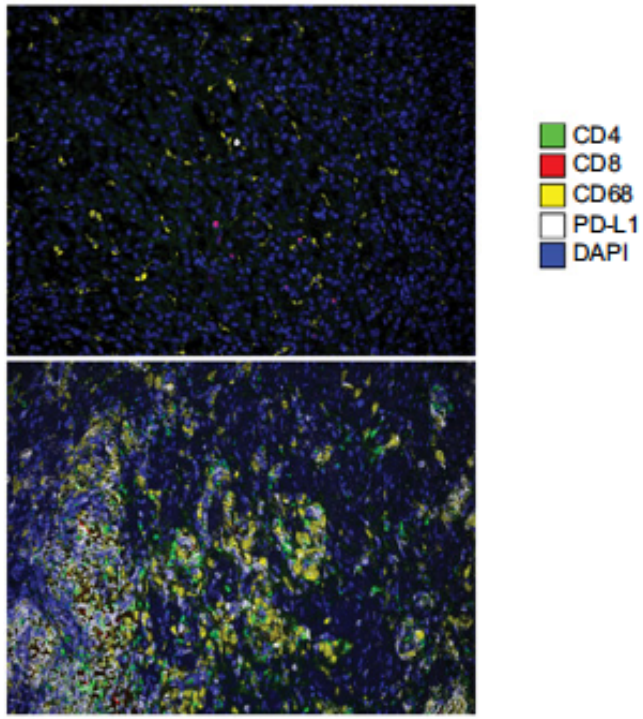
Inflammation in PBMC and Tumor

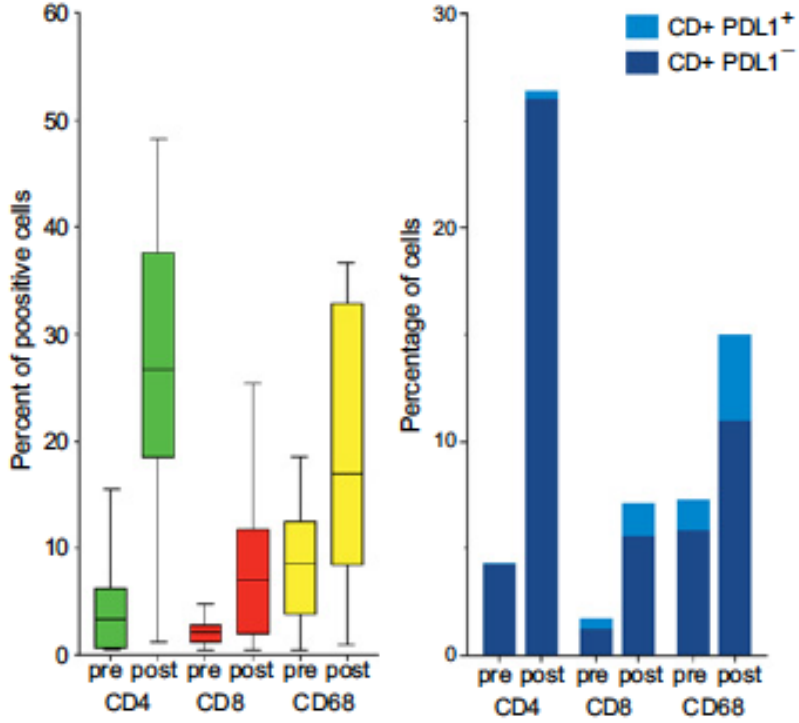


Memorial Sloan Kettering Cancer Center

Ariyan et al, CIR 2018

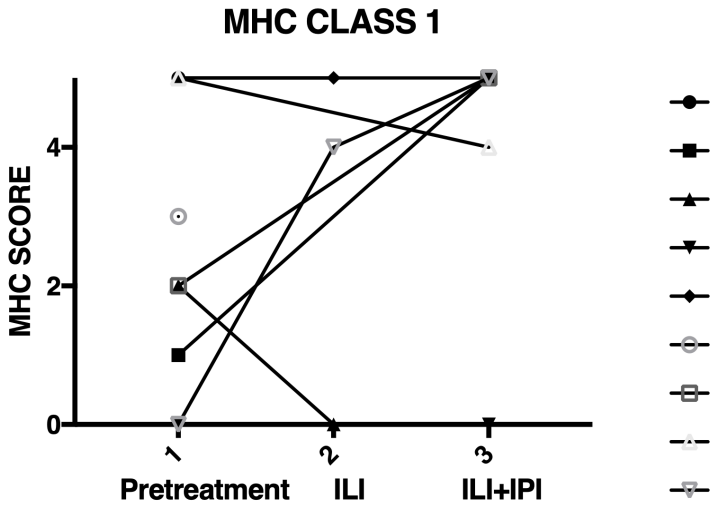
Multiplex IHC

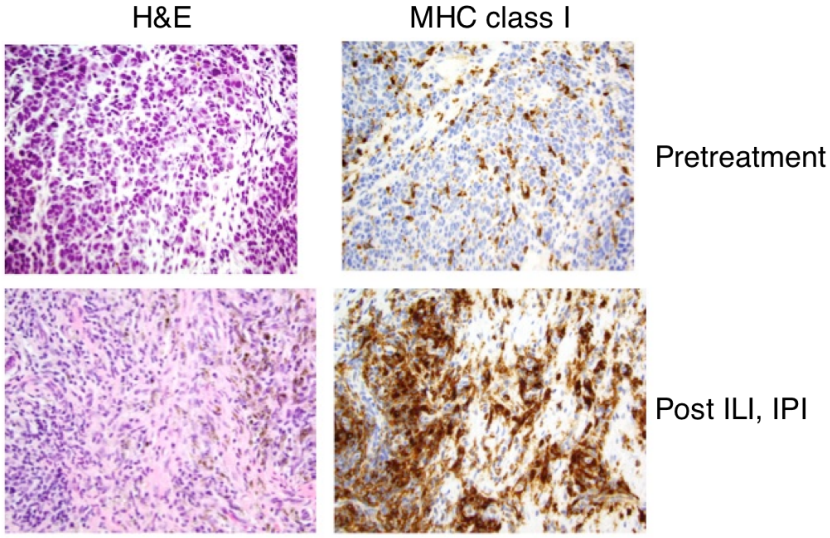




Ariyan et al, CIR 2018

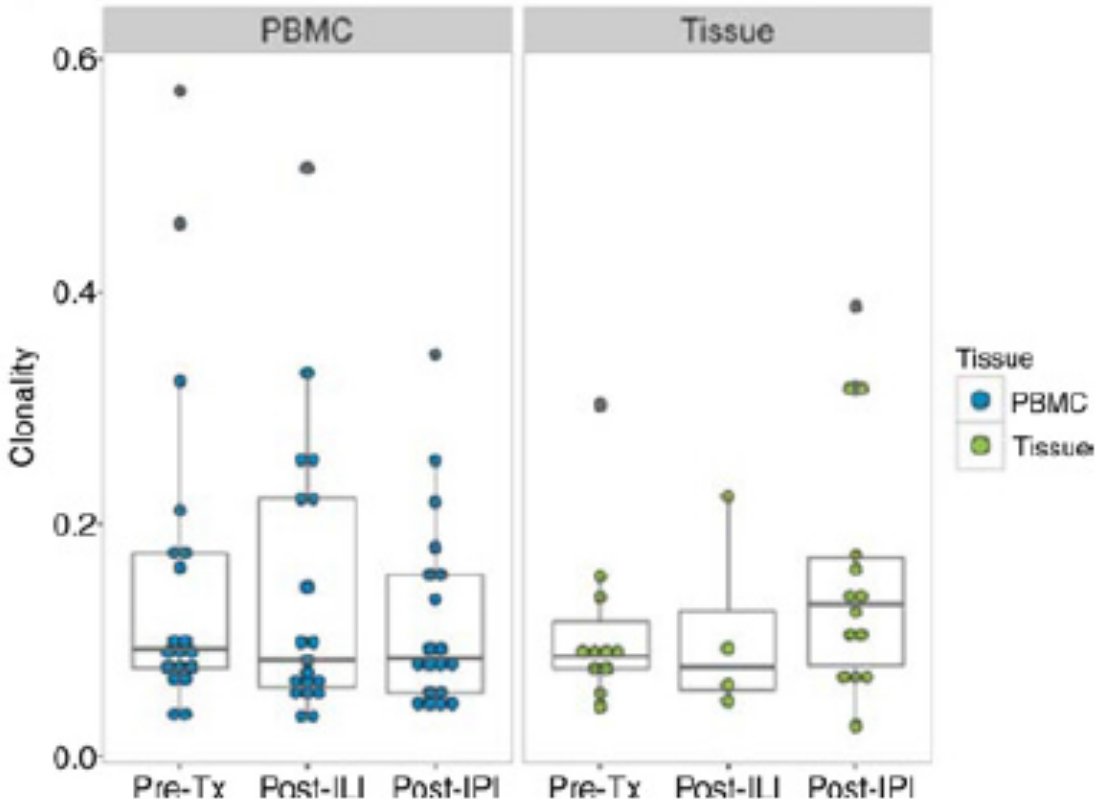
MHC Class I Expression with Treatment





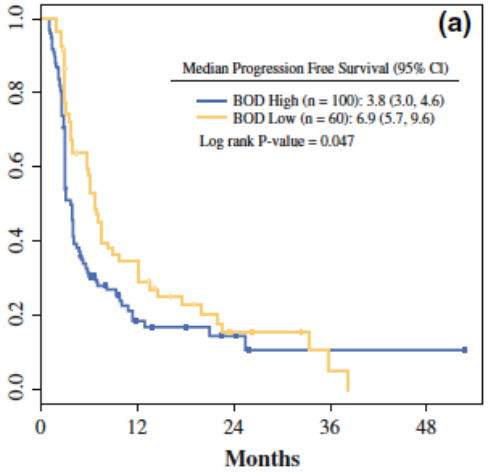
Ariyan et al, CIR 2018

Increased TCR Clonality in Tumor



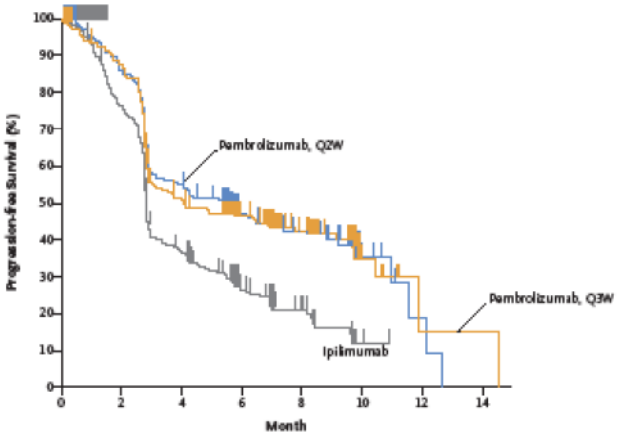
A Phase II trial of Systemic CTLA-4 blockade after Isolated Limb Infusion

Progression Free Survival
Chemotherapy alone (ILI)



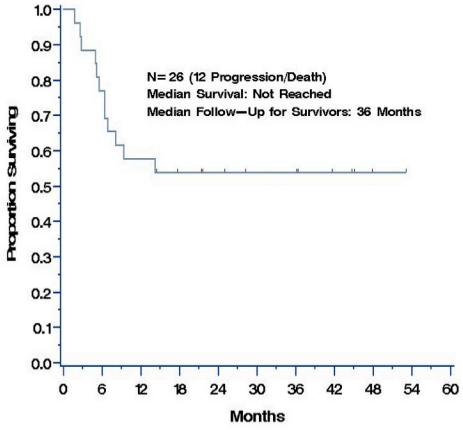
Zager et al, ASO 2015

Progression Free Survival
Immunotherapy (IPI or PD1)



Robert et al, NEJM 2016

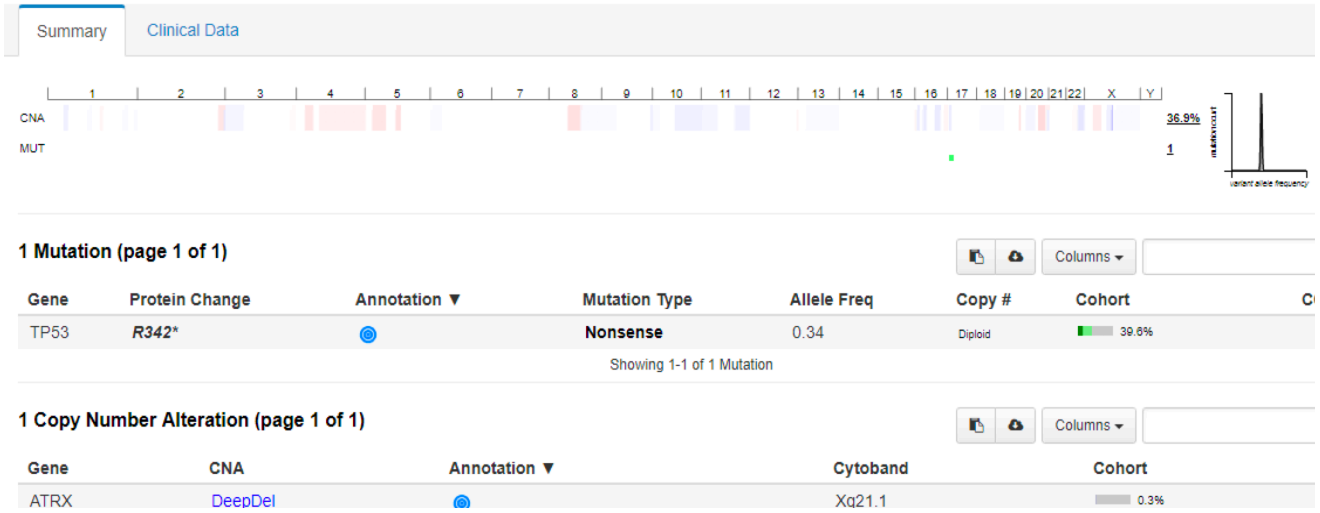
Progression Free Survival
Chemotherapy (ILI) + IPI



Ariyan et al, CIR 2018

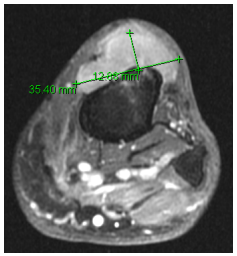
How about “cold” tumors? Local Chemotherapy and Immunotherapy in Sarcoma

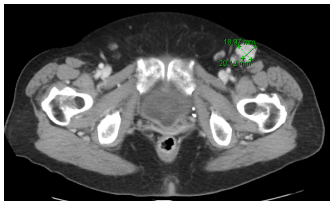
- 77 year old female, s/p seven surgeries for recurrent myxofibrosarcoma
  - Last resection 1 year ago with flap coverage
  - Postop radiation
- Functional, still works, wears brace for foot drop
- Presents with local recurrence and nodal disease (groin)

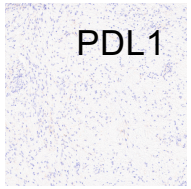


Chemotherapy and Immunotherapy in Sarcoma

Pretreatment

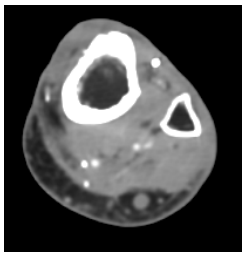






s/p 7 resections
Radiation
Palpable nodal disease

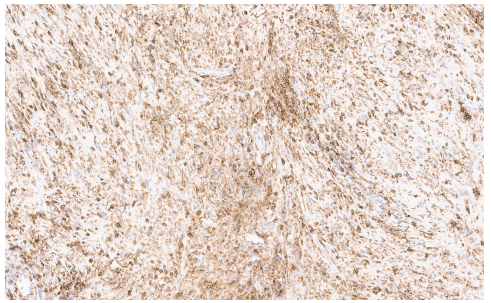
Post ILI, PD1



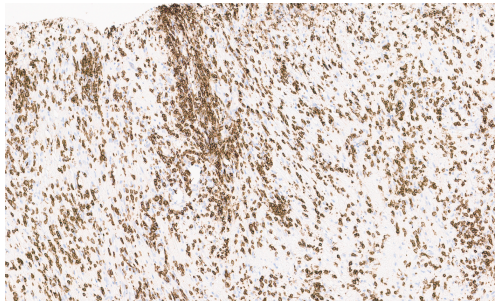
Leg lesion flat
nodal disease not
palpable

Biopsy

CD4
cell



CD8
cell



Antonescu

Conclusions

Local therapies have renewed efficacy in era of Immunotherapy

- » Removal of “escape” lesions
- » Local therapies to augment systemic immunity
  - › Radiation
  - › Viral Injections
  - › Local Chemotherapy

LONG TERM OUTCOMES AND BIOMARKERS NEEDED

NASDC
NCI Awardee Skills Development Consortium

Integrating Surgery and Local Regional Therapy into Immunotherapy(IO) Treatment

Questions