A PHASE I STUDY OF INTRAVENOUS RECOMBINANT HUMAN IL-15 (rhIL-15) IN ADULTS WITH METASTATIC MALIGNANT MELANOMA AND METASTATIC RENAL CELL CANCER

Society for the Immunotherapy of Cancer

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Presenter Disclosure Information

Kevin Conlon

The following relationships exist related to this presentation:

No relationships to disclose

Protocol Eligibility

- **Metastatic melanoma or renal cell carcinoma**
  - Refractory, intolerant or refused standard treatments
  - ~~No prior treatment with IL-2~~ (October 2010)
- **Measurable disease, adequate physiologic and laboratory parameters, ECOG ≤ 1, life expectancy > 3 months**
- **Negative serology for HIV, hepatitis A , B and C**
- **Treated CNS metastases allowed**
  - (> 3 months radiographic stability)
- **No history of autoimmune diseases or systemic corticosteroids**
  - prior Ipilimumab immune related adverse events allowed (October 2010)
- **Medical or psychiatric illness that would preclude safe participation in the trial**

Treatment Plan

Drug administration

- rhIL-15 as 30 min intravenous infusion daily X 12 days
- Dose levels: 0.3*, 1*, 3, 7, 10, 15 , 20 and 25 μ g/kg/day
  - added after first patient had DLT

Fluid management

- Basal: IVF NS at 100 cc/hr → increased up to 150 (200) cc/hr for anticipated BP nadir in 3 μ g/kg pts
- IV 25% albumin and furosemide PRN

Antipyretics

- Initially no empiric premedication
- If Temperature > 38^0 start q6 hour acetaminophen → if persistent temperature > 38.5^0 ↑ acetaminophen 4g/day in combination with timed ibuprofen (400 to 800 mg)

Anti-emetics

- Initially no antiemetic premedication
- If nausea or vomiting → routine premedication for all subsequent cycles

Other treatments

- Blood products PRN
- If rigors: IV meperidine (Demerol)
- If O_2 saturation <92% → intranasal O_2

Patient Histories

Diagnosis/Age	Prior treatment	Number of doses	Discontinuation
3 μg/kg Patients			
Melanoma/83 F	None	1	DLT grade 3 hypotension
Ocular melanoma/43 M	None ineligible for HD IL-2	12	Completed Rx
Melanoma /53 M	HD IL-2, Ipilimumab, TILs with LD IL-2, AZD-6244, XRT	10	Non-DLT hypotension, pleural effusion
Ocular melanoma/57 F	Anti-CD137, Ipilimumab, CR011 Immunotoxin, XL-184	12	Completed Rx
Melanoma/34 M	HD IL-2, TILs with HD IL-2, young TILs with HD IL-2, Ipilimumab, XRT	6	DLT grade 3 thrombocytopenia
1 μg/kg Patients			
Renal Cell/57 M	IMRT to jaw, XRT to pelvis, TroVax vaccine with sunitinib, pazopanib, everolimus	4	DLT persistent grade 3 AST/ALT abnormalities
Renal Cell/67 M	Sunitinib, axitinib, sorafenib with LBH589, everolimus	12	Completed Rx
Melanoma/21 F	Young TILs with HD IL-2, Ipilimumab, IL-12 transduced TILs	12	Completed Rx
Mucosal melanoma/50 M	None	4	DLT persistent grade 3 AST/ALT abnormalities

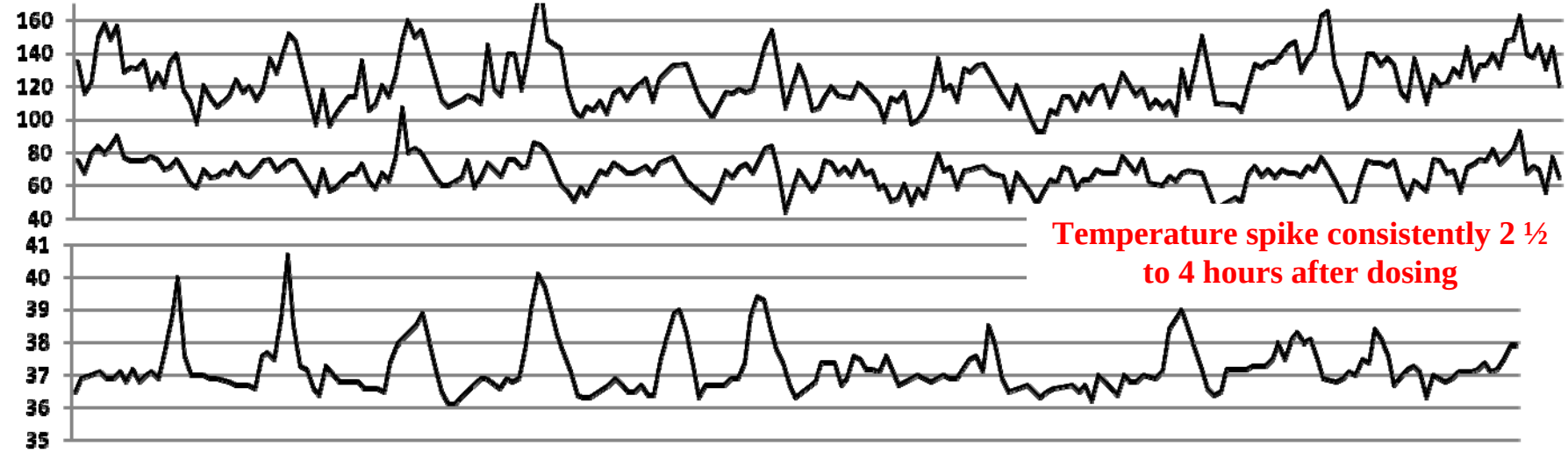
Clinical Toxicities

Patient	GI		Fevers		Capillary Leak		Chills, Rigors	
	Type	Anti-emetics	T-Max	Anti-pyretics	Maximum weight	IV albumin	Episodes	Treated
Melanoma/ 83 F	N, D	Z PRN	37.8	-	-1 kg	-	C X 1	
Ocular melanoma/ 43 M	N,V	Z Sch	40.7	Tyl, IB Sch	+ 4 kgs	6X	R X 10	D X 10
Melanoma / 53 M	N,V	Z Sch	38.8	Tyl, IB Sch	+7 kgs	7 X	C X 4, R X 5	D X 5
Ocular melanoma/ 57 F	-	-	38.6	IB PRN	+6 kgs	4 X	C X 3, R X 7	D X 7
Melanoma/34 M	-	-	38.2	Tyl Sch	+5 kgs	2 X	C X 3, R X 1	D X 1
Renal Cell/57 M	-	-	39.6	Tyl Sch	+1 kg	-	R X 4	D X 4
Renal Cell/67 M	-	-	39.3	Tyl Sch, IB PRN	+4 kgs	3 X	C X 3, R X 7	D X 5
Melanoma/21 F	N, V*	Z, Com Sch	39.4	Tyl, IB Sch	+ 6 kgs	4 X	C X 12	-
Mucosal melanoma/50 M	-	-	39.3	Tyl →IB Sch	+ 2 kgs	2 X	C X 4	-

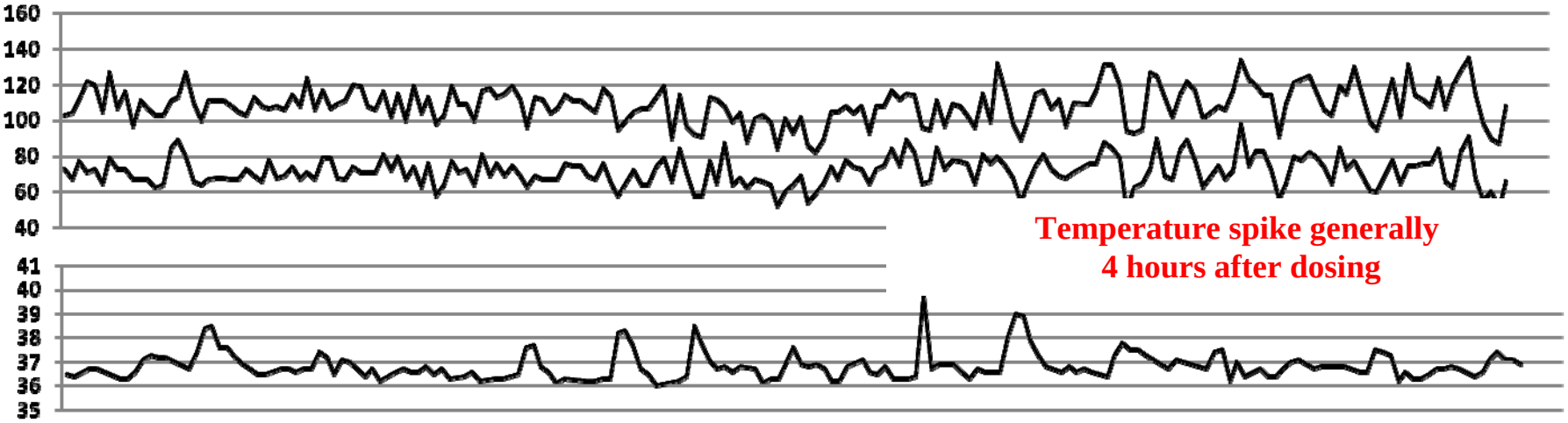
*present a baseline and after Rx patient had multiple liver metastases

Typical Blood Pressure and Temperature Courses

3 μg/kg Patient



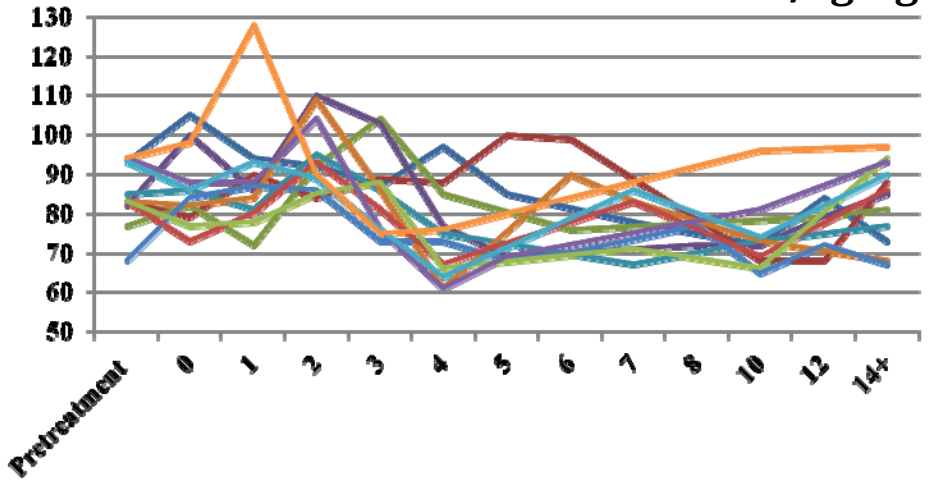
1 μg/kg Patient

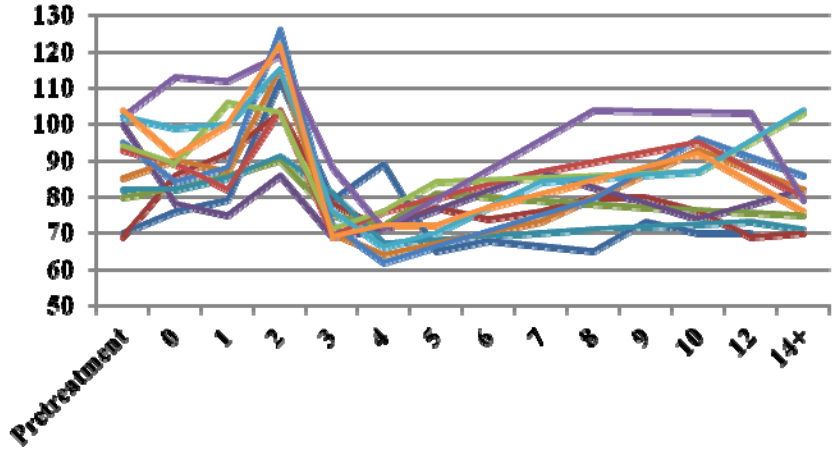


Daily Mean arterial Blood Pressures

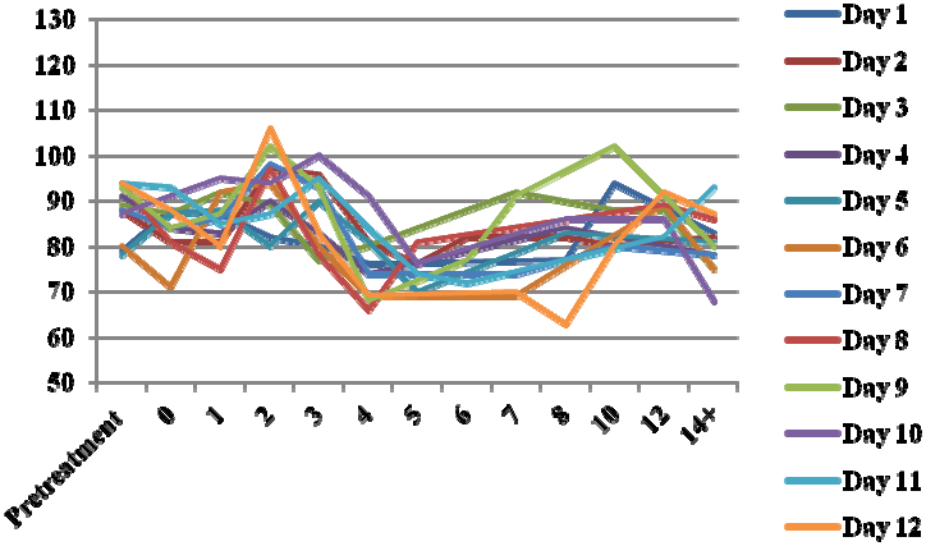
Normalized to time of IL-15 infusion

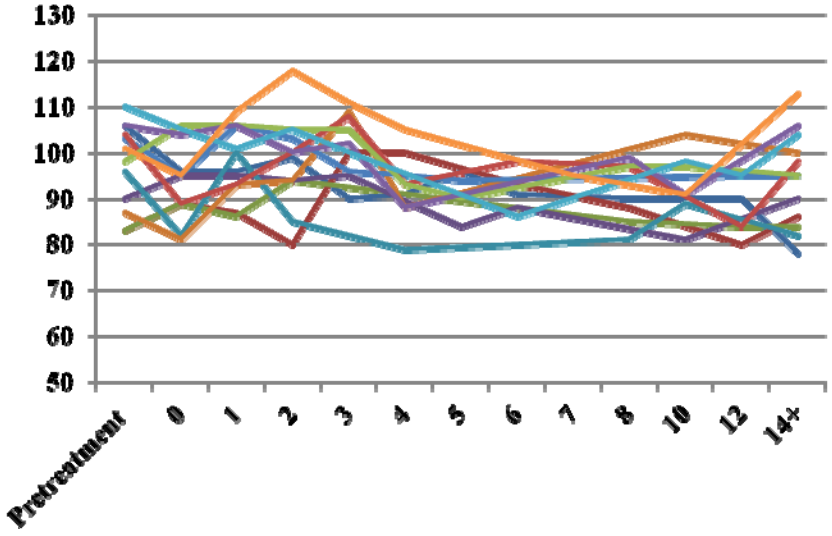
3 μg/kg Patients





1 μg/kg Patients





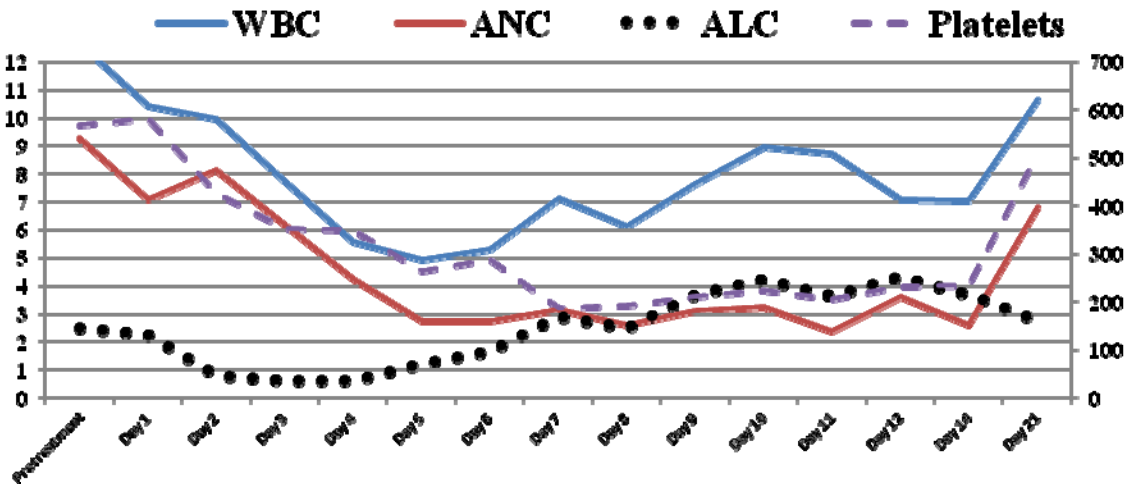
Hematologic Effects

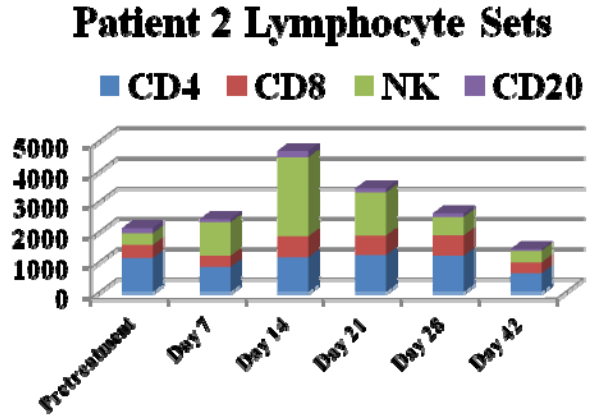
No discernible difference between 3 μ g/kg and 1 μ g/kg patients

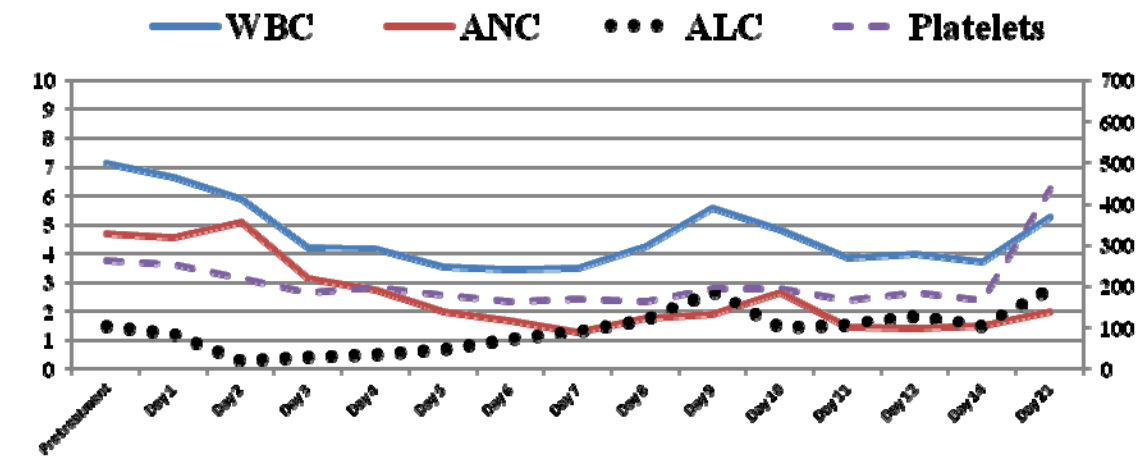
↓ Platelets and ANC with recovery late in course or after treatment was stopped

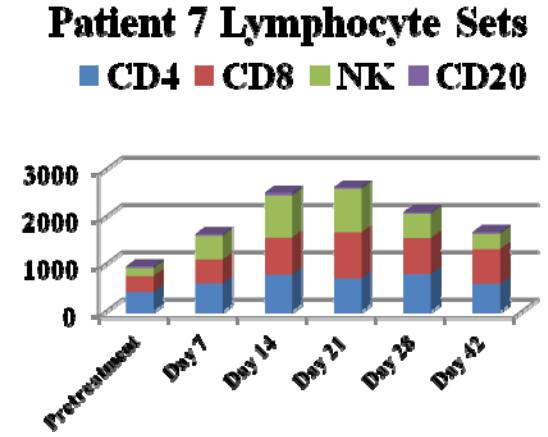
Initial ↓ in WBC and ALC with recovery with lymphocyte expansion day 4-7

Lymphocytosis 2-4 X ↑ due to 2-3 X ↑ CD8 cells and 4-14 X ↑ NK cells → day 21+



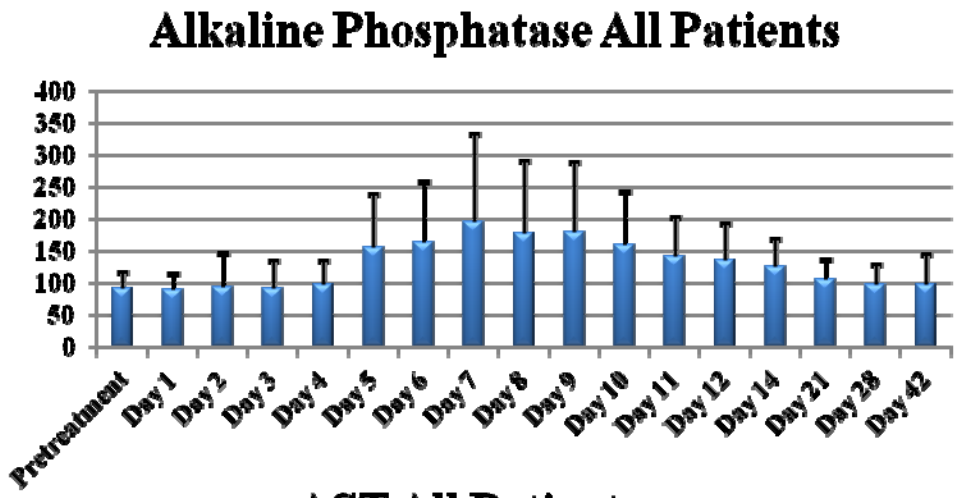


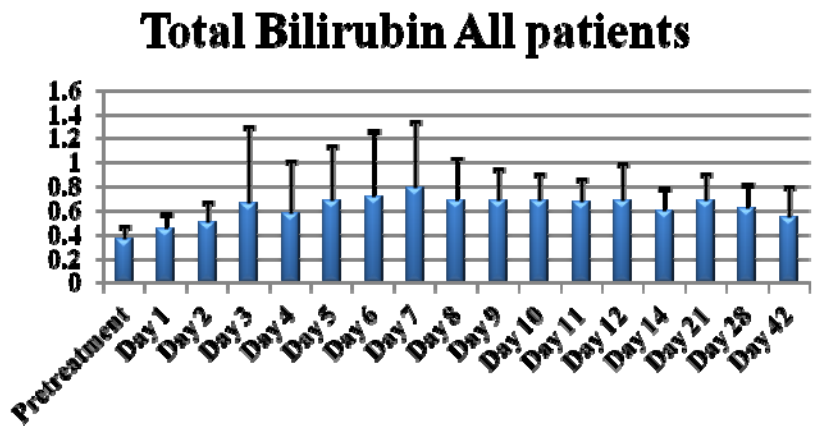


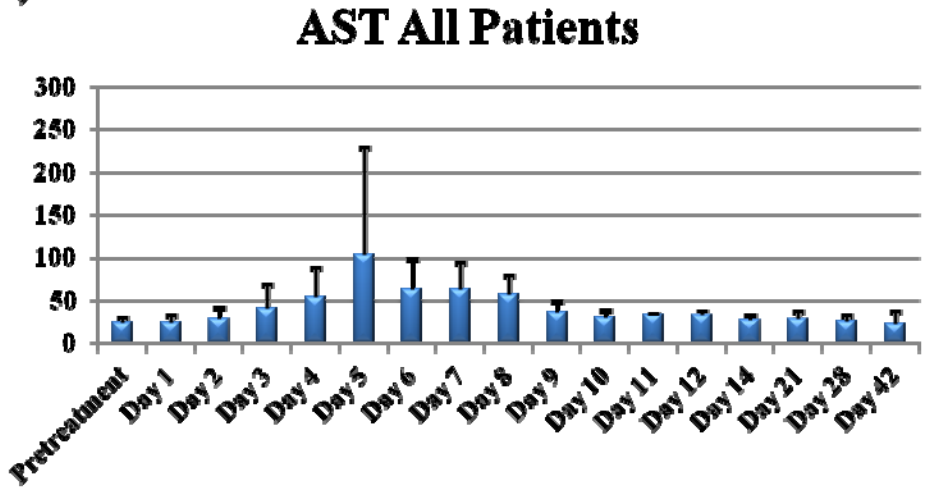


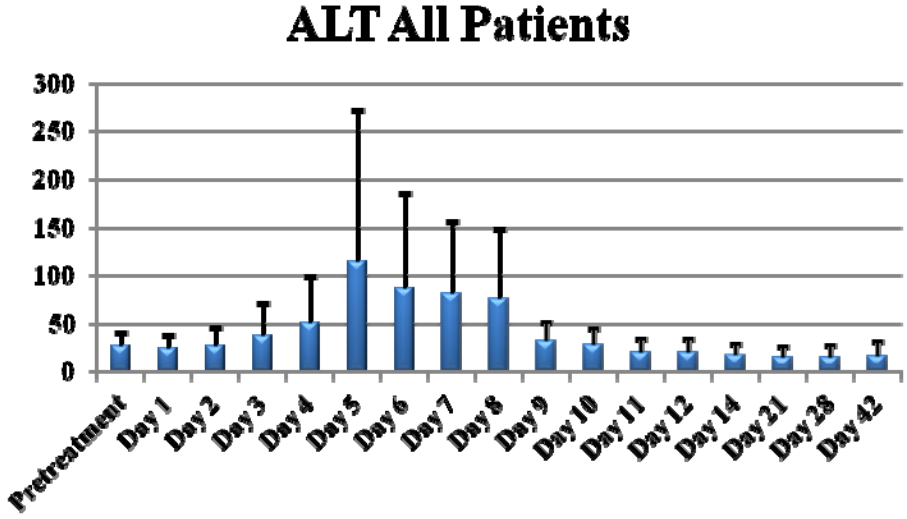
Biochemistry abnormalities

Virtually no changes in serum creatinine → one patient CCr ≈ 60 ml/min maximum SCr ↑ 0.18 mg/dl



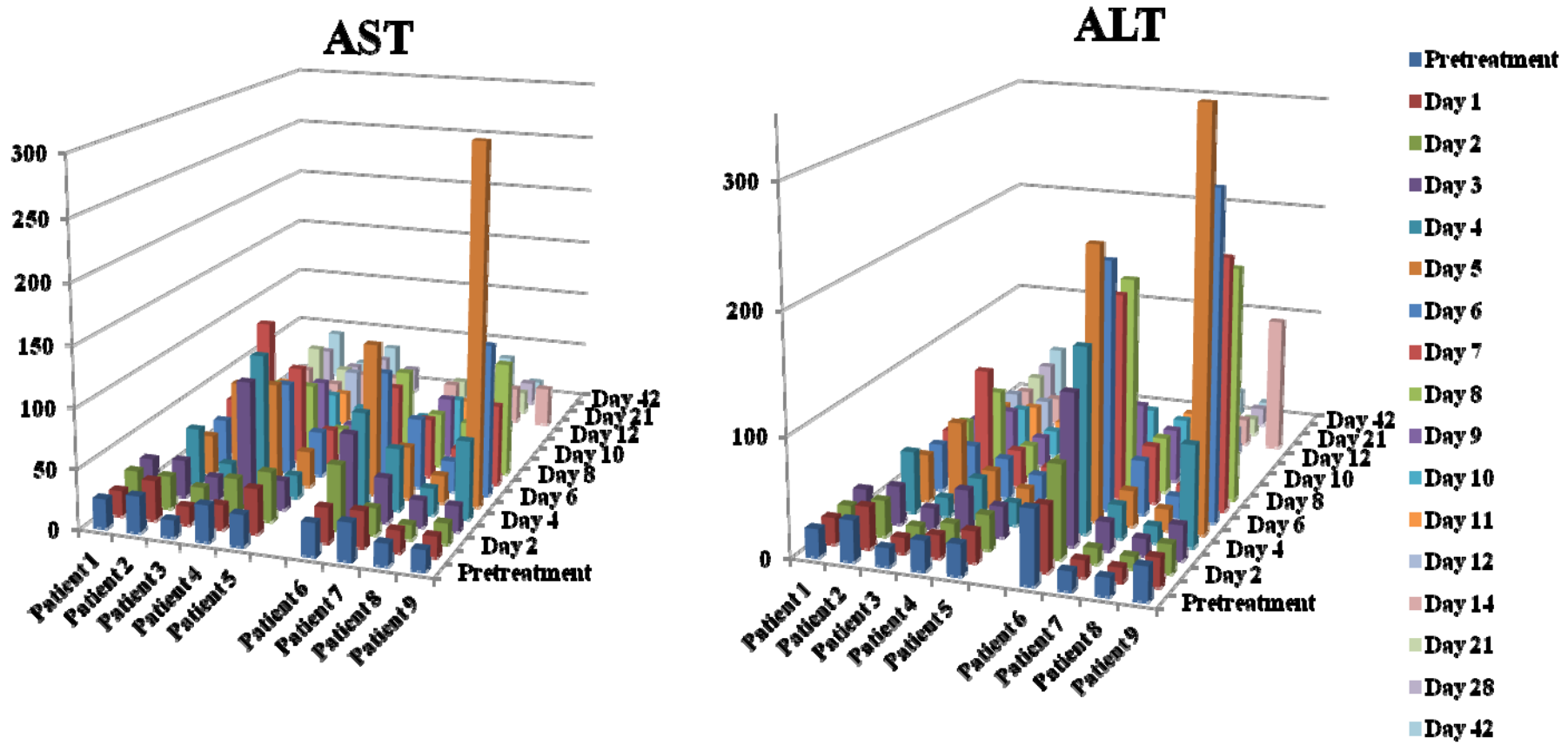




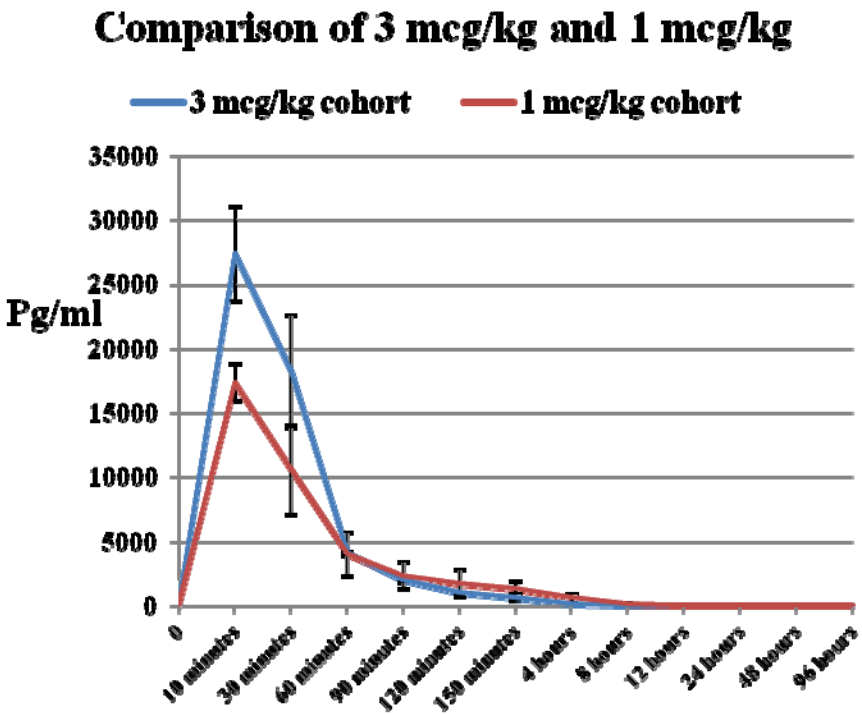


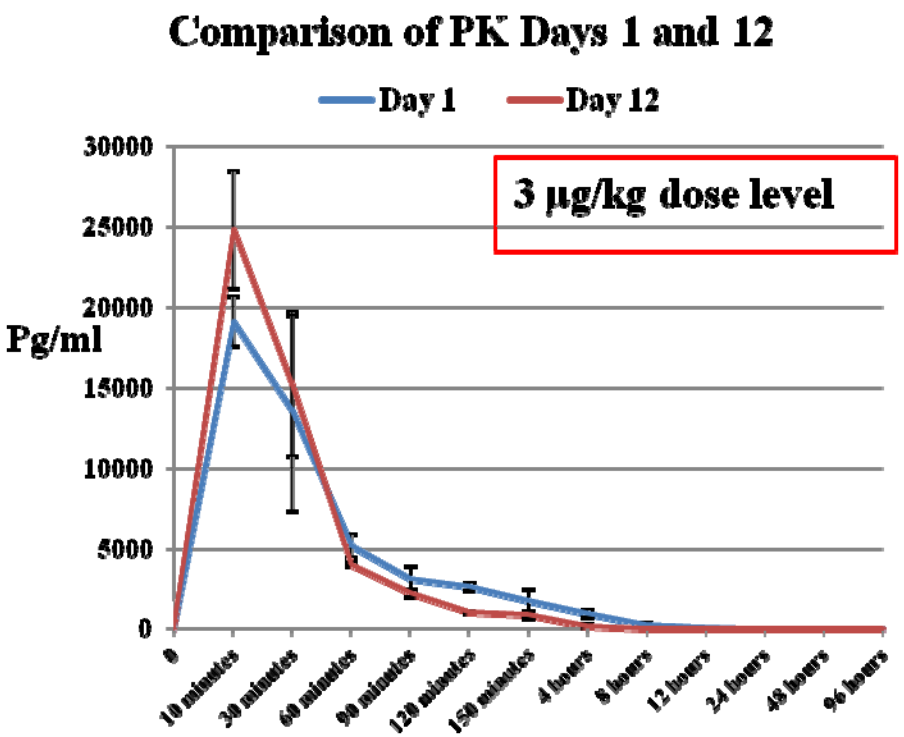
LFT Abnormalities: Details

- Three of the five 3 μg/kg patients had grade 2 CTC LFT abnormalities
- Alkaline Phosphatase 2. 5, 3 and 4.5 X baseline
- 2 had elevated total bilirubin (2.3 and 1.7 mg/dl maximum) back to baseline by the last treatment day
- 2 of these 3 metastatic ocular melanoma with substantial liver metastases



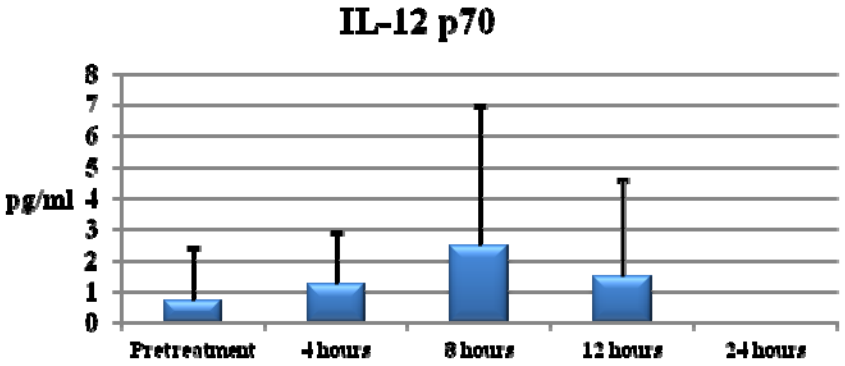
Pharmacokinetics

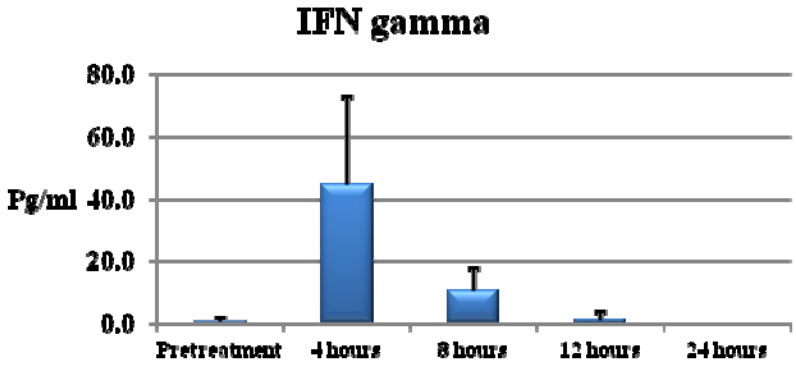


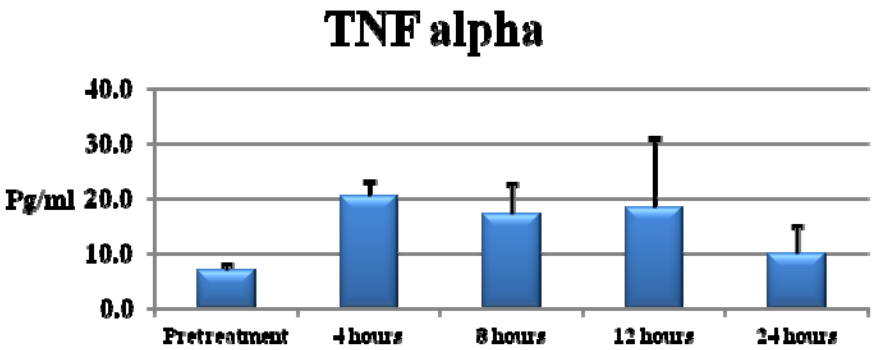


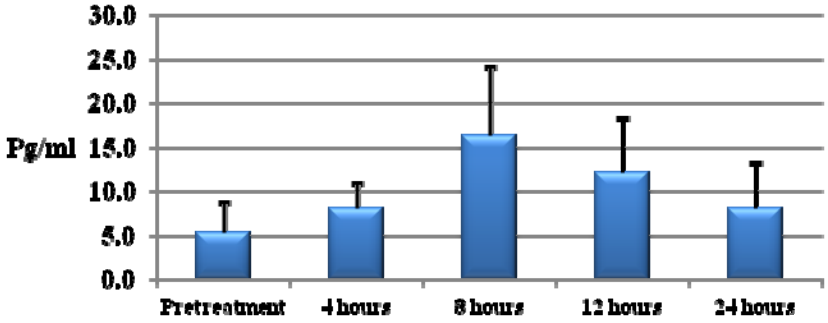
Dose Level	3 µg/kg Patients						1 µg/kg Patients		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5		Patient 6	Patient 7	Patient 8
Cmax (pg/ml)	80590	20211	11400	18000	21900		8520	15520	9160
Anti-IL-15 Antibodies	-	-	-	-	-		-	-	-

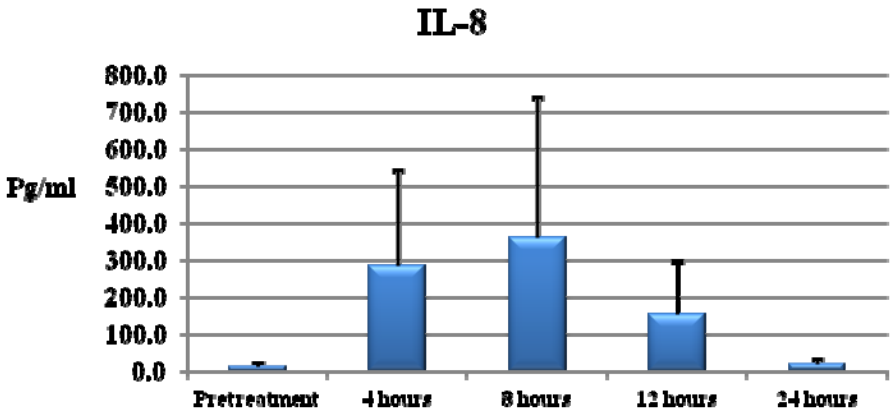
Cytokine Production Day 1

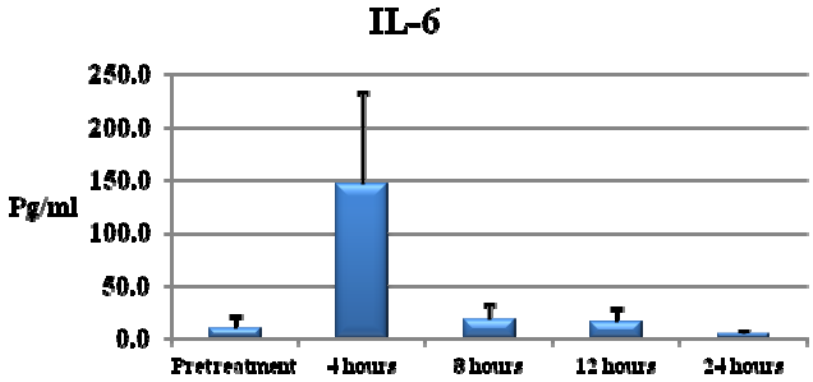








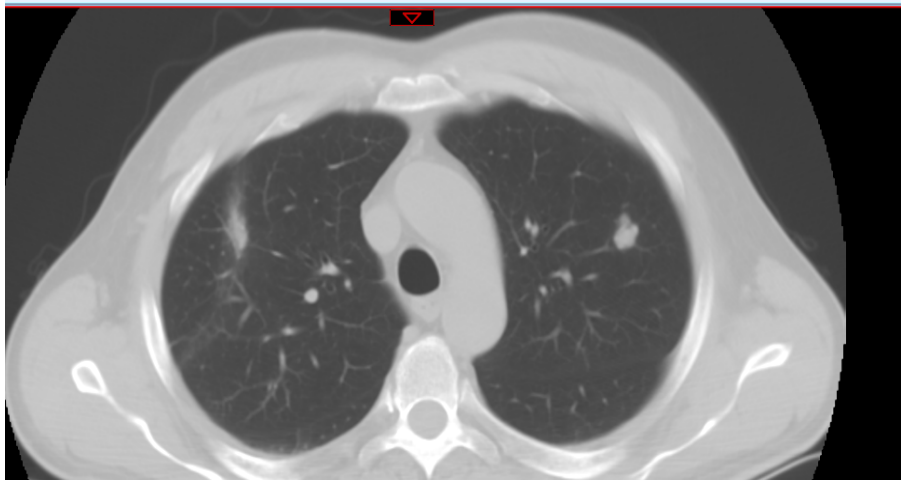




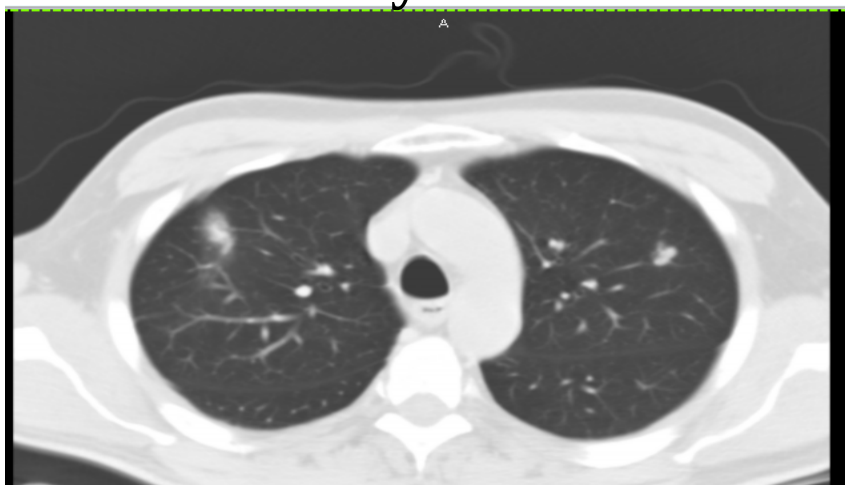
Clinical Activity

Patient	Evaluation	Time to progression
1	Not evaluable	
2	SD (↓20% day 28 and 42)	3 months +
3	SD day 28	Day 42
4	SD	3 months
5	PD	Day 21
6	Not evaluable*	6 months +
7	SD day 28 and 42	3 month
8	PD	Day 21
9	TE	TE

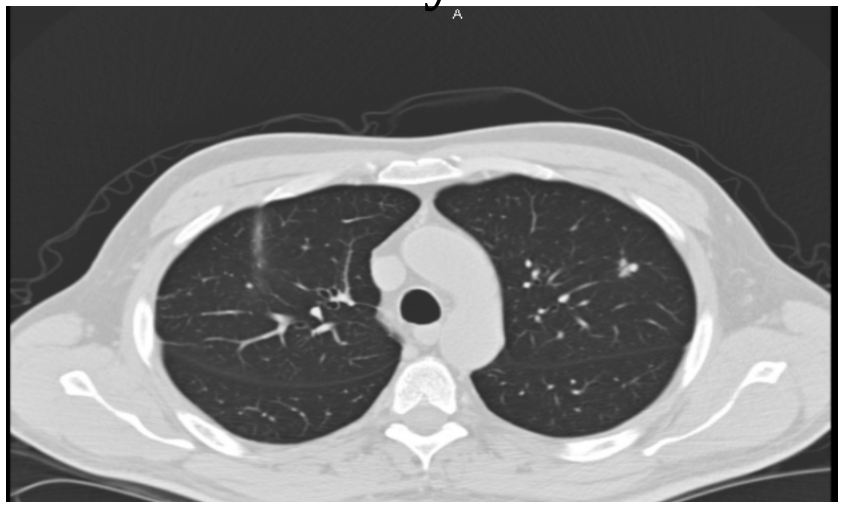
Patient 6 Baseline



Day 37



Day 57



Conclusions

Immune activation was observed at either dose 1 or 3 μg/kg/day

- 2 to 4 fold increase in absolute lymphocyte counts (ALC)
  - 2-3 fold expansion of $CD8^+$ T-cells and 4-14 fold expansion in NK cell numbers
- Production of the inflammatory cytokines at early time points

Toxicities were manageable and resolved after treatment was stopped

- Decreases in BP at the 3 μg/kg but not 1 μg/kg dose level
- Capillary leak was seen, but no significant pulmonary toxicities or end organ dysfunction

PK results

- Half life ≈ 1 hour, no anti-IL-15 antibodies
- No significant changes in PK Day 1 vs. 12

Laboratory abnormalities were mild

- Transient decreases in platelets, neutrophils
- Elevation of liver function tests peaking mid cycle (days 5→ 7)
- Clinically Asymptomatic

Clinical Activity

- Biological indications of in vivo activity?
- no responses by RECIST criteria were observed

3 μg/kg IVB is above the MTD without dedicated nursing

1 μg/kg rhIL-15 given as IVB appears to be a tolerable dose*

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