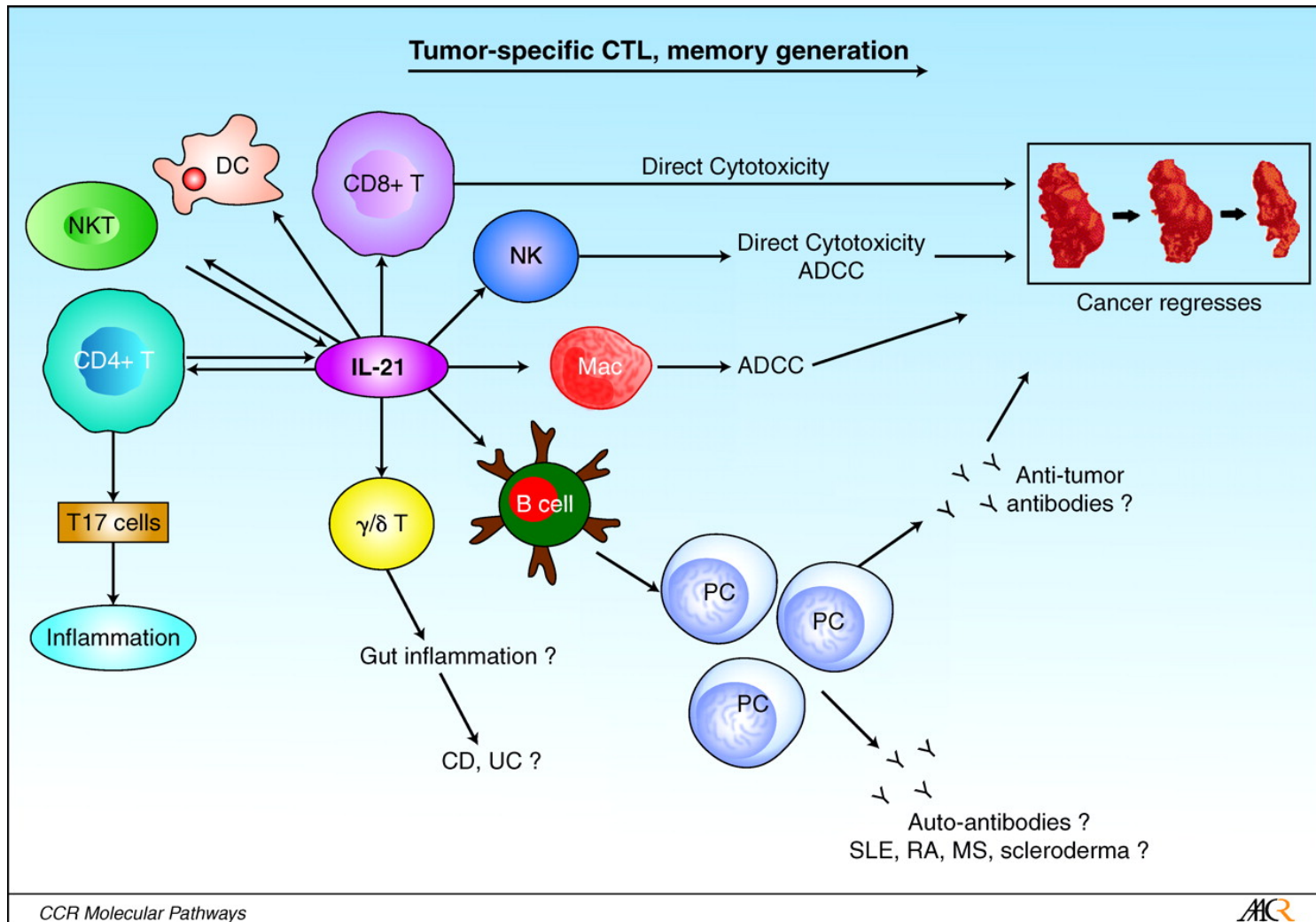


Recombinant Interleukin-21 Plus Sorafenib for Metastatic Renal Cell Carcinoma (mRCC): A Phase 1 Dose Escalation Study

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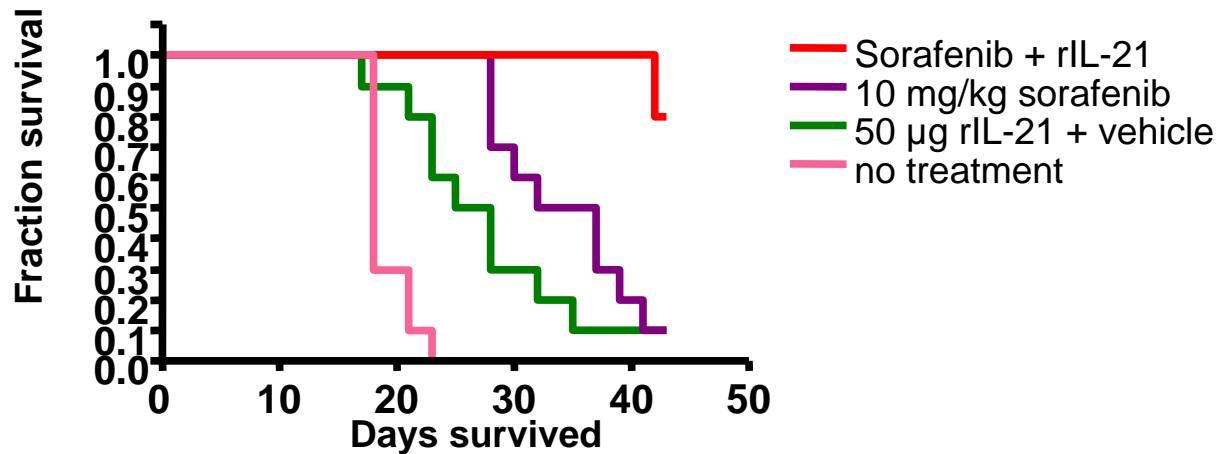
Role of IL-21 in Cancer and Autoimmunity



Davis et al, *Clinical Cancer Research* 13(23):6926-6932, December 1, 2007

rIL-21 in Renal Cell Carcinoma

- Antitumor activity as single agent in patients with RCC¹
- Additive effects with sorafenib on tumor shrinkage and survival in murine RENCA model of RCC



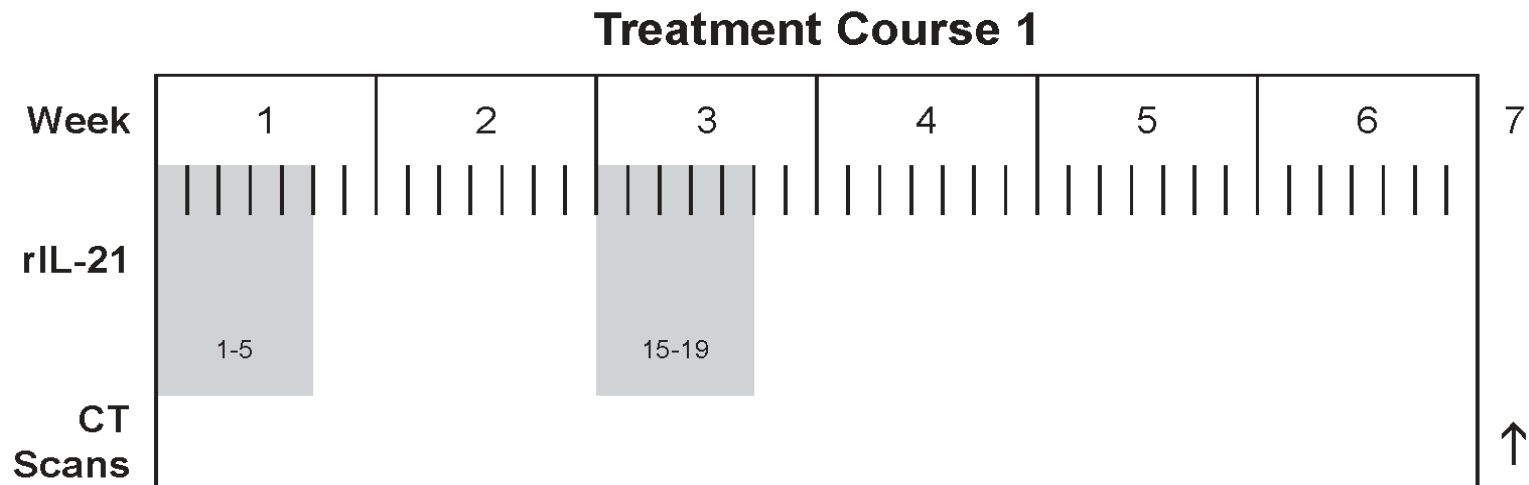
¹ Thompson JA et al, J Clin Oncol 2008; 26(12):2034-2039.

rIL-21 + Sorafenib in Metastatic RCC: Phase 1 Study Design

- Study design
 - ▶ Dose escalation of rIL-21 + sorafenib (400 mg po BID)
 - ▶ “3+3” design
- Objectives
 - ▶ MTD of rIL-21 in combination with sorafenib
 - ▶ Pharmacokinetics of rIL-21 and sorafenib
 - ▶ Anti-tumor activity per RECIST
- Patient population
 - ▶ Clear cell histology
 - ▶ Up to 2 prior treatments for metastatic disease

Treatment Schedule

- 7-week treatment course (TC)
 - ▶ rIL-21 on Days 1-5 and 15-19 of each TC
 - ▶ Sorafenib administered at standard dose (400 mg po BID)
 - ▶ Dose reductions allowed for toxicity



Subject Characteristics

N=19

Gender

Male

15 (79%)

Female

4 (21%)

Age, median (range)

63 years (48–77)

ECOG performance status score

0

15 (79%)

1

4 (21%)

Motzer risk

Favorable

12 (63%)

Intermediate

7 (37%)

Prior nephrectomy

18 (95%)

Prior systemic treatments for mRCC

None

12 (63%)

Any

7 (37%)

Sunitinib

3 (16%)

IL-2




2 (10%)

Other

3 (16%)

Dose Escalation

- MTD determined to be 30 $\mu\text{g}/\text{kg}$

Dose	Enrolled	DLT	Evaluable for dose escalation	Evaluable for tumor response
10 $\mu\text{g}/\text{kg}$	N=8	1 (Grade 3 erythroderma)	6	6
				
30 $\mu\text{g}/\text{kg}$	N=4	0	3	3
				
50 $\mu\text{g}/\text{kg}$	N=4	2 (Grade 3 rash, n=2)	4	2
				
40 $\mu\text{g}/\text{kg}$	N=3	0	3	3
Total:	N=19	3	16	14

Overview of Safety

- Manageable safety profile
 - ▶ **Most common AE's** –
Diarrhea, flu-like symptoms, hand-foot syndrome, rash, and dysphonia (mostly grade 1 or 2)
 - ▶ **Grade 3 AE's** –
Skin rash, hand-foot syndrome, fatigue, hyponatremia, and hypophosphatemia
- Sorafenib dose reduction required in majority (68%) of subjects
- No increased toxicity with repeat treatment courses

Subject Disposition by Treatment Course

- As of 15 Oct 2008, 3 subjects remain on study

	TC1	TC2	TC3	TC4	TC5	TC6	TC7	TC8	TC9	TC10
N starting treatment	19	13	12	10	7	5	3	2	1	1
Completed with SD or better	13	12	11	9	6	3	2	1	1	
Withdrew during or at end of TC	6	1	2	3	2	1		1		
Toxicity	3									
PD	1	1	1	1	1	1		1		
Other reason	2		1	2	1					
Still receiving treatment						1	1			1

Best Response per RECIST any Time on Study^a

	Independent Assessment N = 14 ^b n (%)	Investigator Assessment N = 14 ^b n (%)
Disease control rate (PR + SD) ^c	12 (86%)	13 (93%)
PR	2 (14%)	2 (14%)
SD	10 (71%)	11 (79%)
PD	2 (14%)	1 (7%)

a Snapshot of data as of Sept 2008; treatment and assessment of tumor response is ongoing

b Based on assessment of 14 subjects; 5 subjects who discontinued prior to completion of TC 1 due to DLT or were withdrawn early due to overdose are excluded

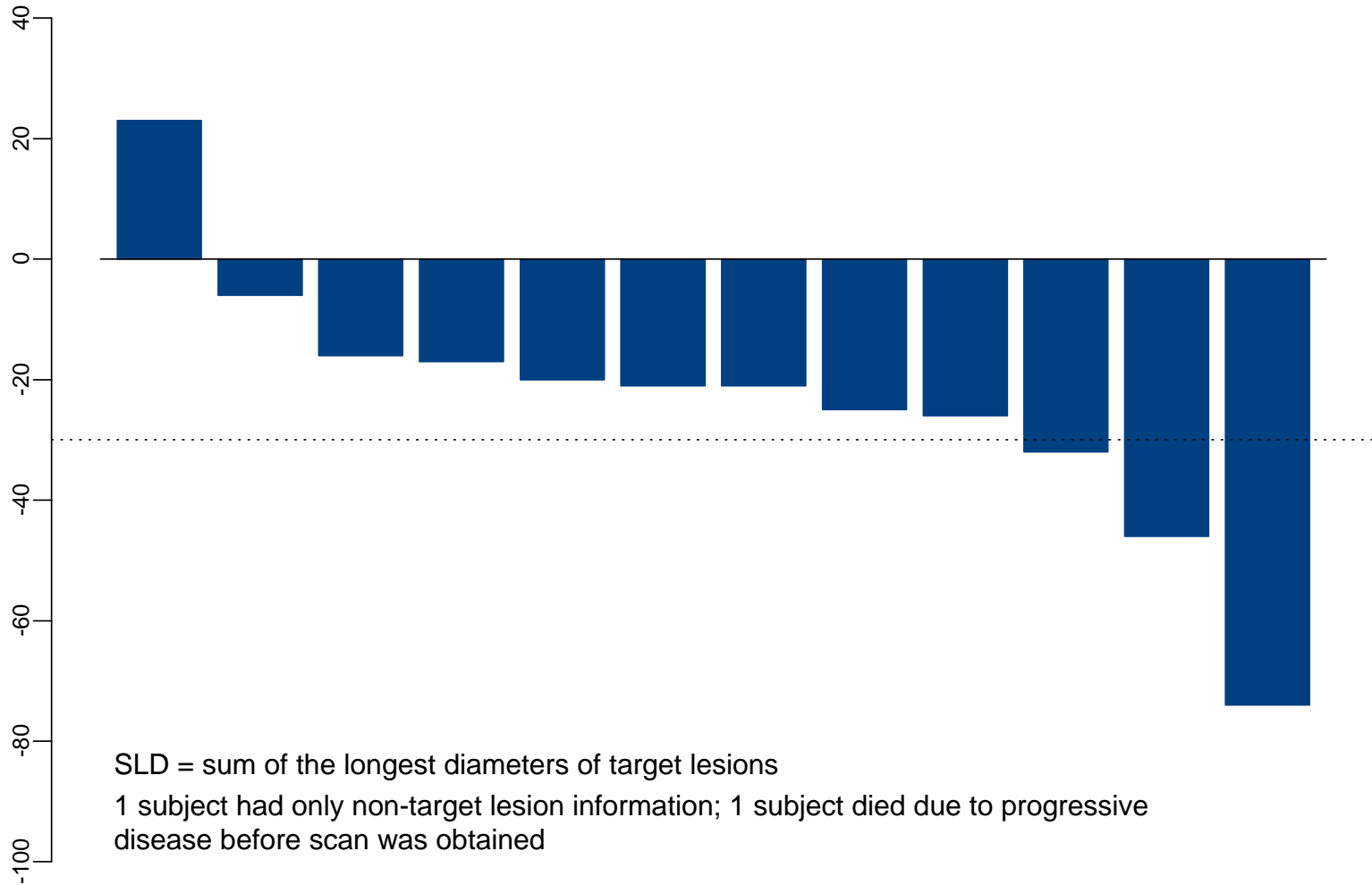
c No subject achieved a CR on study

Duration of Disease Control

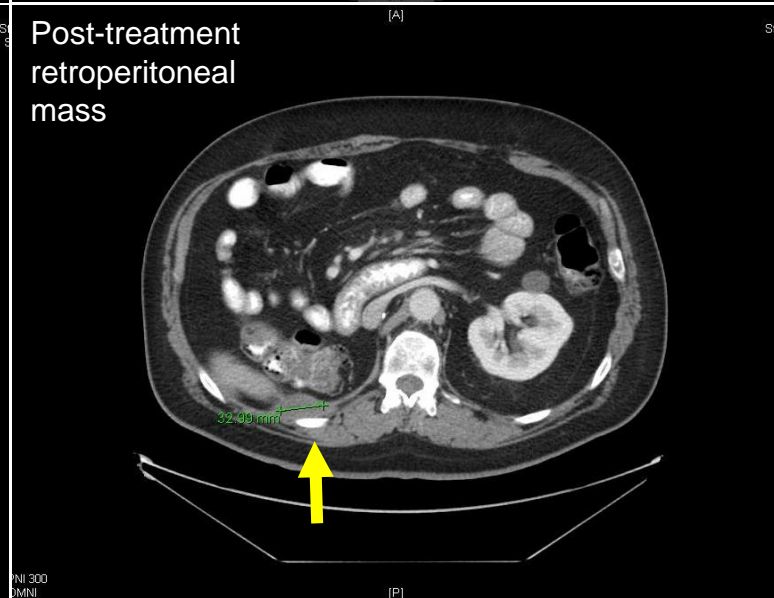
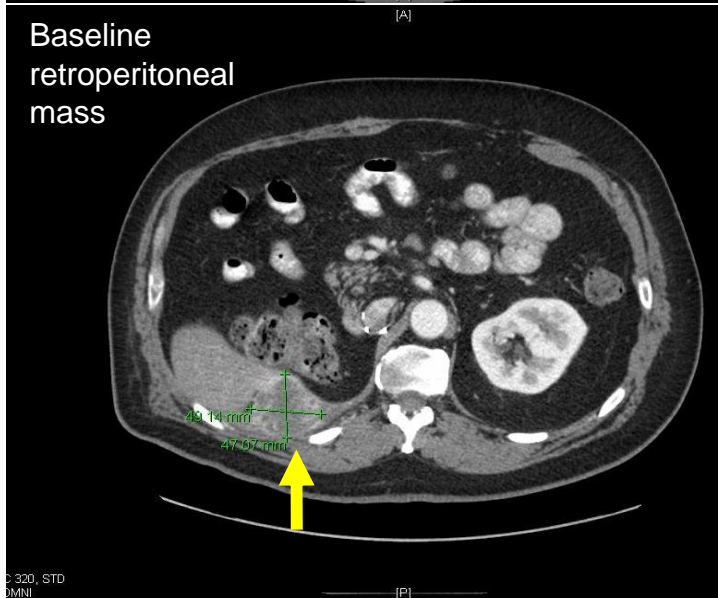
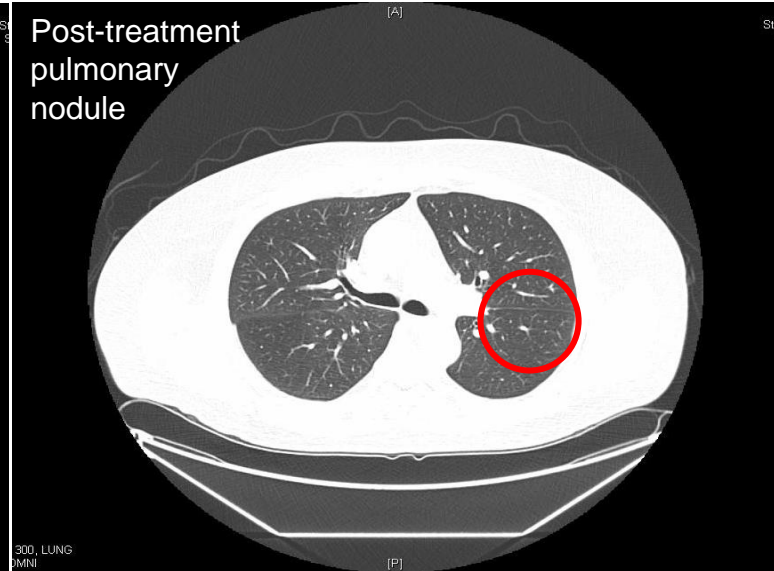
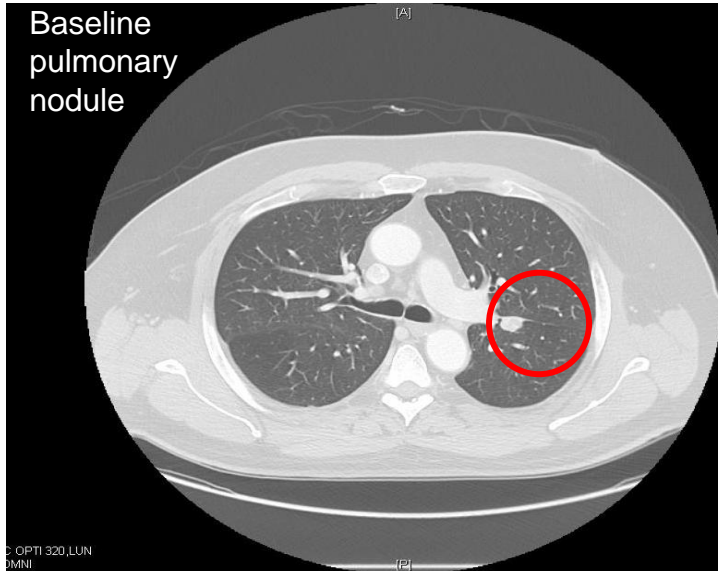
	Independent Review	Investigator Review
Median PFS	N/A	40.4 weeks
DCR (CR+PR+SD) at 24 weeks	9 (75%) ^a	8 (67%) ^a

^a N = 12; data for 2 subjects not available

Maximum Tumor Reduction on Study by Independent Assessment



Subject 1014: Baseline (Jul 2007) & Post-treatment (Nov 2007) Scans

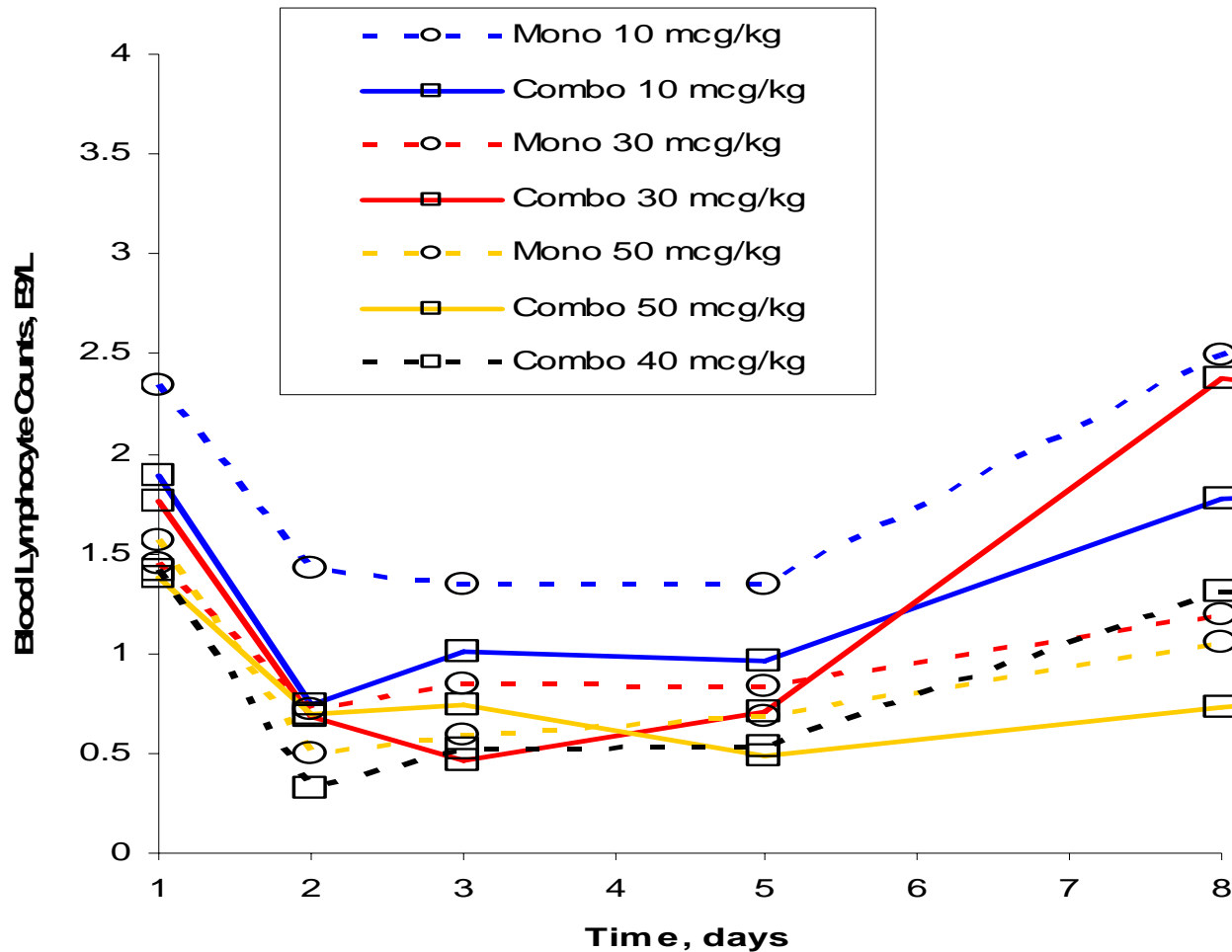


Pharmacokinetics

- Pharmacokinetics
 - ▶ No apparent accumulation with repeated dosing
 - ▶ rIL-21 serum concentrations in presence of sorafenib similar to that of single-agent rIL-21
 - ▶ Sorafenib exposure (AUC) in the presence of rIL-21 was comparable to reported values for single-agent sorafenib

Pharmacodynamics

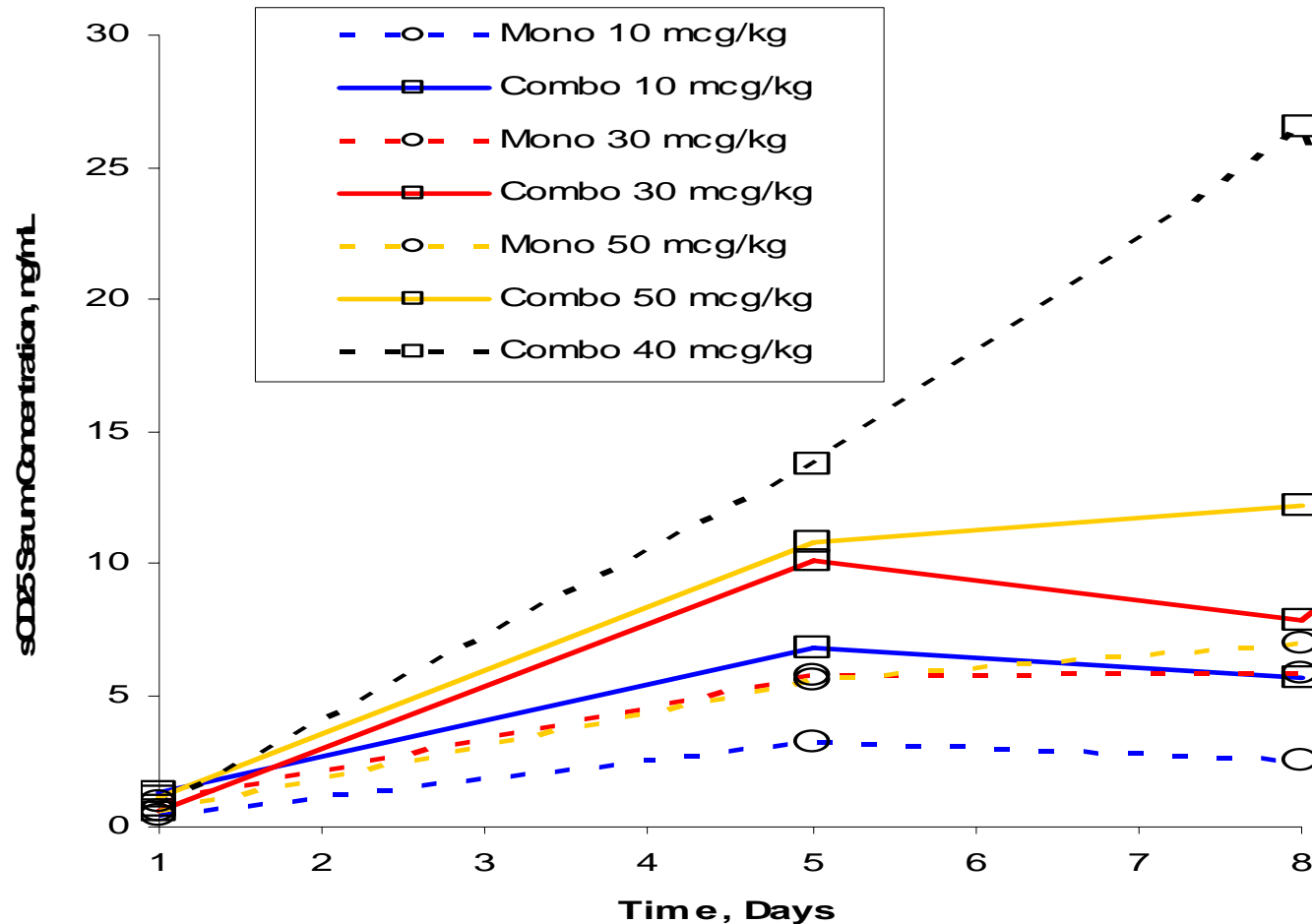
Sorafenib does not alter rIL-21 effects on lymphocyte number*



*Compared to results of rIL-21 monotherapy

Pharmacodynamics

Sorafenib does not diminish rIL-21 effects on lymphocyte activation *



*Compared to results of rIL-21 monotherapy

Summary and Conclusions

- Combination therapy with rIL-21 and sorafenib is feasible with manageable outpatient toxicity
- Encouraging antitumor activity observed
 - ▶ Median PFS of 40.4 weeks
 - ▶ ORR of 14%
- Pharmacokinetics of rIL-21 and sorafenib in combination were not different from pharmacokinetics of either agent administered alone
- Sorafenib did not diminish rIL-21 effect on lymphocyte numbers and activation

Acknowledgments

Investigators

■ John Thompson, MD	Univ of Washington/Seattle Cancer Care Alliance
■ Brendan Curti, MD	Providence Medical Center
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■ David Quinn, MD, PhD	Univ of Southern California
■ Peter VanVeldhuizen, MD	Univ of Kansas Hospital Cancer Center

rIL-21 being developed by **ZYMOGENETICS**