Alliance Symposium:
Interdisciplinary Efforts to Increase the Translational Potential of Neoadjuvant Trials
November 7th, 2014

Breaking New Ground:
Neoadjuvant Trials in Advanced "Resectable" Melanoma

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Spectrum of Advanced Disease

- Nodal disease
  - Stage IIIb/c
  - with or without known primary
  - resectable vs “unresectable”
- Resectable (oligometastatic) stage IV disease

Definition of “Unresectability”

- Categorically / technically unresectable

- “Unresectable”
  - technically resectable
  - but not meaningful in terms of long term survival and regional disease control

Advanced Nodal Disease
Competing Risks

- Development of systemic (stage IV) disease
  - at least 50%
  - may be as high as 80%
- In basin failure
  - source of significant morbidity
  - difficult to treat
  - 20%-50% risk
- Toxicity of therapies
- Underlying co-morbidities

Advanced Stage III Melanoma
Management Goals

- Durable Local/Regional Control
  - long term survival
  - palliation
  - minimize morbidity and functional deficit
- Reduce the risk for distant failure
  - role of adjuvant therapy

Adjuvant Therapy for High risk Melanoma

FDA approvals and published phase III trials

- High dose Interferon (IIb, IIc, IIIa/b/c)
  - RFS benefit, minimal OS
  - high toxicity, long duration
- Pegylated Interferon (IIIa/b/c)
  - RFS only
  - moderate toxicity, longer duration
- Ipilimumab (10mg/kg)
  - modest RFS
  - high toxicity, short without maintenance
- Biochemotherapy (CVD / IL-2/ IFN)
  - RFS compared to HD IFN
  - high toxicity, shorter duration

Adjuvant Therapy for High risk Melanoma

Completed and future phase III trials

- DERMA Trial
  - Mage A3 ASCI vs placebo
  - stage IIIb/c
- ECOG 1609
  - Ipi (3mg) vs ipi (10mg) vs HD IFN
  - stage IIIb/c, IV m1a/b
- BRAF inhibitors vs placebo
- Anti PD-1 vs HD Interferon (planned to start)

The New / Evolving Landscape of Advanced Melanoma

- Recent approval of BRAF / MEK inhibitors and checkpoint blockade for unresectable stage III and stage IV disease
- Exciting data with combination checkpoint blockade therapy (most active)
- Recently reported randomized trial of Oncolytic Immunotherapy (T-VEC)

Biomarkers for Response and or Efficacy

- BRAF V600E, C-KIT, NRAS
- Ulceration
- Auto-immunity
- PDL-1 expression
- Extent of T cell infiltration

Neo-Adjuvant Therapy for Advanced Stage III and Stage IV Disease

Potential Benefits

- Ability to study tissue samples pre- and post-treatment
  - Biologic correlates/predictors of response & resistance
  - Endpoints: biologic, response rate, % pCR
- Endpoints may be achieved with a small number of patients
- In-situ marker for response
- Surgery more effective in the context of tumor responding to systemic therapy

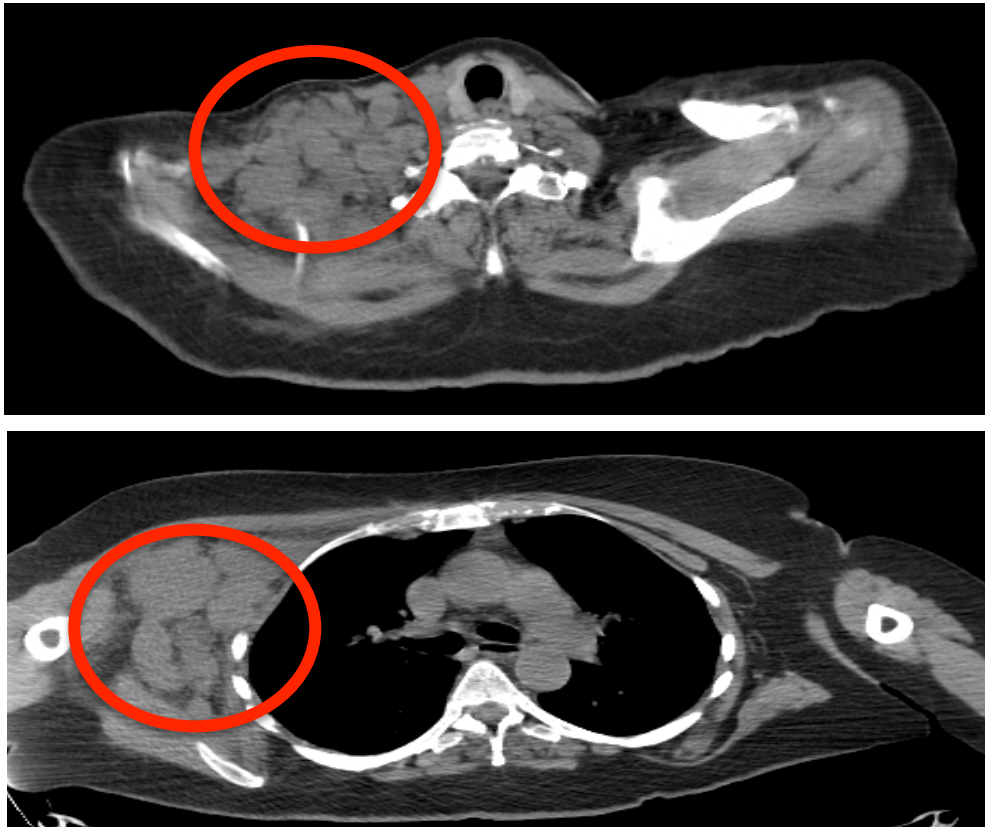
Neo-Adjuvant Experience

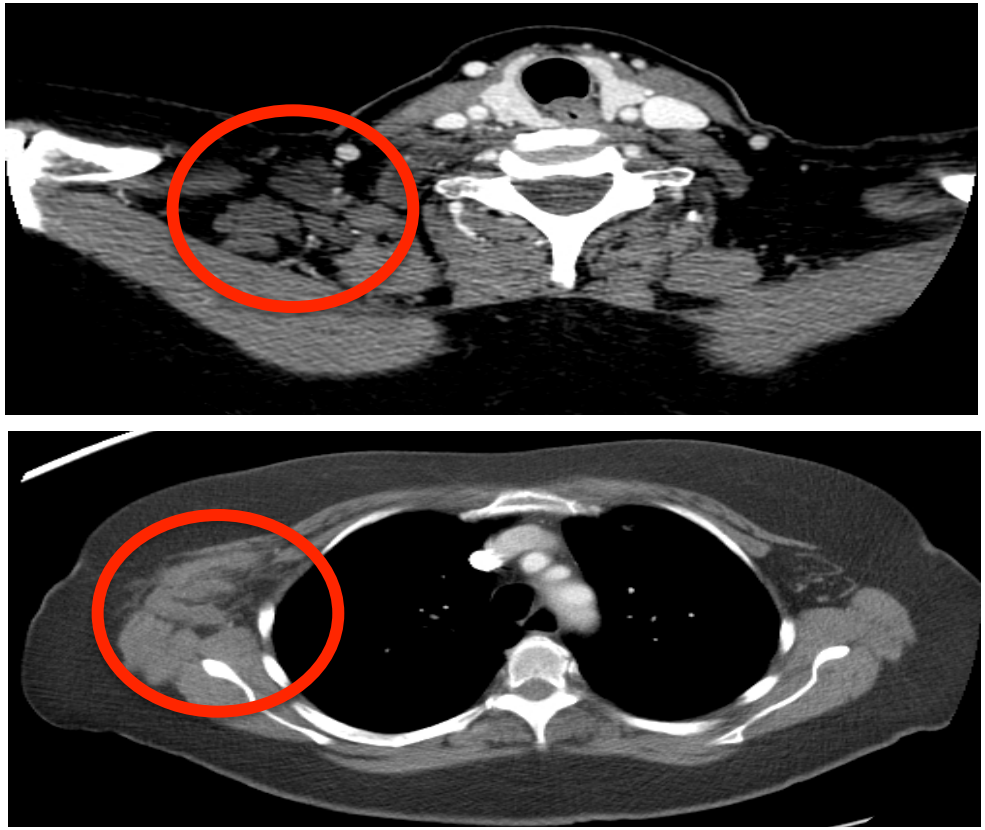
- Combination chemotherapy
  - CVD
- Bio-chemotherapy
  - CVD(T), IL-2, Interferon
- High Dose Interferon
- Ipilimumab

Case Example (2)

- 69 yo female presented with bulky adenopathy in R axilla and R neck
- Biopsy showed metastatic melanoma - told by outside oncologist she had 3-6 months to live. Offered palliative radiation.
- Presented to MD Anderson, found to have BRAF mutation. Unresectable at presentation, treated with neoadjuvant BRAF/MEK x 8 weeks
- Re-staged - excellent response

Path = fibrosis, rare viable tumor cells

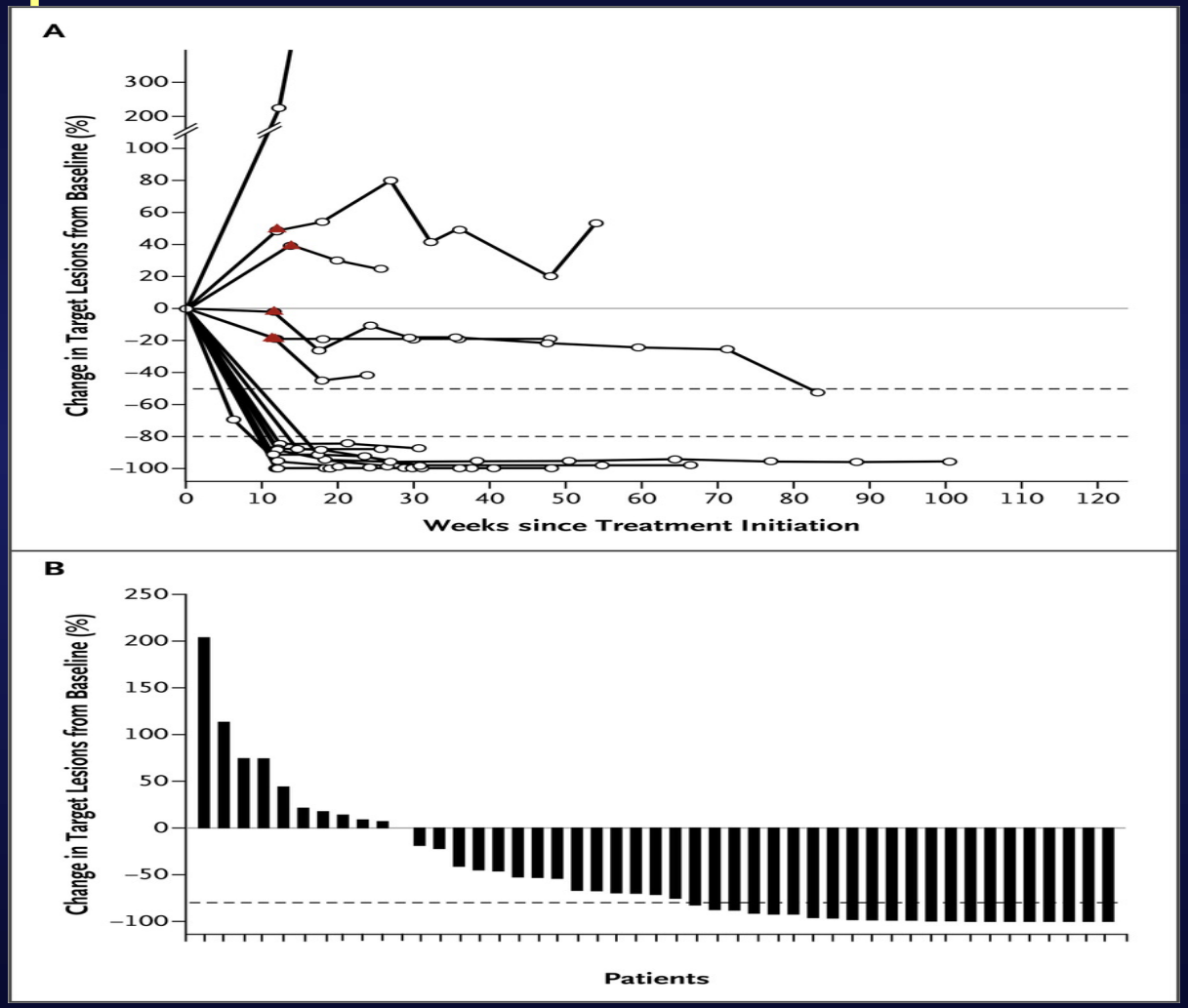




April 2014 (Pre-BRAF/MEK)

July 2014 (Post-BRAF/MEK)

Prospects for Neo-Adjuvant Approaches
Ipilimumab and Anti-PD-1



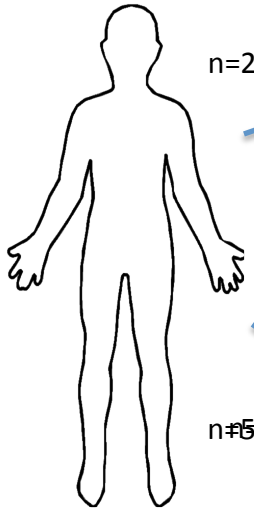
Neoadjuvant Trial Concepts

- Identify high risk groups who would be candidates for post-op adjuvant treatment (IIIB/C and stage IV oligometastatic
  - can justify higher toxicity regimens
- Access to tumor before, during, and after treatment
- Designed to have biologic events as primary endpoints (markers of response and resistance)
  - single arm for bio-marker
  - randomized phase II

Neoadjuvant Trial Concepts

- Randomized Phase II of Dabrafenib/Trametinib vs SOC (surgery +adjuvant): approved and funded, actively accruing
- Randomized Phase II of Ipi/Nivo vs Nivo alone: approved and funded will open by end of year
- Pembro/Peg intron vs Pembro alone: in development
- Neo-Adjuvant T-VEC will open soon

Neoadjuvant BRAF/MEK Trial



n=28

n=56

Patients with stage IIIB/ IIIC or oligometastatic stage IV (<3 lesions), + BRAF mutation

Randomize 2:1
BRAF/MEK vs. upfront surgery

Arm A
Upfront surgery

Scheduled within 0-4 weeks

Surgical resection

Pathologic assessment of tumor + research biopsy

Standard of care adjuvant therapy (interferon vs. observation)

Clinical and radiographic follow up

Assess relapse-free survival, overall survival, toxicity

Arm B
Neoadjuvant BRAFi/MEKI

Neoadjuvant BRAF/MEK x 8 weeks

Restaging via CTs followed by surgical resection

Adjuvant BRAF/ MEK x 44 weeks

Clinical and radiographic follow up

Blood draw and tumor biopsy Pre-treatment

On treatment biopsy / blood draw (arm B only)

Blood draw and tumor biopsy at surgery

Restaging CT scans every 3 months with blood draws

Blood draw and tumor biopsy at relapse

Endpoints

- Primary – relapse-free survival (at 1 year)
- Secondary

- overall survival
- pathologic complete response rate (pCR)
- safety of dabrafenib and trametinib in this population
- biomarkers (tumor-based and blood-based)

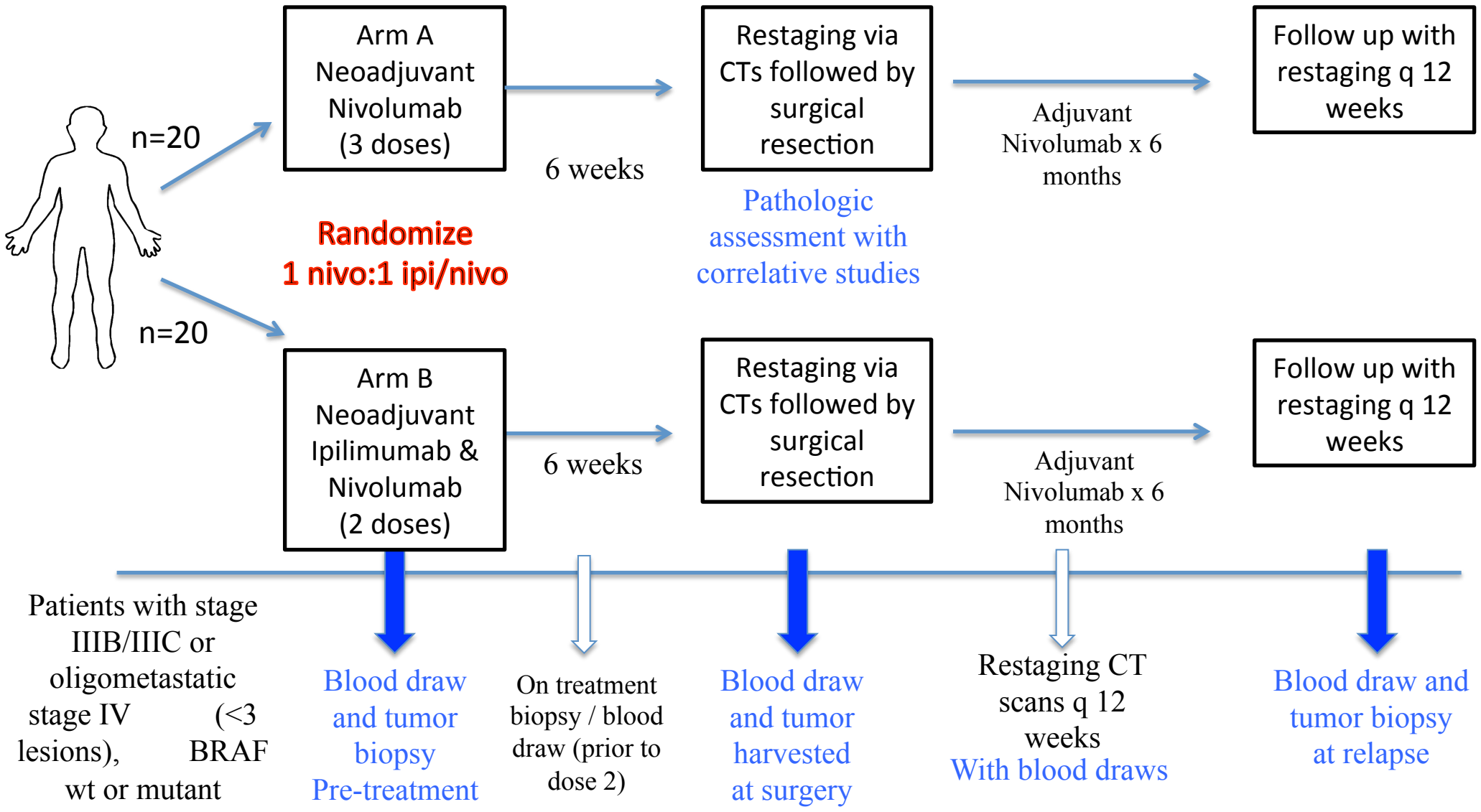
1: Symmans et al. J Clin Oncol 2007; 25: 4414-22

Ipilimumab + Nivolumab Neoadjuvant Trial Concept

Melanoma Medical Oncology and Surgical Oncology

MD Anderson Cancer Center

Winter 2015


n=20
Arm A
Neoadjuvant
Nivolumab
(3 doses)
6 weeks
Restaging via
CTs followed by
surgical
resection
Adjuvant
Nivolumab x 6
months
Follow up with
restaging q 12
weeks
Randomize
1 nivo:1 ipi/nivo
Pathologic
assessment with
correlative studies
n=20
Arm B
Neoadjuvant
Ipilimumab &
Nivolumab
(2 doses)
6 weeks
Restaging via
CTs followed by
surgical
resection
Adjuvant
Nivolumab x 6
months
Follow up with
restaging q 12
weeks
Patients with stage
IIIB/IIIC or
oligometastatic
stage IV (<3
lesions), BRAF
wt or mutant
Blood draw
and tumor
biopsy
Pre-treatment
On treatment
biopsy / blood
draw (prior to
dose 2)
Blood draw
and tumor
harvested
at surgery
Restaging CT
scans q 12
weeks
With blood draws
Blood draw and
tumor biopsy
at relapse

Endpoints

- Primary endpoint:
  - Pathologic/biomarker analysis
    - Pathologic markers: residual cancer burden[1], % tissue necrosis, quantification of mitotic activity by phosphohistone H3[2]
    - Immune analyses
- Secondary endpoints: Overall response rate, progression free survival, overall survival, safety analyses

1: Symmans et al. J Clin Oncol 2007; 25: 4414-22;
2: Nielsen et al. Mod Pathol 2013; 26: 404-13

Pembrolizumab + Pegylated Interferon Neoadjuvant Trial Concept

Melanoma Medical Oncology and Surgical Oncology

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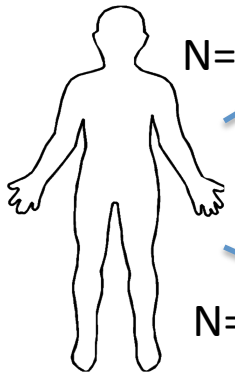


N=?

N=?

Arm A
Neoadjuvant
Pembro
(4 cycles)

8 weeks

Restaging via CTs followed by surgical resection

Pathologic assessment with correlative studies

Adjuvant
Pembro x 18 months
Followed by Peg

Follow up with restaging q 12 weeks

Randomization of Pembro alone vs Pembro + Peg

Arm B
Neoadjuvant
Peg + Pembro
(4 cycles)

8 weeks

Restaging via CTs followed by surgical resection

Adjuvant
?

Follow up with restaging q 12 weeks

Patients with stage IIIB/IIIC or oligometastatic stage IV (<3 lesions), BRAF wt or mutant

Blood draw and tumor biopsy Pre-treatment

On treatment biopsy / blood draw (prior to dcycle 3)

Blood draw and tumor harvested at surgery

Restaging CT scans q 12 weeks
With blood draws

Blood draw and tumor biopsy at relapse

Endpoints

- Primary endpoint:
  - Pathologic response/biomarker analysis
    - Pathologic markers: residual cancer burden[1], % tissue necrosis, quantification of mitotic activity by phosphohistone H3[2]
    - Immune analyses: see proposal for full details (done with J Wargo in collaboration with P Sharma and J Allison)
- Secondary endpoints: Overall response rate, progression free survival, overall survival, safety analyses, change in PDL-1 expression and correlation with response

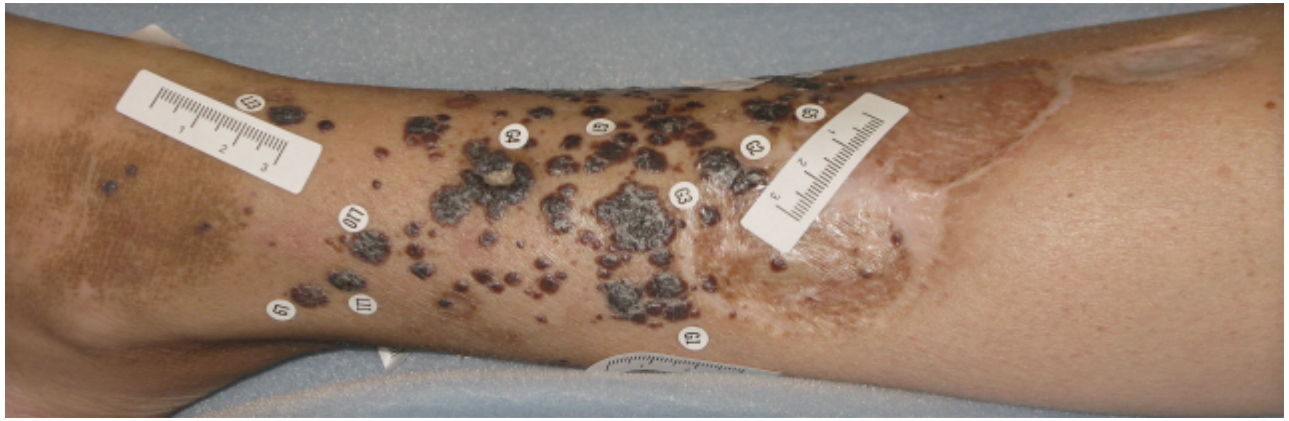
Neo-Adjuvant T-VEC

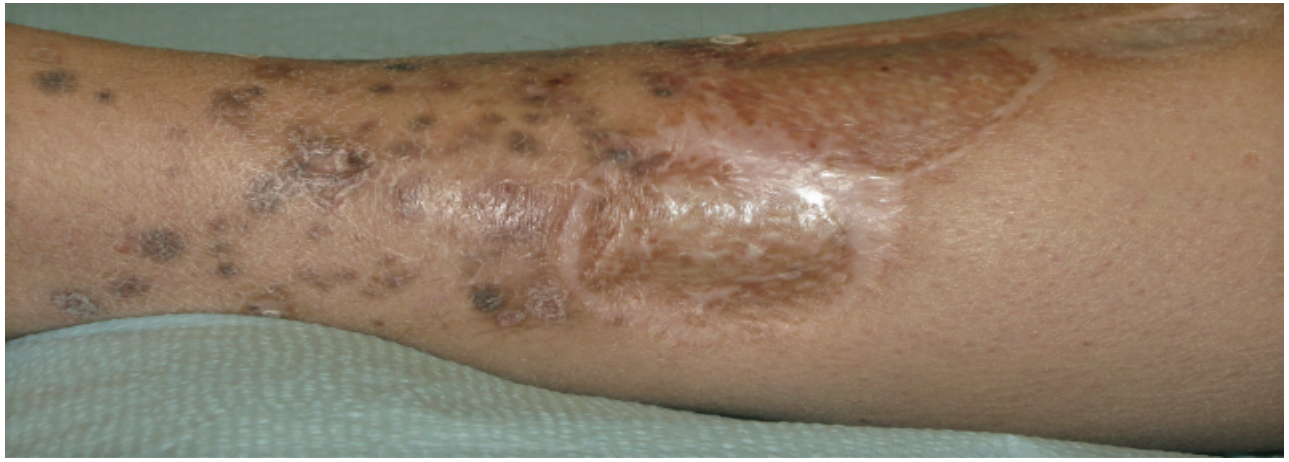
- OPTiM trial met primary endpoint of DR
- Borderline OS endpoint secondary endpoint
  - subset of Stage IIIb/c and M1a OS advantage
- Resectable stage IIIb/c and M1a

- Randomized phase 2 of surgery followed by adjuvant vs pre-op T-VEC 12 weeks

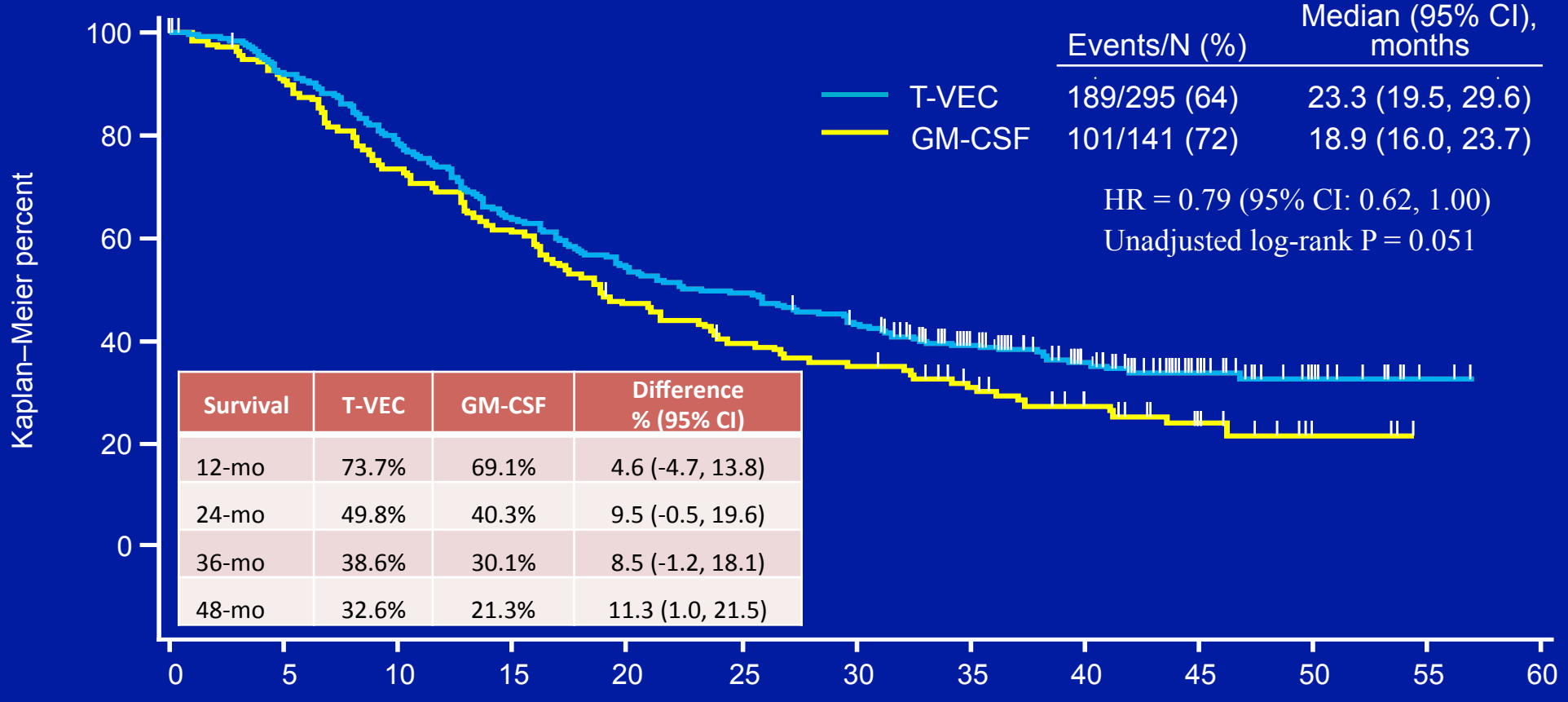
1: Symmans et al. J Clin Oncol 2007; 25: 4414-22

T-VEC Responses in Injected And Uninjected Lesions





Primary overall survival



Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-mo	73.7%	69.1%	4.6 (-4.7, 13.8)
24-mo	49.8%	40.3%	9.5 (-0.5, 19.6)
36-mo	38.6%	30.1%	8.5 (-1.2, 18.1)
48-mo	32.6%	21.3%	11.3 (1.0, 21.5)

Patients at risk:

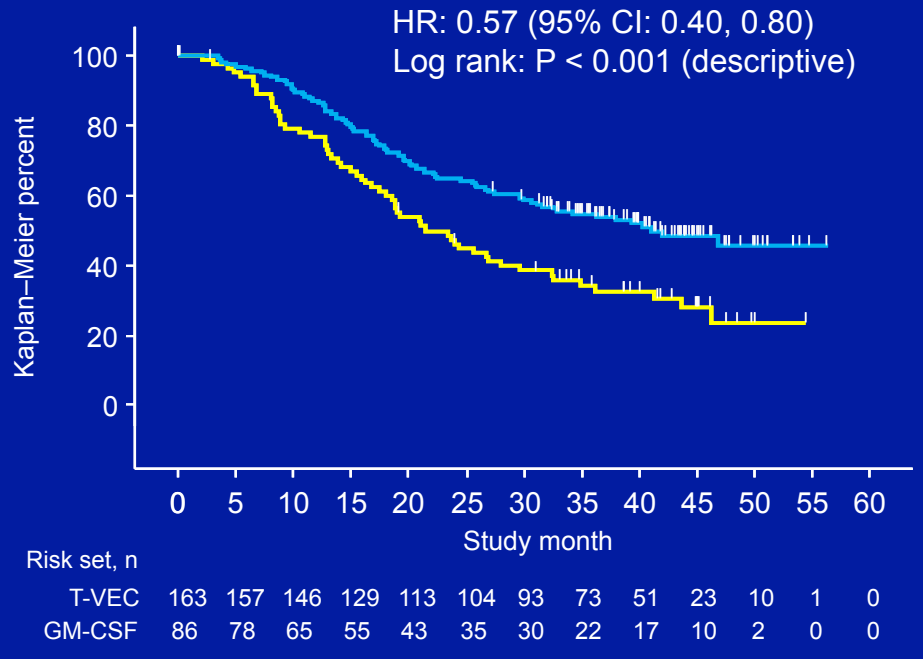
T-VEC	295	269	230	187	159	145	125	95	66	36	16	2	0
GM-CSF	141	124	100	83	63	52	46	36	27	15	5	0	0

HR, hazard ratio.

Kaufman H, et al. ASCO 2014 abstract 9008a.

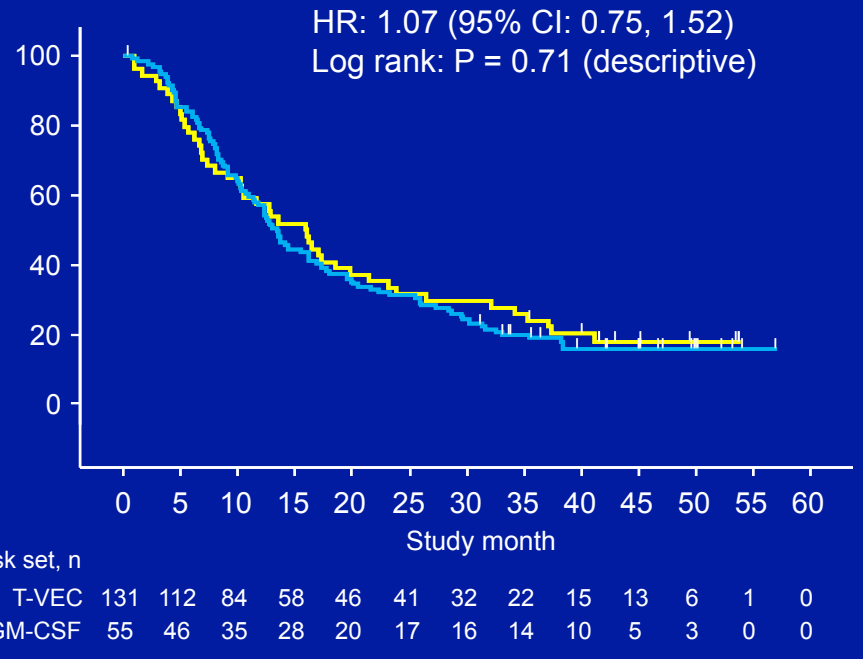
Exploratory OS subgroup analysis by disease stage

Stage IIIB/C, IV M1a



	Events/n (%)	median (95% CI), mo
T-VEC	80/163 (49)	41.1 (30.6, NE)
GM-CSF	57/86 (66)	21.5 (17.4, 29.6)

Stage IV M1b/c



	Events/n (%)	median (95% CI), mo
T-VEC	109/131 (83)	13.4 (11.4, 16.2)
GM-CSF	44 /55 (80)	15.9 (10.2,19.7)

Mo, months.

Kaufman H, et al. ASCO 2014 abstract 9008a.

Treatment Strategies for Advanced Melanoma

Take Home Messages

- Multi-disciplinary input is critical
- Initial therapy should not be recommended in isolation, but as part of a comprehensive plan
- Combinatory strategies are rational and offer the promise of future advancement
- Neoadjuvant trials hold the promise of insights into rational and more personalized treatment strategies