

**Point-Counter-Point**  
 Treatment of Stage IV Disease-  
 Patient with BRAF Mutant Melanoma

*Immunotherapy is the first line treatment of  
 choice for patients with advanced  
 melanoma*

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 October 13, 2011  
 7th Annual Oncology Congress

**Financial Disclosure**

- Bristol-Myers Squibb - Consultant Member  
 Advisory Committee
- Genesis Biopharma - Scientific Advisory  
 Board/Consultant

**Basic Principles and Goals of  
 Treatment**

- Select treatment for individual patient to give  
 best outcome for that patient
- Order of desired outcomes
  - Cure (or long-term unmaintained remission) with  
 minimal to no long-term detrimental effects of Rx
  - In the absence of cure:
    - Reduction of symptoms
    - Extension of survival
- Presence of target and effective targeted drug ≠  
 optimal therapy for that patient

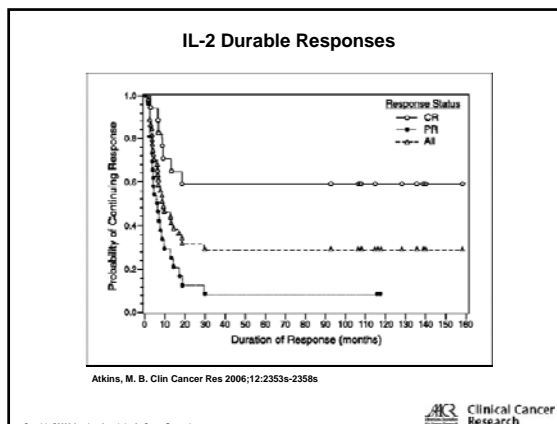
**Immune Therapies  
 Producing Long-Term Remissions**

- High Dose Interleukin-2 (IL-2)
- Ipilimumab (anti-CTLA4)
- *\*Adoptive T-Cell Therapies*
  - *Lymphoablation + Tumor-infiltrating lymphocytes  
 + IL-2*
- *\*Anti-PD1*

• *\* = investigational*

**High Dose IL-2 for Metastatic Melanoma**  
*Atkins et al, J Clin Oncol, 1999*

Number of Patients	270
Responders	43 (16%)
Complete Responders	17 (6%)
Durable Responses > 24 months	12 (4.4%)
Median Survival	12 months
Median duration of response	8.9 months
Durable Ongoing Responses > 24 months (in months) (staging based on disease site only)	CR: 24,40,41,59,62,65,72,86,103,106 (all M1a/b) PR: 55,92 (both M1c) +Salvage Surgery (4/5 M1c): survival: 54,60,64,66,87,103
Treatment-related deaths (all sepsis-related)	6 (2.2%)

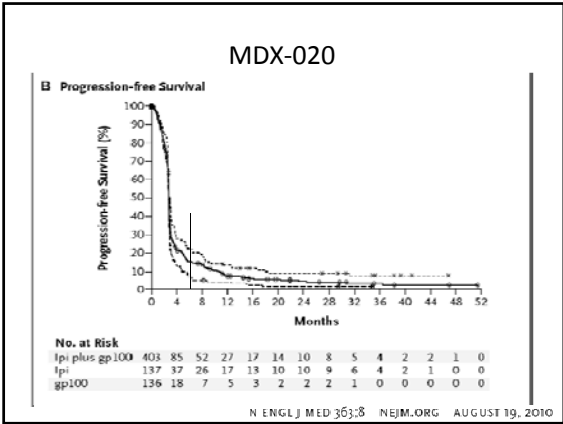
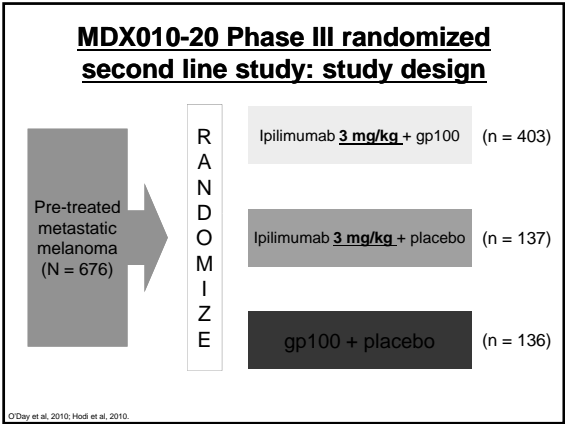
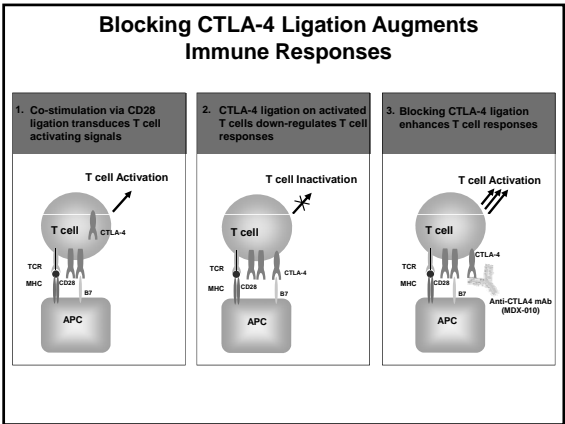




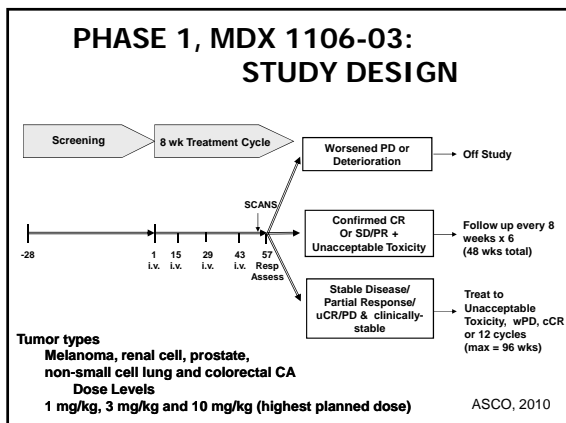
### IL-2 Grade 3-4 Toxicity

	NCI-SB HD IL-2	CWG HD IL-2
Median Doses per Course	12 (28)	68% (19 doses)
Death	0	1%
Hypotension	36.4%	56.8%
Pulmonary	4.2%	13.7%
CNS orientation	10.2%	14.7%
CNS consciousness	2.5%	
Infection	2.8%	3.2%
Nausea/vomiting	13.4%	9.5%
Diarrhea	9.2%	
Hyperbilirubinemia	3.2%	11.6%
ALT	3.2%	
Creatinine > 8.0 mg/dL	1.1%	13.7% (gr 3-4)
Oliguria (< 80 ml/h)	12%	
Atrial Arrhythmia	4.2%	8.4% (all cardiac)
Malaise	20.5%	3.2%

Therefore → Only selected patients are eligible for treatment







### CLINICAL ACTIVITY: BEST OVERALL RESPONSE<sup>‡</sup>

Diagnosis	Dose (# evaluable for response)	PR	SD	PD	NA
MEL	1 mg/kg (16)	5	5	3	3
	3 mg/kg (14)	5*	4	5	-
	10 mg/kg (16)	5	1	7	3

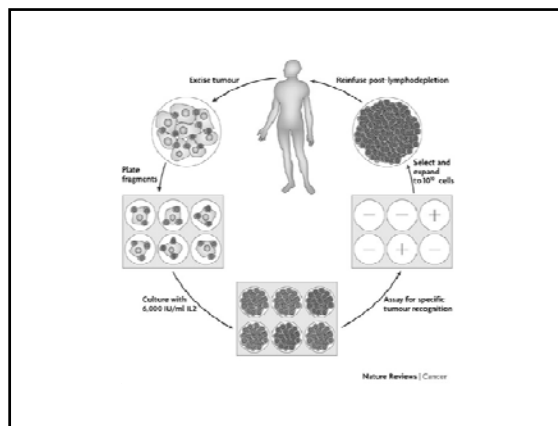
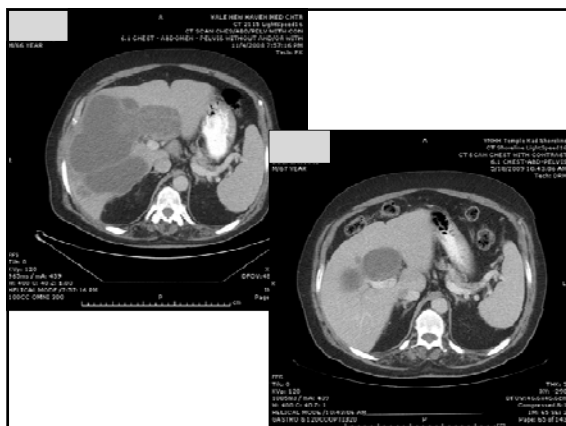
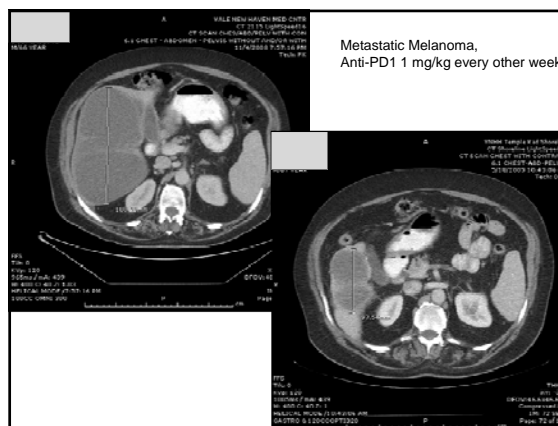
<sup>‡</sup>Best overall response measured using RECIST (v 1.0)  
 Stable Disease (SD) = patients not meeting criteria for CR/PR/PD  
 NA = Not available  
 \* - 1 pt subsequently converted to CR

Data cutoff date: 5/3/2010

### RESPONDERS TIME ON STUDY

Dose Level	Diagnosis	Time on Study
1	Melanoma	18+ months
	Melanoma	8+ months
	Melanoma	9+ months
	Melanoma	9+ months
	Melanoma	6+ months
3	Melanoma	14+ months
	Melanoma	7+ months
	Melanoma	6+ months
	Melanoma	5+ months
	Melanoma	5+ months
10	Melanoma	12+ months
	Melanoma	8+ months
	Melanoma	8+ months
	Melanoma	7+ months

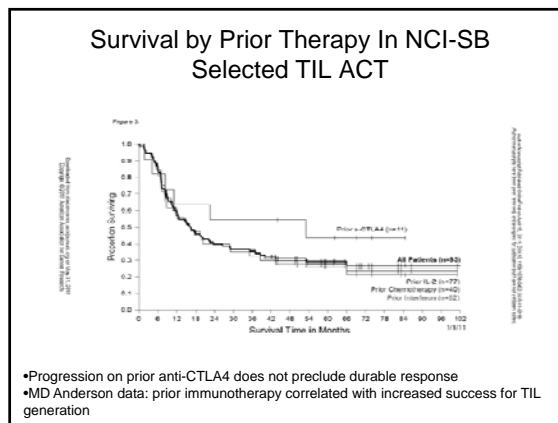
As of May, 2010



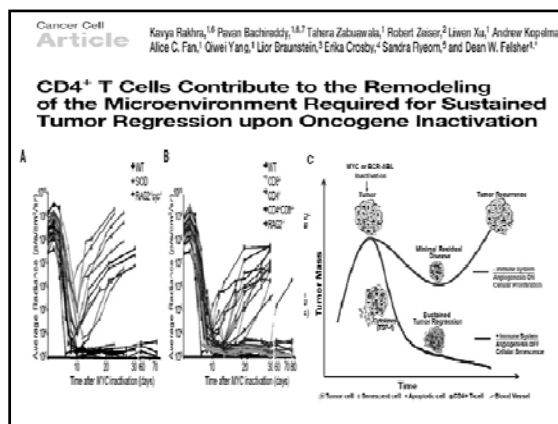
CELL TRANSFER THERAPY (n=111)				
Endpoint	Total	PR	CR	CR (%)
number of patients (number in subset)				
% TCR	43	16 (37%)	1 (2%)	31 (69%)
		(94, 20, 29, 28)	(82, 11, 7)	
		(14, 12, 11, 7)	(20, 14, 1)	
		7, 7, 7, 4		
		4, 3, 3, 3		
200 TCR	25	8 (32%)	3 (12%)	11 (42%)
		(11, 4, 4, 4)	(88, 44, 88)	
		5, 4, 3, 2	(75, 34)	
1000 TCR	25	10 (40%)	0 (0%)	10 (40%)
		(11, 11, 7, 6)	(40, 47, 44)	
		6, 1, 1, 2	(18, 19, 24)	
			(20, 19, 25)	
			(8)	
TOTAL	93	32 (34%)	20 (22%)	52 (56%)

**Durable Complete Responses in Heavily Treated Patients with Metastatic Melanoma Using T Cell Transfer Immunotherapy**  
 Olson R, Rosenberg J, et al. J Clin Oncol. 2011;29:155-162.  
 doi:10.1200/JCO.2010.32.4111

- Complete response to ACT is very durable
- CR rate may increase over time as response evolves/improves
- A small subset of PR and Mixed responses may achieve durable PFS



	Mutant BRAF inhibitors	Immune Therapies
Overall response rate	~ 50% (80% tumor regression)	IL-2/ipi/anti-PD1: ~15/~15/~33%
Kinetics of response Median Progression-free survival (PFS)	Rapid; PFS increased	Variable, slower, may take weeks; possible PD before response; minor to no effect on median PFS
Induction of long-term unmaintained response	Unproven, but data not mature	Yes, in approximately 10% (possibly higher for sequential use)
Effect on median survival	Yes, magnitude?	For ipi, yes, 2-4 months
Effect on 2-year survival	Probable, magnitude?	For ipi, yes, ~ 10%
Activity against brain mets	Yes, smaller lesions respond better?	Low rate, limited to small lesions
Activity against high tumor burden, rapid progression	Yes	May not have sufficient time for anti-tumor effect
Activity M1C/high LDH	Yes, lower objective response rate	Yes, but high LDH may adversely impact activity (IL-2)
Activity with baseline low lymphocyte count	Yes	Reduces activity?
Activity with prior normal tissue autoimmunity/steroids	Yes	Increased risk for toxicity; steroids at onset may reduce activity
Acute toxicity	Rarely severe	Agent dependent, can be very severe in small subset
Chronic toxicity	Yes, low grade?	Usually minimal



### Treatment Recommendations for Metastatic BRAF mutant Melanoma

- Low to moderate tumor burden with 4-6 month expected survival, no contraindication to immune therapy
  - Consider immunotherapies first for durable remission
  - Ipilimumab → consider re-induction and local Rx for limited progression post response or SD
  - Other options – IL-2, anti-PD1 clinical trials, TIL (adoptive cell transfer)
  - Because of long antibody half-life, BRAF inhibitor second line may give 'combination effect'
- Rapidly progressing disease, large tumor volume, ECOG PS > 1, life expectancy < 3 months
  - Vemurafenib
  - GSK BRAF + MEK inhibitor
  - May obtain additional benefit by treating beyond mild progression
  - Ipilimumab or other immune therapy second-line?

### Metastatic Melanoma Treatment - 2011

- Clinical Trial preferred for all patients to answer key therapeutic questions
  - Ipilimumab dose and schedule, induction and maintenance
  - Vemurafenib + ipilimumab
  - Addition of MEK1 to mutant BRAF inhibitor
  - Addition of agents blocking pathways responsible for resistance
  - Targeted agent trials for NRAS mutant and WT population (15% and 35%)
  - Role of anti-PD1
  - Combination immunotherapies