



AMERICAN SOCIETY OF CLINICAL ONCOLOGY



Abstract 2502

Preliminary Tolerability and Anti-tumor Activity of Intravenous Recombinant Human Interleukin-21 (IL-21) in Patients With Metastatic Melanoma and Metastatic Renal Cell Carcinoma

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Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function

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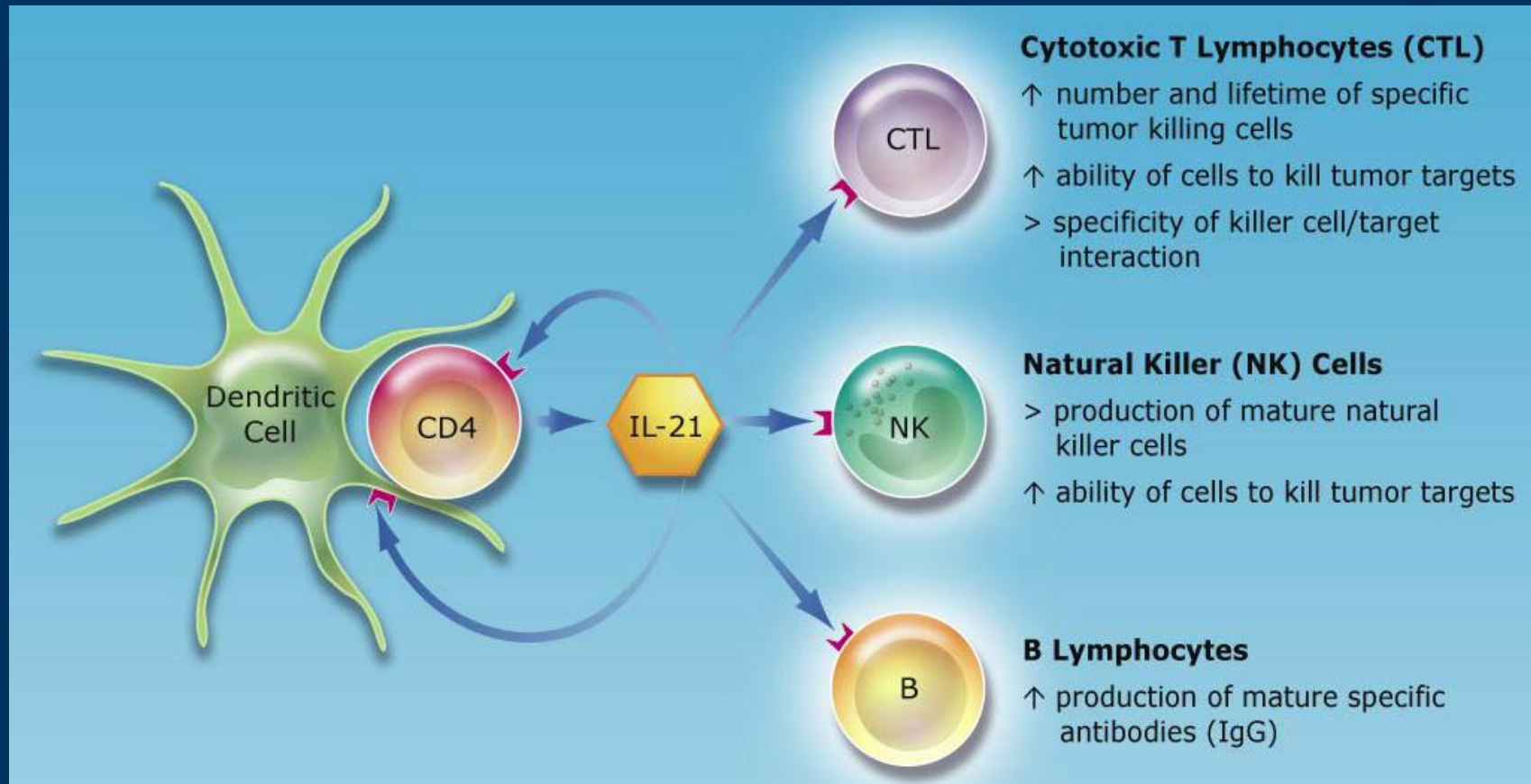
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NATURE | VOL 408 | 2 NOVEMBER 2000 | www.nature.com

Interleukin 21

- Novel class I cytokine
- Produced by activated CD4+ T cells
- Signals through gamma common chain
- Demonstrated anti-tumor efficacy in preclinical models

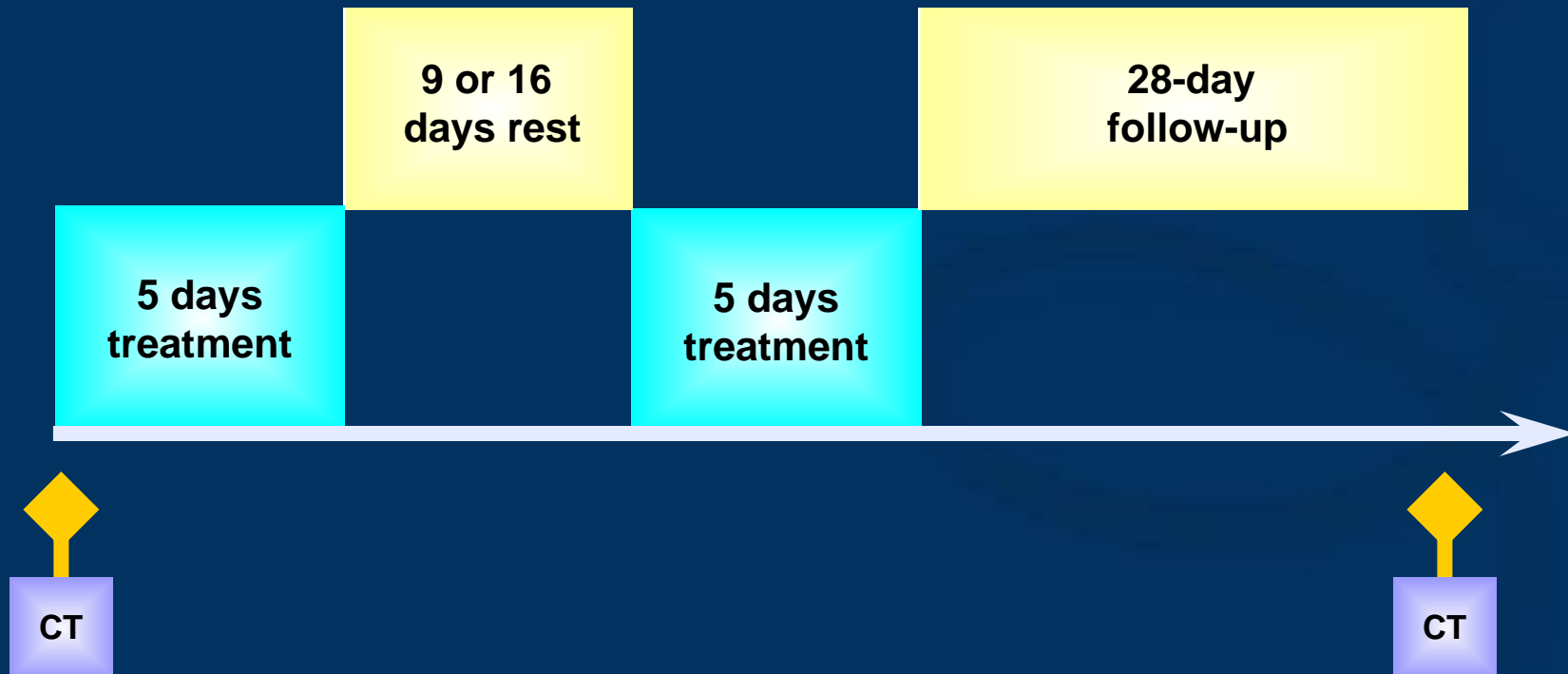
IL-21 Elicits Pleiotropic Immune Modulation



Open Label, Phase I Dose Escalation Study: Objectives

- Primary: Determine maximum tolerated dose of IL-21
- Secondary
 - pharmacokinetics
 - immunogenicity
 - clinical or biological parameters that may correlate with efficacy
 - immunogenicity
 - anti-tumor effect

IL-21 Treatment Schedule



Escalating doses given at half-log increments in cohorts of three

Study Demographics

Characteristic	Number
Gender	
Male	10
Female	2
Age, median (range)	61 (39 – 76)
Malignancy	
Melanoma	8
Renal Cell	4

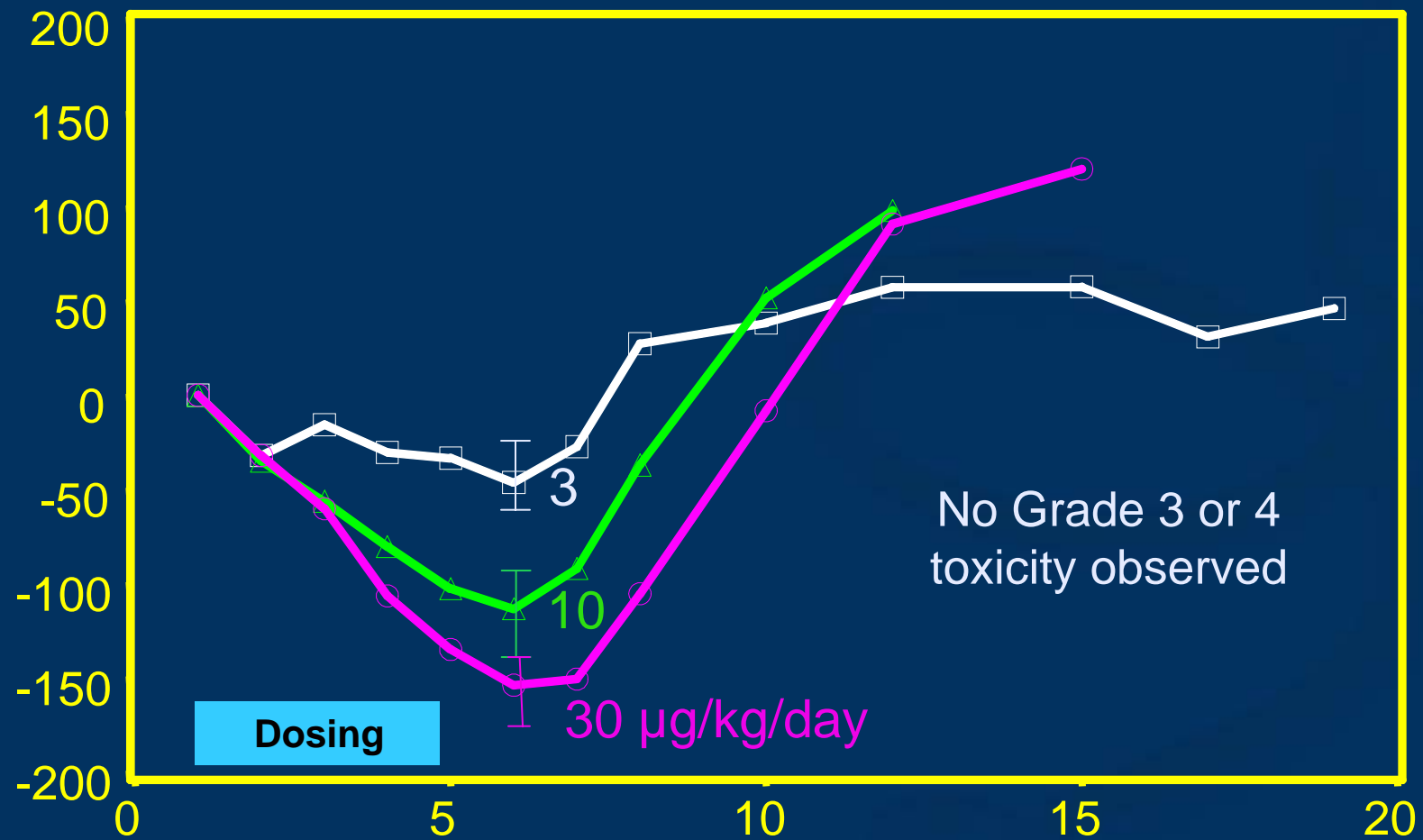
Grade 2 AEs Possibly Related to Study Drug

	3 µg/kg (n = 3)	10 µg/kg (n = 3)	30 µg/kg (n = 6)
Rash	0	1	4
Fatigue	0	0	2
Fever	0	0	2
Anemia	0	0	1
Anorexia	0	0	1
Headache	0	1	0
Hyperhidrosis	0	1	0

Laboratory values of Grade 3

	3 µg/kg (n = 3)	10 µg/kg (n = 3)	30 µg/kg (n = 6)
ALT	0	0	1 (single day)
Lymphopenia	0	0	2 (transient)

Mean Platelet Change from Baseline ($10^9/L$)



Tolerability of Four 5-day Cycles of IL-21 (N=2)

■ 3 µg/kg/day

- Subject with renal cell carcinoma achieved PR after 2 cycles
- Two additional 5-day cycles were well tolerated
- Maintains partial remission at 7+ months

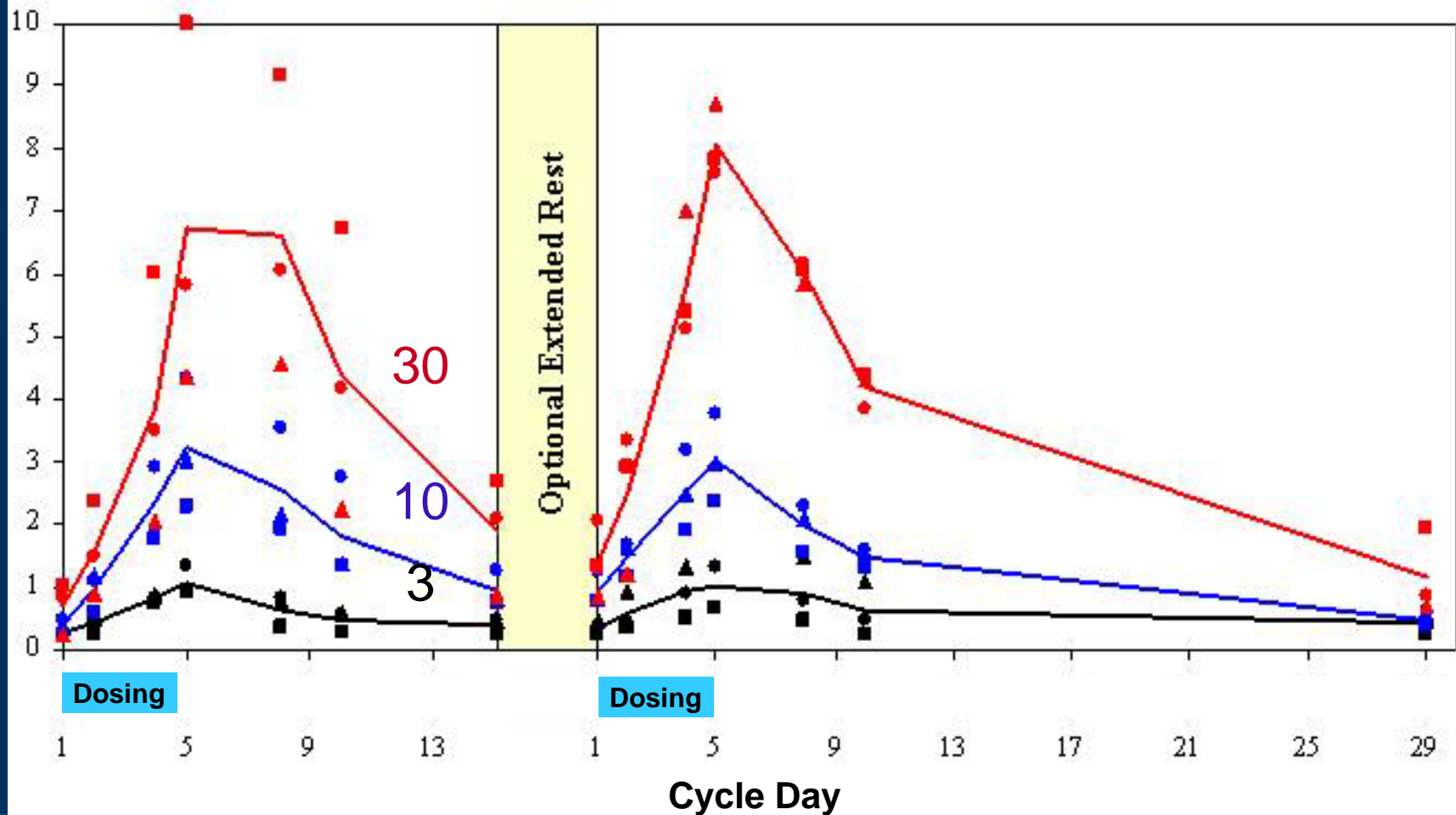
■ 30 µg/kg/day

- Subject with melanoma had stable disease after 2 cycles
- Tolerated 3 cycles of IL-21 well
- Developed acute hepatic injury by fifth day of 4th cycle
 - Transient Grade 4 AST, ALT, and bilirubin with hepatic necrosis
 - Hepatic function recovered during follow-up

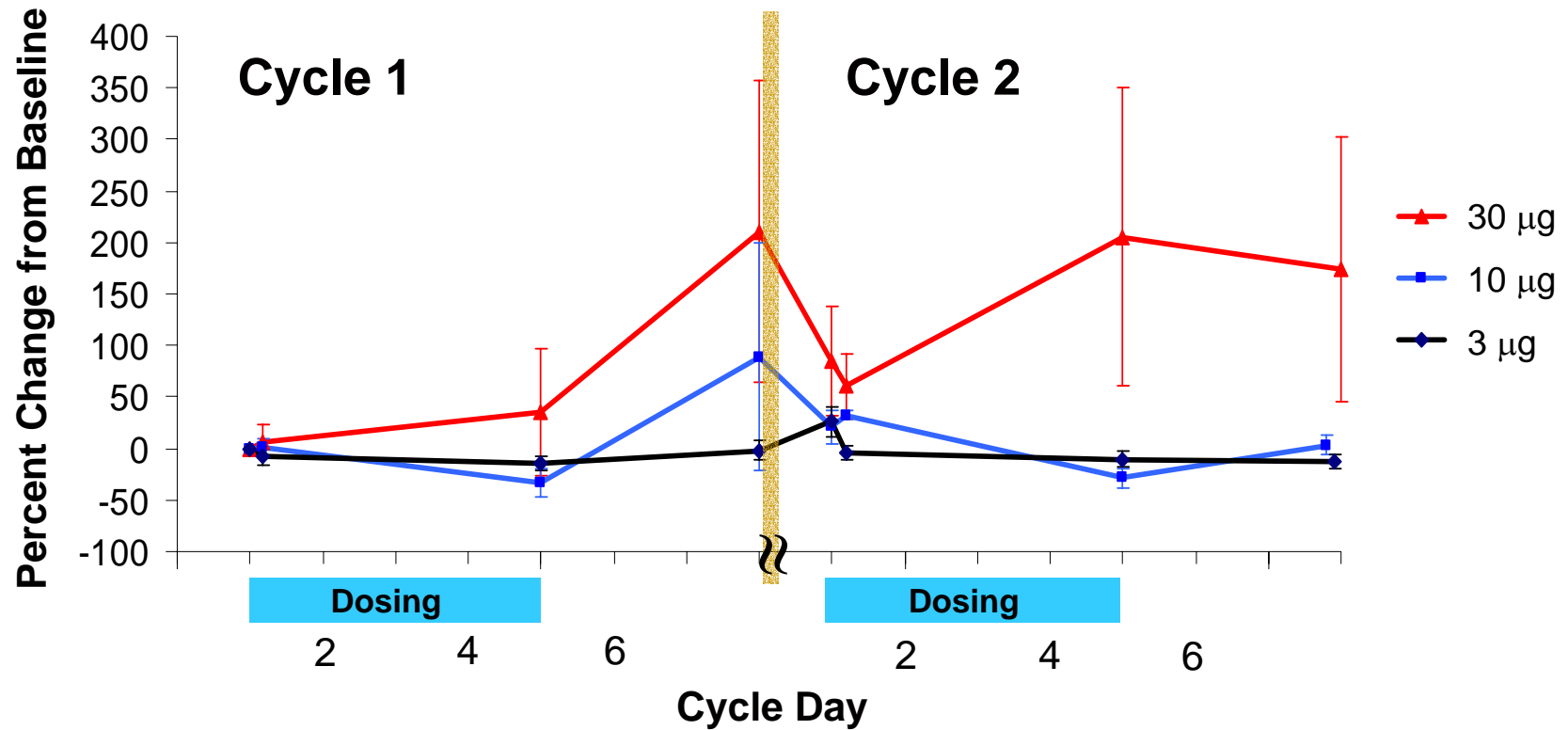
Dose-Dependent Changes in Circulating Leukocytes by Flow Cytometry

- Cytotoxic T cell and natural killer (NK) cell numbers:
 - Decreased during dosing interval
 - Rebounded during recovery period
- Monocytes increased during dosing
- NK cells expressed more surface CD25 (IL-2 receptor)

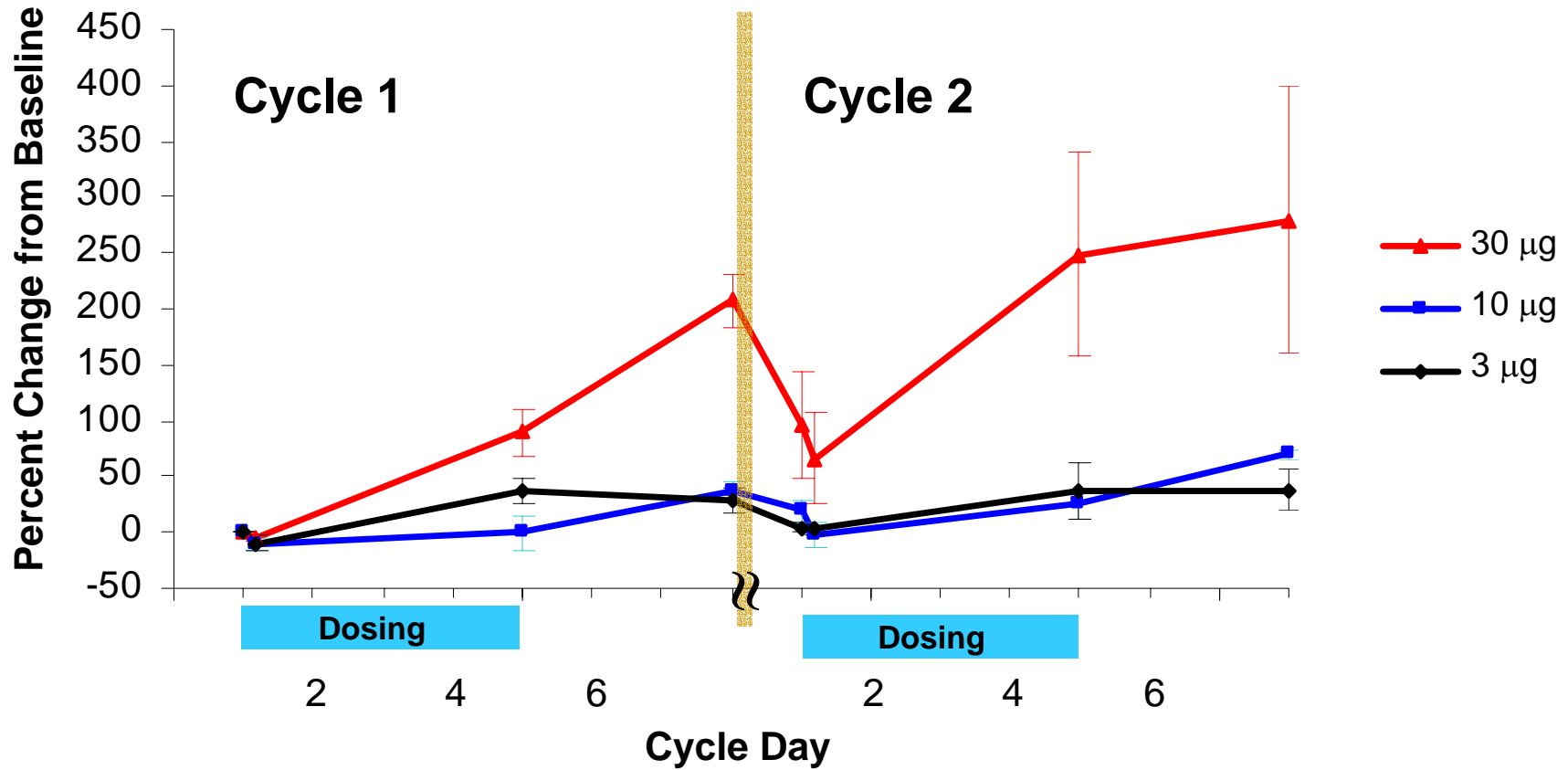
Relationship Between Dose Level of IL-21 ($\mu\text{g}/\text{kg}/\text{dose}$) and Serum Levels of Soluble CD25 (ng/mL) Over Time



Dose-Dependent Changes in IL-15



Dose-Dependent Changes in IL-18



Anti-tumor Responses by Dose Level ($\mu\text{g}/\text{kg}/\text{day}$) x 2 Cycles

	3	10	30	All
CR	0	0	0	0
PR	1*	0	0	1*
SD	0	2	4**	6**
PD	2	1	2*	5*
Total	3	3	6	12

*Each asterik represents one renal cell carcinoma subject.

Summary

- Reasonably well tolerated outpatient IL-21 dosing
- Limited and reversible observed toxicities
- No immunogenicity detected
- Modest anti-tumor activity observed
- Dose-related thrombocytopenia and increased soluble CD25, IL-15 and IL-18 levels suggest pronounced activation of both innate and cellular immunity

Acknowledgements

Providence Portland Medical Center, Portland, OR

Brendan Curti
Lisa Justice
Katrina Herz

University of Michigan, Ann Arbor, MI

Bruce Redman
Peg Esper
Barbara Rinna

University of Washington, Seattle, WA

John Thompson
Linda Kirsch
Elissa Ross

ZymoGenetics (Sponsor)

Eric Sievers
Patty Pederson
Susanne Frahm
Todd DeVries
Mary Fleischer
Janet Kramer
Kimberly Wood
Patti Leith

Novo-Nordisk (Development partner evaluating IL-21 for melanoma in Australia)