Immunotherapy's Coming Of Age As An Effective Modality For Cancer Treatment

Robert H. Wiltrout, Director, SD for Basic Science

Lee J. Helman, SD for Clinical Research

NFAC

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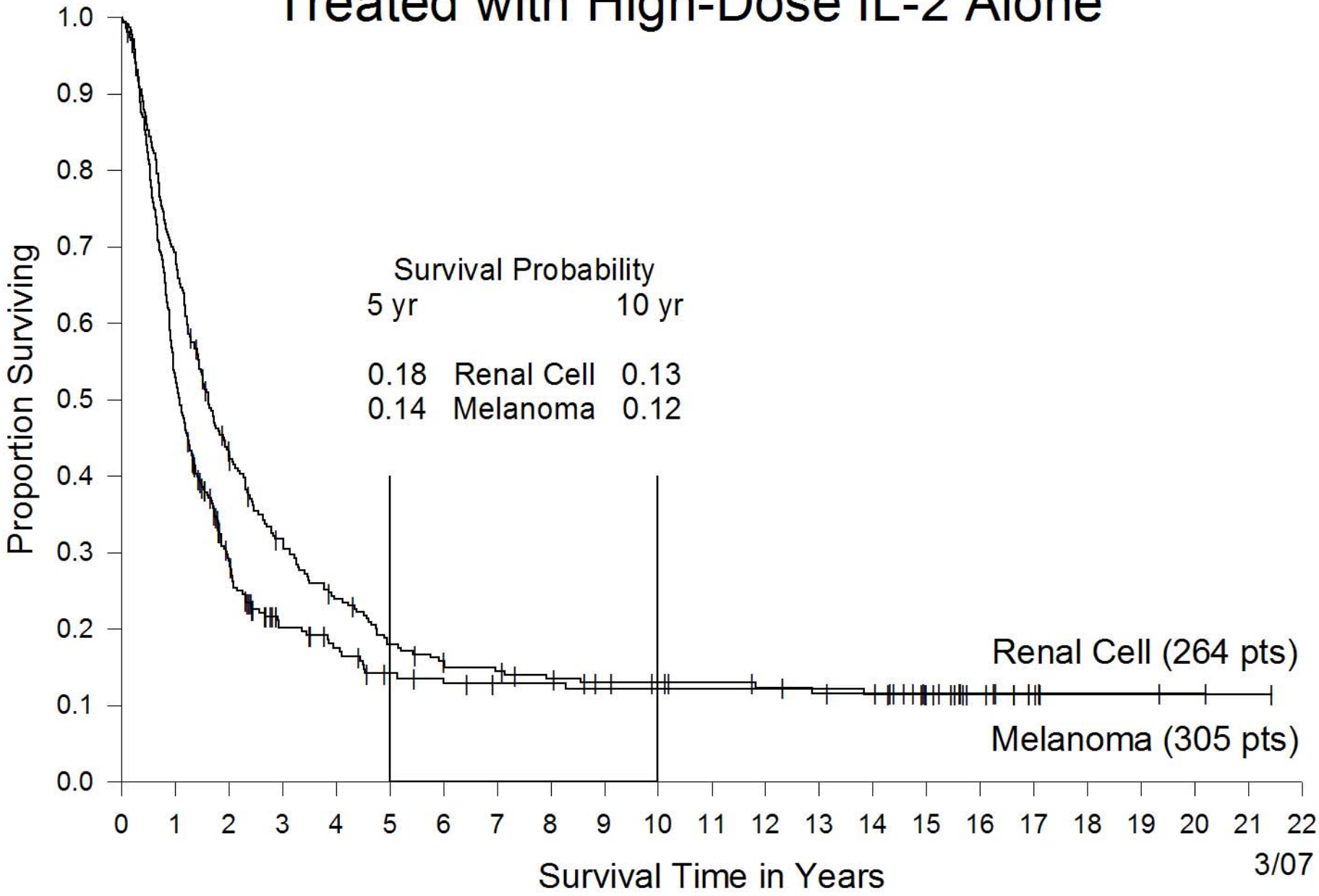
Science
20 December 2013 / $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

Immunotherapy's Coming Of Age As An Effective Modality For Cancer Treatment

- Reports of clinical responses increasing in frequency and across disease types, including for cancers previously thought to be refractory to immunotherapy
  - **B cell lymphomas, sarcomas, lung, pancreatic, ovarian etc**.
- Consistent reports of plateaus (long tails) in survival curves
  - Cytokines, checkpoint inhibitors, chimeric antigen receptors, adoptively transferred cells
- A low frequency of durable responses contrasts with results for many molecularly targeted agents which may induce a higher frequency of short duration responses
- Can we develop better ways to strategically combine molecularly targeted agents with immunotherapy?
- Can a better understanding of durable immune-induced responses provide better insight into overall development of cancer therapeutics?


569 Patients with Metastatic Disease
Treated with High-Dose IL-2 Alone
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival Probability
5 yr
10 yr
0.18 Renal Cell 0.13
0.14 Melanoma 0.12
Renal Cell (264 pts)
Melanoma (305 pts)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Survival Time in Years
3/07

More focused strategies to exploit adaptive/antigen-specific immunity

Adoptive Transfer

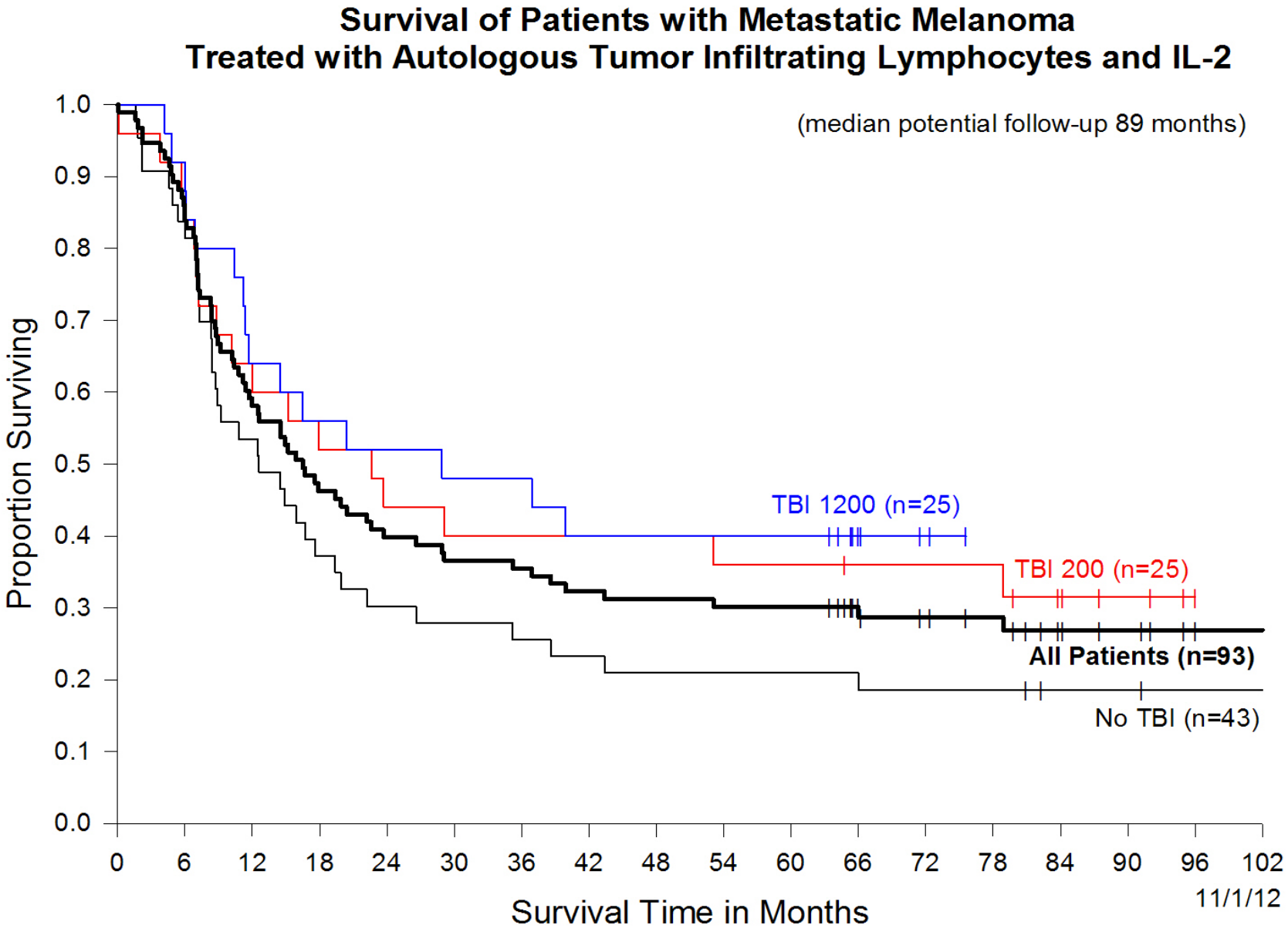
Cellular-targeted modulation of tumor immunity: reinfused patient-autologous T cells manipulated ex vivo

- transduction to express Ab to chimeric antigen receptors (aCD19, aCD20)
- expansion of tumor-infiltrating lymphocytes (TILs)

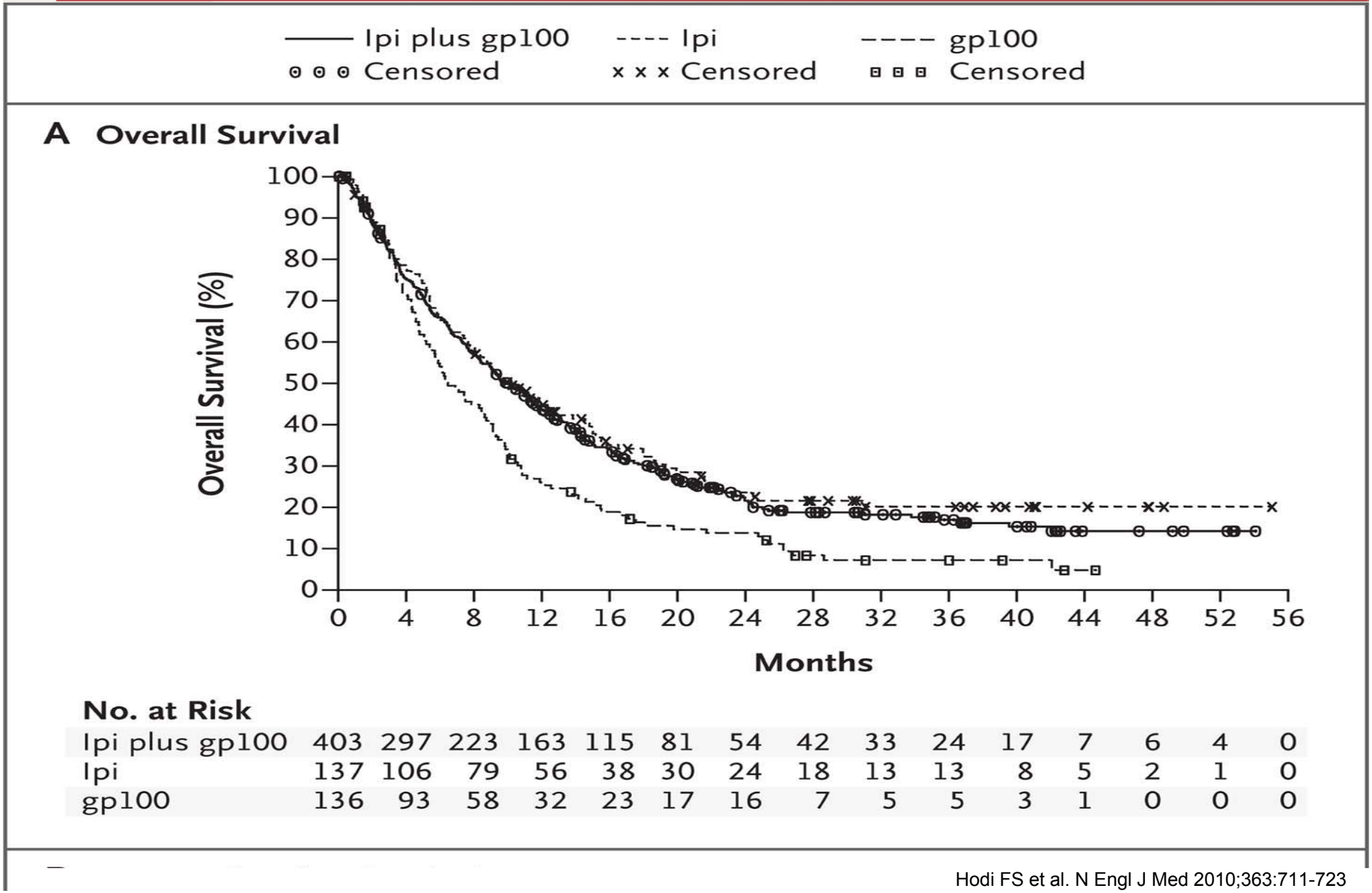
Targeted effects through checkpoints and costimulatory molecules

Molecule-targeted antibody-based modulation of tumor immunity

- aCTLA4 (ipilimumab)
- aPD-1 (nivolumab, lambrolizumab, pidilizumab, AMP-224)
- aPD-L1 (MPDL3280A, MEDI-4736)
- αCD40


Survival of Patients with Metastatic Melanoma
Treated with Autologous Tumor Infiltrating Lymphocytes and IL-2
(median potential follow-up 89 months)
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TBI 1200 (n=25)
TBI 200 (n=25)
All Patients (n=93)
No TBI (n=43)
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96
102
Survival Time in Months
11/1/12

Checkpoint inhibitors: Anti-CTLA4 as a guide



Hodi FS et al. N Engl J Med 2010;363:711-723

While we work forward in developing molecularly targeted agents based on genomic anomalies in human cancers…

Should we not also work backward to understand how the more frequent and durable responses now being seen with immunotherapy might accelerate the overall approach to cancer treatment?