

Phase II Study of Interleukin-21 (rIL-21) in Patients With Metastatic or Recurrent Melanoma IND 189

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ZYMOGENETICS

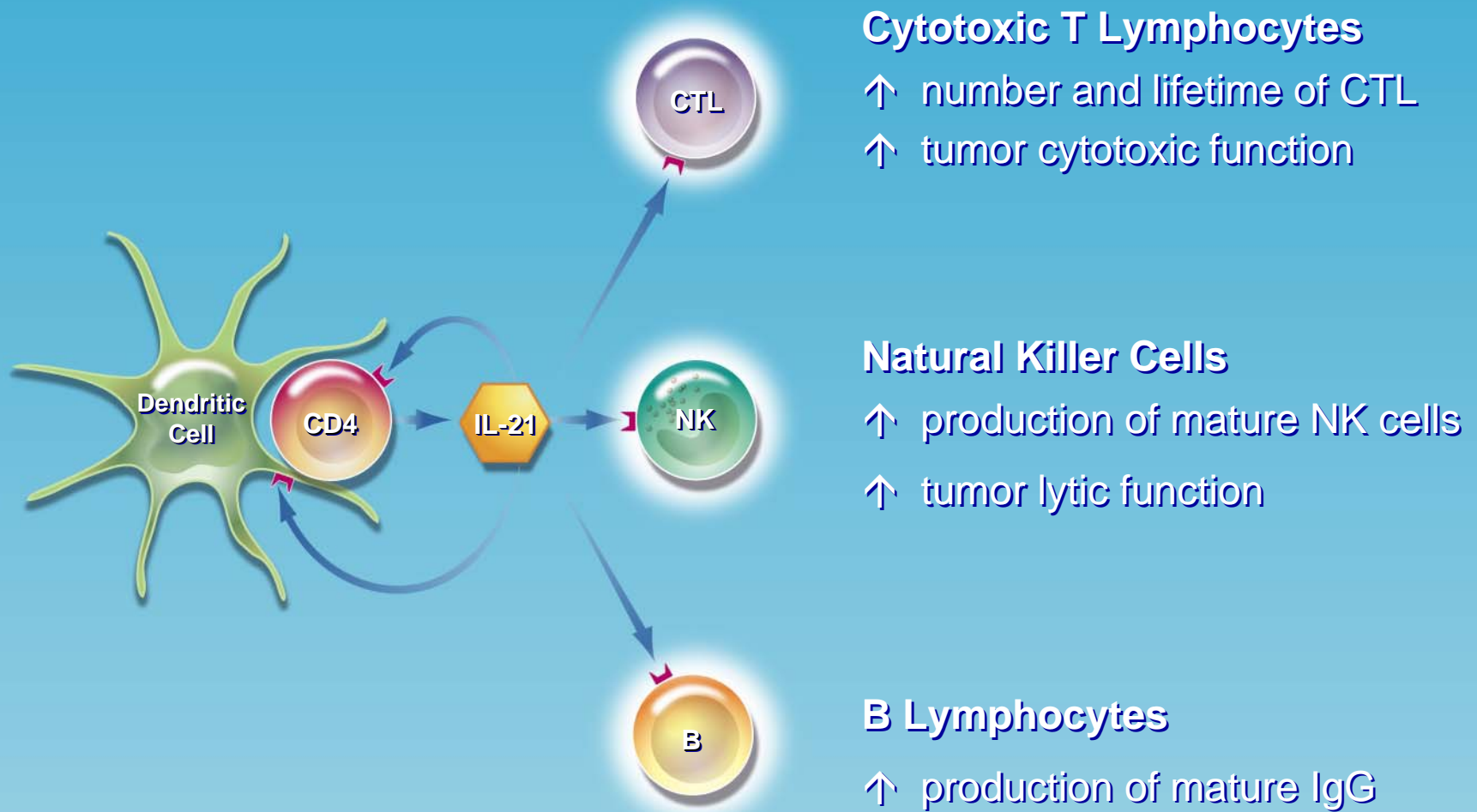
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Interleukin-21 (rIL-21)

- Recently discovered T-cell derived cytokine
- Belongs to family of T cell growth factors that include IL-2, IL-4, IL-7, IL-9 and IL-15
- Most similar to IL-2 and IL-15
 - No stimulatory effect on T regulatory cells, important difference compared to IL-2
- Made mainly by activated CD4+ T cells and NKT cells
- Anti-tumor activity shown to depend on NK cells or CD8+ T cells through induction of central and effector memory cells
- Can also enhance antibody response and ADCC
- Recombinant human IL-21 is produced in E. Coli by recombinant DNA methods

IL-21: Multiple Immunomodulatory Effects



rIL-21 Single Agent: Phase 1 Studies in Metastatic Melanoma

rIL-21 Single Agent: Phase 1 Studies

- 53 patients treated in two Phase 1 studies
- Dose escalation studies with dose 1 to 100 µg/kg with differing schedules
 - Most common AEs **mild to moderate** : mild constitutional symptoms
 - fatigue, pyrexia, headache, nausea, chills, rash
 - Toxicity profile clearly different than IL-2 - No vascular leak syndrome

Efficacy in Phase 1 Studies

- Thompson et al¹ (n=24) 1 patient with CR, 11 with SD
- Davis et al² (n=29) 1 patient with PR, 9 with SD

Phase II Study of rIL-21 in Metastatic Melanoma: IND 189

Study design:

- Multi-centre phase II open label single arm study with test of higher doses in initial cohorts
- Previously untreated patients with metastatic or recurrent melanoma
- Patients with bulky disease $\geq 5\text{cm}$ and those with brain metastases were excluded
- Schedule A:
 - Starting dose of 50ug/kg, IV push d 1-5 wks 1, 3, 5 q 8 wks.
If not tolerated, reduce to 30ug/kg
- Schedule B:
 - Starting dose of 50ug/kg, IV push d 1-5 wks 1, 3, q 6 wks.
If not tolerated, revert to Schedule A, 30ug/kg

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Primary Endpoints:

- Objective response and early progression

Secondary Endpoints:

- Response duration, toxicity, pharmacokinetics, immunogenicity, antigenic markers of archival tumour specimens related to outcome.

Multinomial Phase II Design :

- Response: H0 5%, Ha 20%
- Early progression H0 60%, Ha 40%
- In final sample of 30 pts, would declare agent interesting if ≥ 4 responses OR ≤ 13 early PD

Phase II Study of rIL-21 in Metastatic Melanoma: *IND 189 Study Progress*

Part A:

IL-21 days: 1-5
15-19
29-33

50 ug x 3: **3 subjects, 2 DLTS** 30 ug x 3: **16 subjects enrolled** 30 ug x 3: Expand to total of 30 subjects (21 to date)

Safety eval



Efficacy eval



Part B:

IL-21 days: 1-5
15-19

50 ug x 2:
7 subjects, 4 DLTs (rash and abnormal labs)
Part B terminated

Safety eval



Patient Characteristics

		# Patients
No. enrolled		31
No. with baseline data		28
No. evaluable for toxicity/response		24/23
Median age (range)		54 (35-80)
Gender	Female	11
	Male	17
ECOG PS	0	20
	1	8
Prior Therapy	Adj. Interferon	13
	Radiotherapy	7
No. disease sites	1	5
	2	11
	3	8
	4 or more	4
Sites of disease	Subcut/nodes	8/15
	Lung	20
	Liver	10
	Bone	2

Adverse Events (AEs)

Summary

- Most common AEs were fatigue, rash, diarrhea and myalgias – most grade 1 or 2
- Grade 3 rash occurred in 3/16 (30ug/kg), 1/3 and 3/5 for the 50ug/kg dose Part A and B respectively
- Severe AEs (grade 3/4) were reported in 2/3 patients at 50ug/kg Part A, 3/5 patients at 50ug/kg Part B and 6/16 at 30ug/kg dose

Treatment Related Adverse Events (> 3 patients)

CTC Grade	50ug/kg Part A N=3				30ug/kg Part A N=16				50ug/kg Part B N=5			
	1	2	3	4	1	2	3	4	1	2	3	4
Hypotension		1			1	1				1		
Fatigue	1		1	1	8	4				4		
Fever	3				6	1			2	1		
Rigors	1				4				2	1		
Rash/pruritis	1		1		3/2	4/1	3/2			1/2	3/0	
Diarrhea	1		1		4	1						
Musculoskeletal		2			1							
Neurological (Dizziness)		1			3							
Pain – joint/muscle	1/0	0/1			1/5	1/3	1/0		1/0	1/1		
Hematologic (Grans)				2	1	1	2			1		
Biochemical (ALT/AST)			1/1		6/9	2/1	1/0		3/1	1/1	1/0	0/1

Phase II Study of rIL-21 in Metastatic Melanoma *Objective Response*

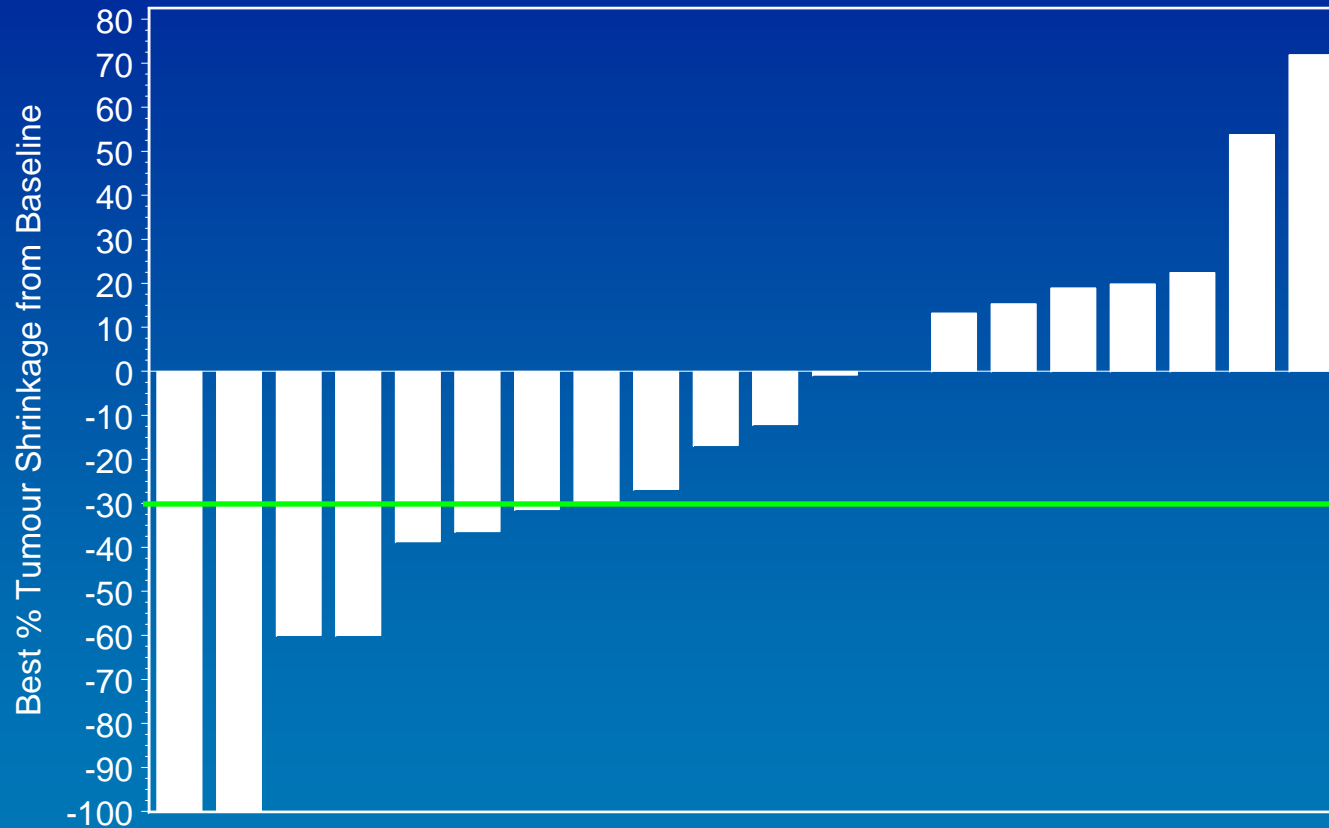
	Schedule A		Schedule B	TOTAL	%
Dose level	50 ug	30ug	50ug	31	
CR	0	0	0	0	
PR	1	4	2	7*	29%
SD	1	5	2	8	33%
PD	1	6	1	8	33%
Ineval	0	1	0	1	4%
Total	3	16	5	24	

* 2 responses are not yet confirmed by follow-up imaging

Objective Response

I189

(n = 20 evaluable patients)



Conclusions

- rIL-21 administered at 30ug/kg at 5 day cycles, weeks 1, 3 and 5 is well tolerated
- rIL-21 is biologically active with an overall RR of 29% in first line metastatic melanoma patients
 - With overall RR 25% at recommended dose/schedule
- rIL-21 warrants further exploration in a larger trial

Conclusions

- Correlative studies in progress
 - archival tissue blocks received from all patients
 - IL21 receptor expression using immunohistochemistry appears to be a promising approach