Identification of a well-tolerated outpatient regimen of intravenous recombinant human interleukin-21 (IL-21) in patients with metastatic melanoma and metastatic renal cell carcinoma

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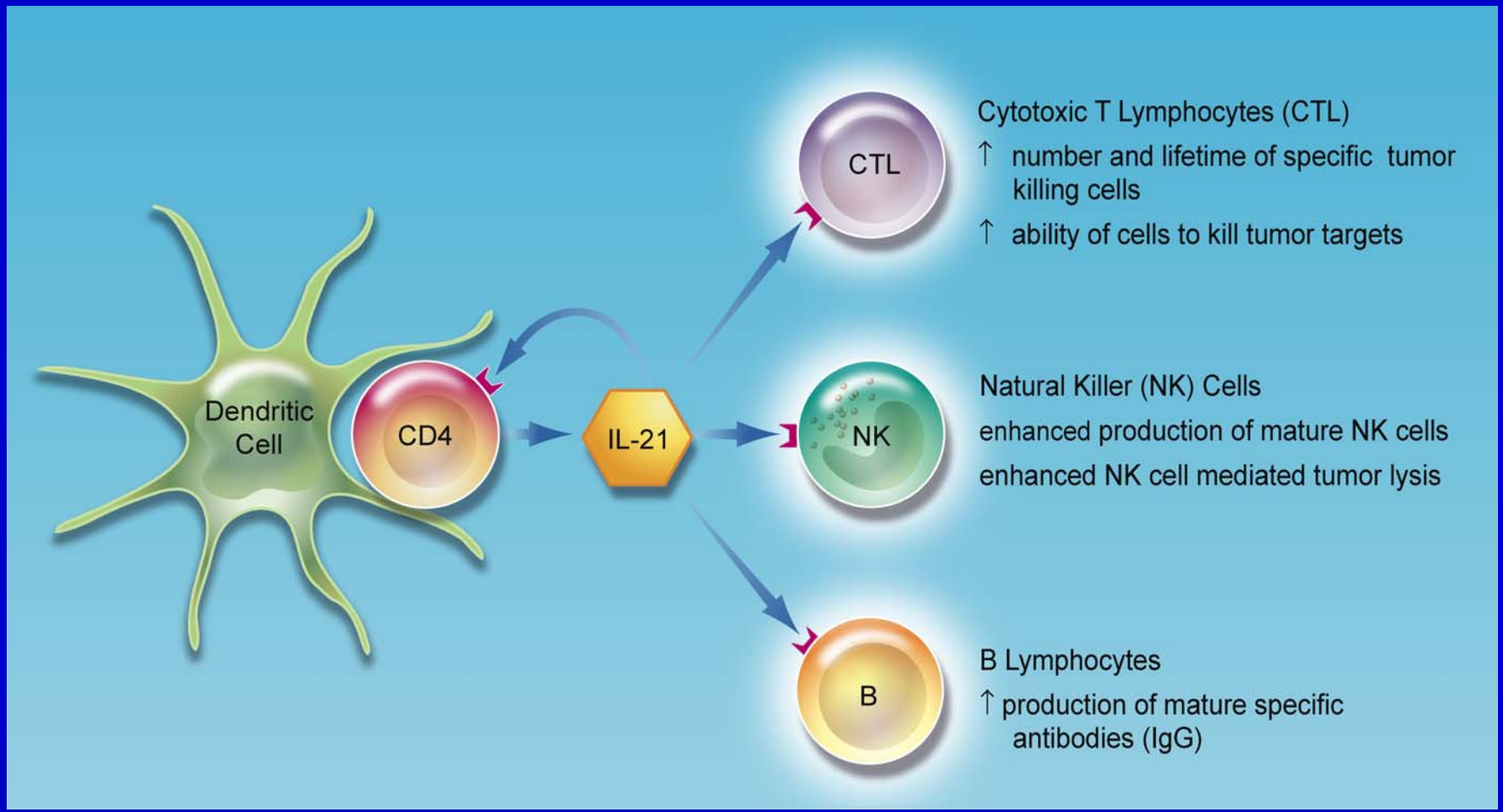
Interleukin 21

- Novel class I cytokine
- Produced by activated CD4+ T cells
- Signals through dimer of unique IL-21 receptor and common gamma chain
- Recombinant IL-21 has demonstrated anti-tumor efficacy in preclinical models

IL-21 Elicits Pleiotropic Immune Modulation



Open Label, Phase 1 Dose Escalation Study

- Population
  - Patients with measurable metastatic melanoma or renal cell carcinoma
- Objectives
  - Primary
    - Determine maximum tolerated dose of IL-21 (using CTCAE criteria)
  - Secondary
    - Pharmacokinetics
    - Immunogenicity
    - Clinical or biological parameters that may correlate with efficacy
    - Anti-tumor effect

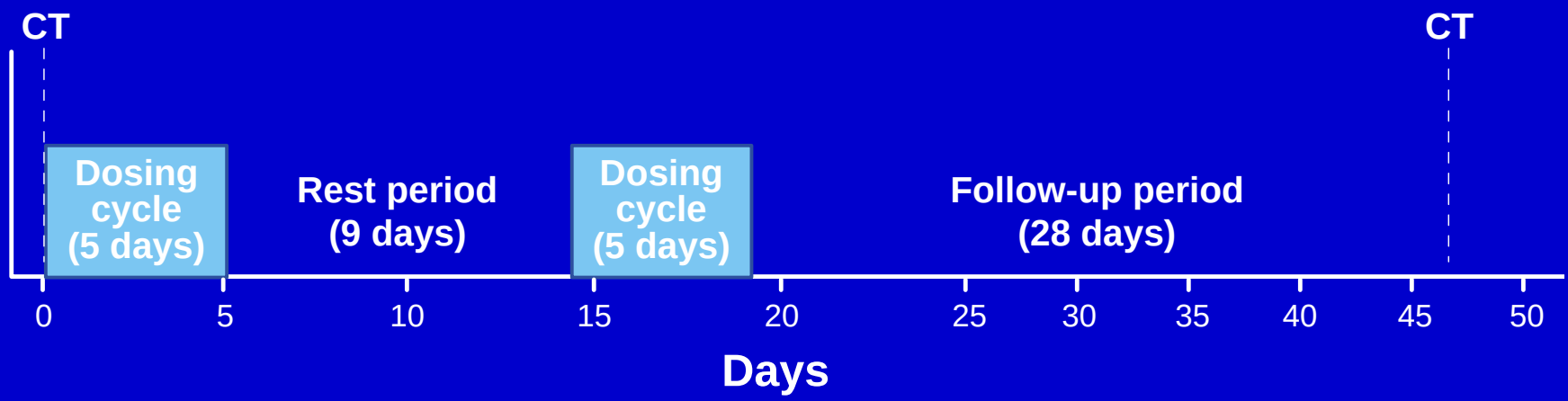
Key inclusion criteria

- Metastatic melanoma (non ocular) or metastatic renal cell carcinoma (clear cell)
- ECOG 0 or 1
- “Standard” laboratory parameters
- No more than one prior treatment
- Hemoglobin > 12 g/dL

Part 1a
Study Demographics (n = 15)

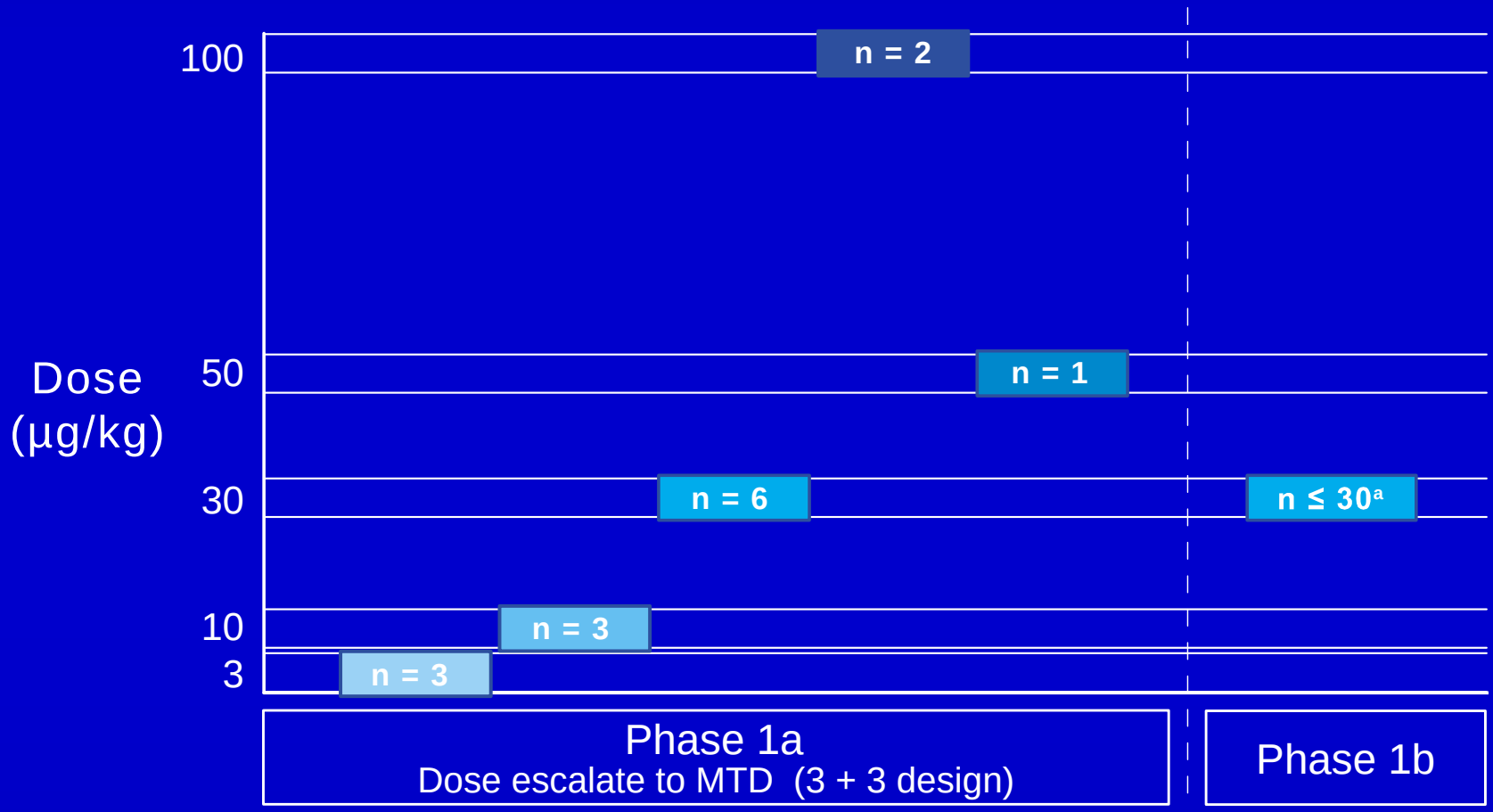
- Gender
  - Male 13
  - Female 2
- Age, median (range) 61 (39 – 76)
- Malignancy
  - Melanoma 9
  - Renal Cell 6
- Mean years since diagnosis 4
- Number with prior immunotherapy
  - IL-2 5
  - Interferon 4

IL-21 Treatment Schedule



Dosing cycle = 5 consecutive daily doses of IL-21 delivered by IV push in the outpatient setting

IL-21 Monotherapy Phase 1 Study (U.S.)



[a] n = up to 30 subjects (15 of each disease type) including Phase 1a subjects dosed at 30 µg/kg

IL-21 Safety

- All but 2 adverse events were mild to moderate in severity
- Most common adverse events
  - Fatigue, Pyrexia, Arthralgia, Chills, Headache, Myalgia, Rash
- Grade 3 or higher adverse events included
  - Grade 4 acute liver toxicity probably related to IL-21 (occurred in Cycle 4) – 30 µg/kg
  - Grade 3 hemoptysis unrelated to IL-21 – 3 µg/kg
- 0/15 patients treated with $\leq$ 2 cycles developed specific antibody response

Most Common Adverse Events through 2 Cycles by Dose (µg/kg)

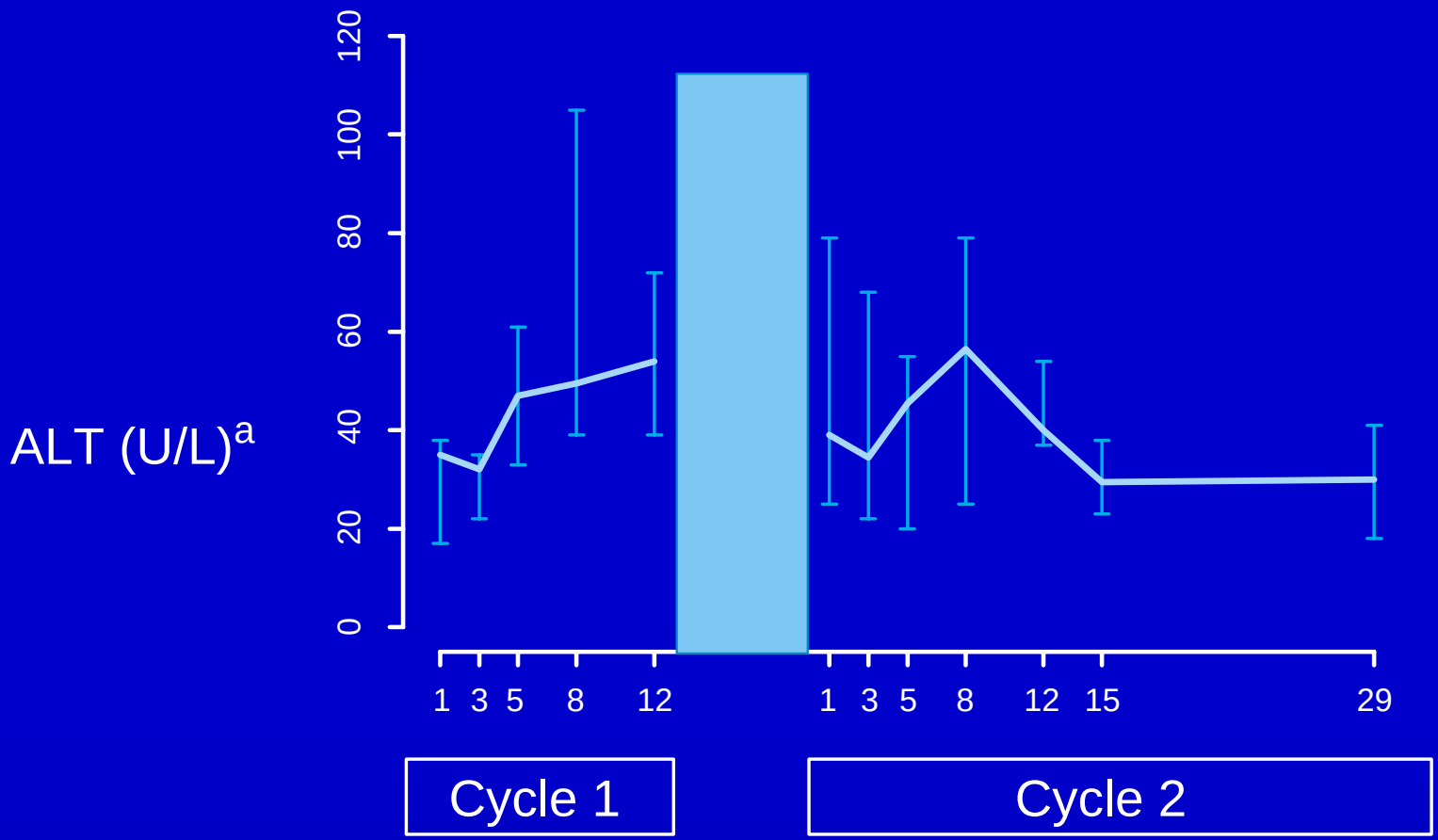
	3 (n = 3)	10 (n = 3)	30 (n = 6)	50 (n = 1)	100 (n = 2)	Total (n = 15)
Fatigue	2	2	6	1	2	13
Pyrexia	1	2	6	1	1	11
Arthralgia	2	2	5	0	1	10
Chills	2	2	3	1	2	10
Headache	2	2	4	0	1	9
Myalgia	0	2	4	1	2	9
Rash	0	1	5	1	2	9
Constipation	0	1	4	1	1	7
Nausea	1	0	3	1	2	7
Edema Peripheral	2	1	3	1	0	7
Anorexia	0	0	3	1	2	6
Insomnia	1	1	3	0	1	6

Grade 3 Laboratory Toxicities through 2 Cycles by Dose (µg/kg)

- 7 of 9 patients at doses ≥ 30 µg/kg experienced Grade 3 toxicity
- One patient at 100 µg/kg experienced transient Grade 4 lymphopenia

	≤ 10 (n = 6)	30 (n = 6)	50 (n = 1)	100 (n = 2)	Total (n = 15)
Lymphopenia	0	2	1	2	5
Hypophosphatemia	0	1	0	1	2
Increased ALT	0	1	0	0	1
Hyperbilirubinemia	0	0	0	1	1
Thrombocytopenia	0	0	0	1	1
Leukocytosis	0	0	0	1	1
Neutropenia	0	0	1	0	1
Hyponatremia	0	0	0	1	1

Median ALT Over Time for 30 µg/kg



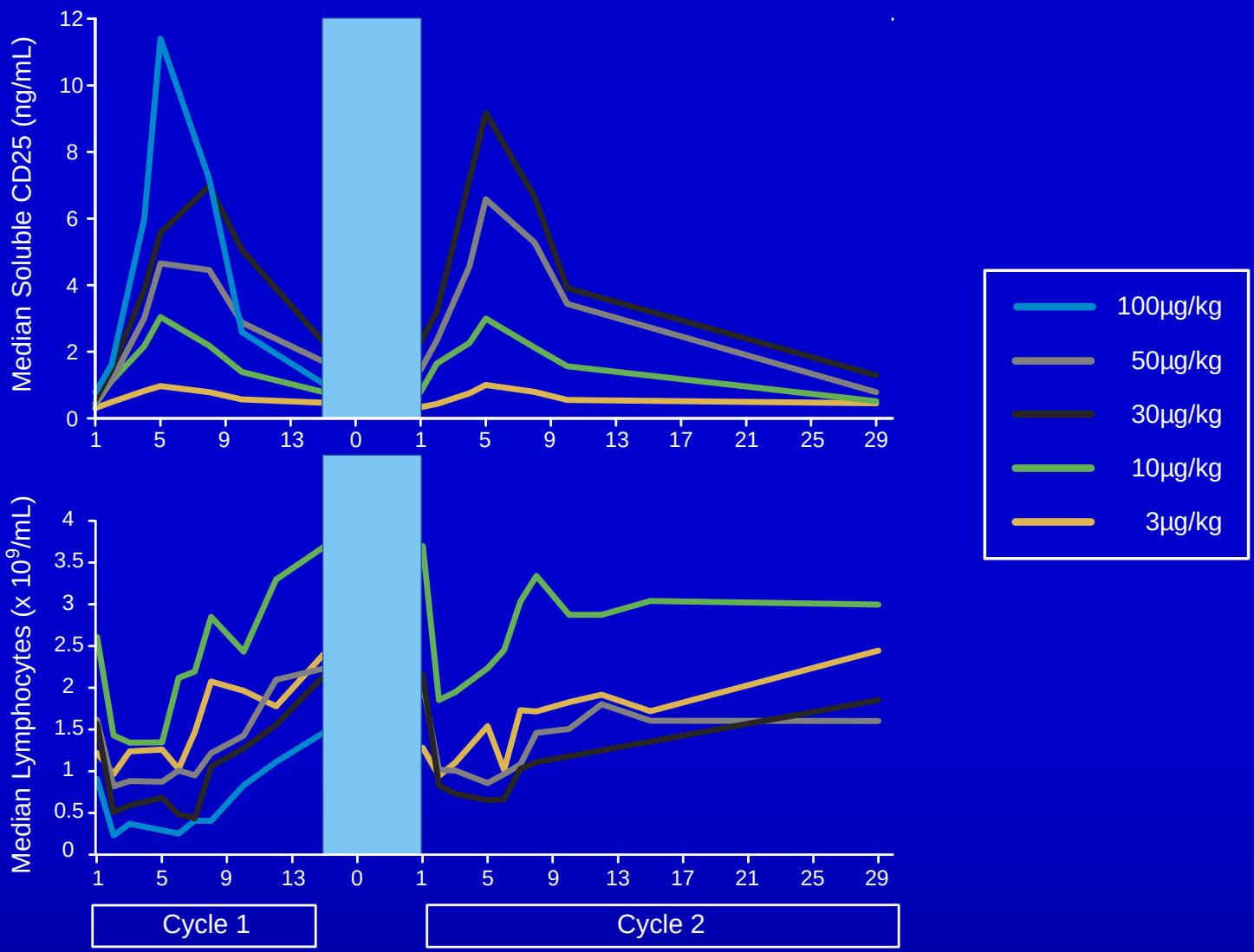
[a] median with IQR

IL-21 Pharmacokinetics

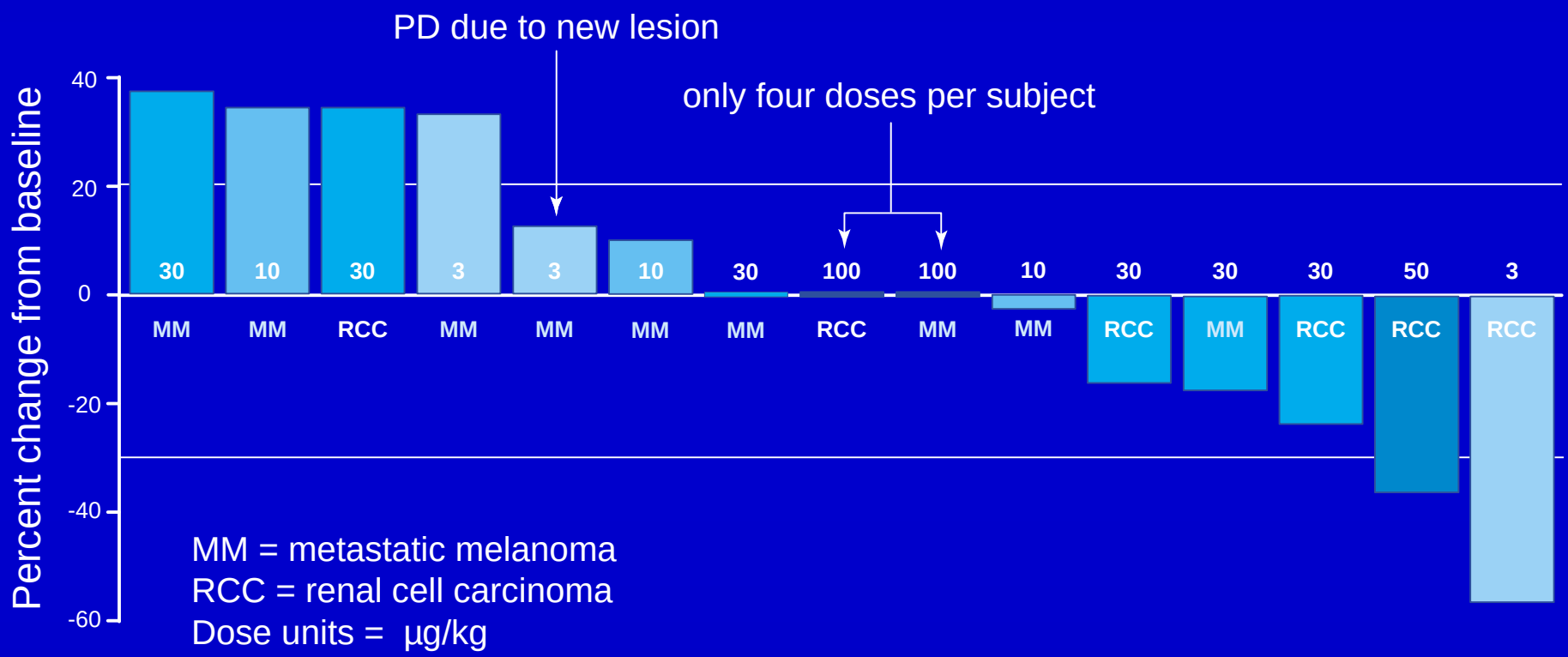
The half-life ($t_{1/2}$) of IL-21 was approximately 1.5 hours

Dose (µg/kg)	N	Median *(CV%)* Cmax (ng/mL)	AUC_{INF} (hr*ng/mL)	$t_{½}$ (hr)
3	3	39.7 *(70.8)*	22.9 *(37.3)*	1.88 *(13.4)*
10	3	33.5 *(80.0)*	68.2 *(14.5)*	1.31 *(15.5)*
30	6	107 *(115)*	206 *(41.6)*	1.69 *(11.8)*
50	1	102 *(--)*	195 *(--)*	1.40 *(--)*
100	2	347 *(48.0)*	602 *(41.3)*	1.89 *(2.63)*

Median Lymphocytes and Median Soluble CD25



Changes in Target Lesion Diameter after Receiving 2 Cycles of IL-21 Treatment



RECIST Responses through 2 Cycles by Dose (µg/kg)

	3 (n = 3)	10 (n = 3)	30 (n = 6)	50 (n = 1)	100[a] (n = 2)
PR	1 (RCC)	0	0	1 (RCC)	0
SD	0	2 (MM)	2 (MM) 2 (RCC)	0	1 (RCC) 1 (MM)
PD	2 (MM)	1 (MM)	1 (RCC) 1 (MM)	0	0

a Each patient at 100 µg/kg received only 4 of 10 planned doses

MM = metastatic melanoma

RCC = renal cell carcinoma

Conclusions

- Outpatient MTD selected for further study in Part b:
  - 2 cycles of 30 µg/kg/day x 5 days with 9-day rest interval
  - Reasonably well-tolerated by 6 patients
- AUC of IL-21 increased in dose-proportional manner
- Dose-related biological effects as measured by sCD25 and lymphocytes
- Objective evidence of anti-tumor activity

Plans

- Completing enrollment of 30 patients treated at 30 µg/kg/day
  - 15 renal cell carcinoma
  - 15 metastatic melanoma

- Goals
  - Further characterize safety of this outpatient regimen
  - Estimate overall response rate for each cancer
  - Plan Phase 2 studies

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Maximum ALT by Patient