

# Interleukin-21 has Activity in Patients with Metastatic Melanoma

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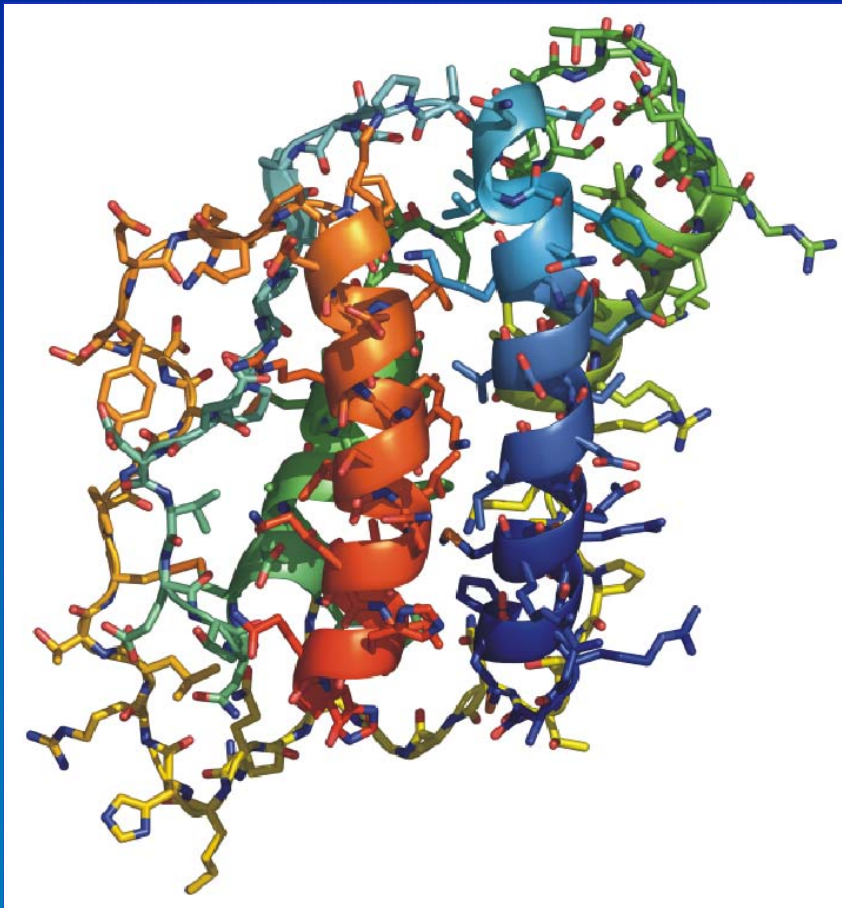


## Author Disclosures:

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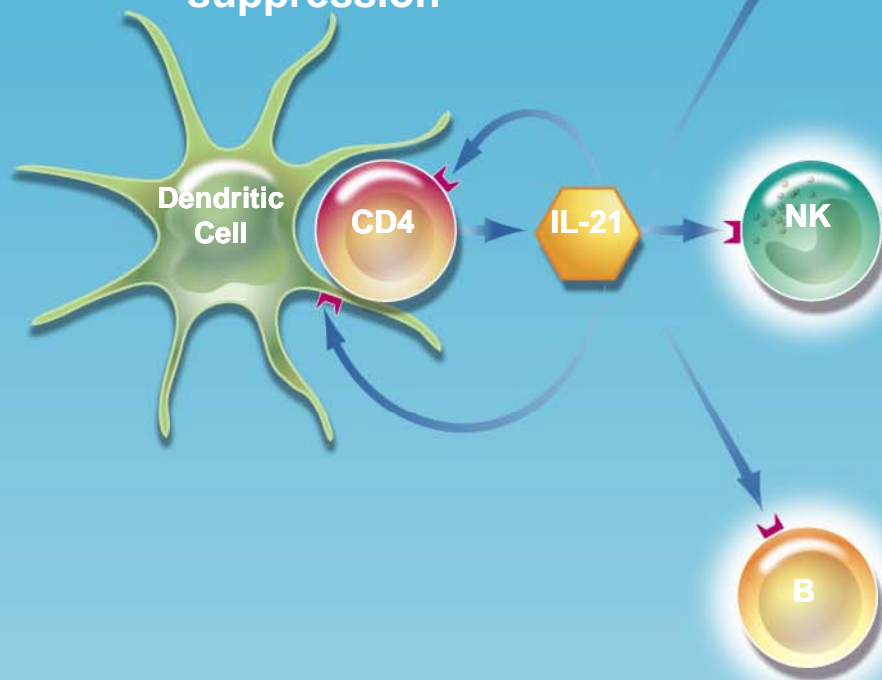
# IL-21 – basic biology and activity



- Discovered in 2000
- Member of four-helix bundle cytokine family
- Expressed by CD4<sup>+</sup> T cells (including Th17 cells) and NKT cells
- Signals through the unique IL-21 receptor along with the common gamma chain ( $\gamma_c$ )
- Receptor is normally expressed on B & T lymphocytes, NK cells, monocytes and dendritic cells

# IL-21: Multiple Immunomodulatory Effects

**CD4+ T Lymphocytes**  
↑ Proliferation  
↑ Increased T<sub>H</sub>17 differentiation  
↑ Increased resistance to T<sub>reg</sub> suppression



**CD8+ T Lymphocytes**  
↑ number and lifetime of high affinity antigen specific CTL  
↑ tumor cytotoxic function

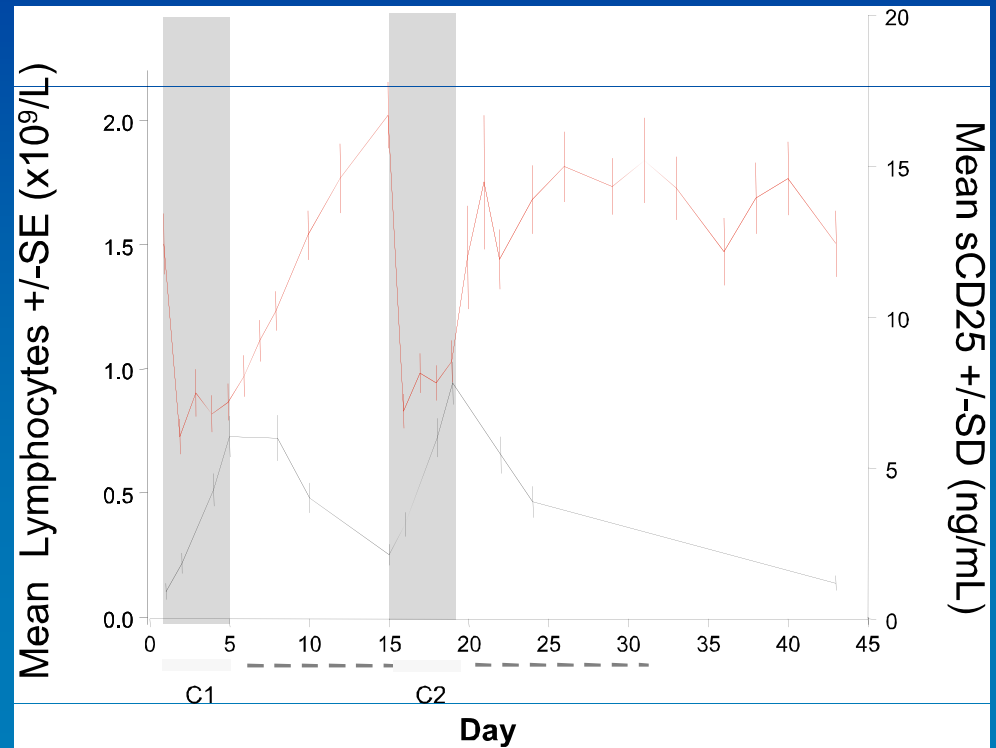
**Natural Killer Cells**  
↑ production of mature NK cells  
↑ tumor lytic function  
• Enhanced ADCC

**B Lymphocytes**  
↑ production of mature IgG  
• Co-stimulates proliferation, differentiation and Ig class switching

# Phase I Experience: IL-21

- 2 open-label dose escalation studies evaluated multiple schedules
- Similar toxicities: pyrexia, fatigue, chills, headache, nausea, pruritus or rash
- Evidence of tumor response in metastatic melanoma
- Immune activation: 50% ↓ in lymphocytes and 8-fold ↑ in soluble CD25

Thompson et al <sup>1</sup>	Davis et al <sup>2</sup>
N=24	N=29
3 to 100 µg/kg	1 to 100 µg/kg
day 1-5, 15-19	day 1-5, 15-19, 29-33, or 3x/week
1 CR 0 PR 11 SD	0 CR 1 PR 9 SD



**NCIC CTG Phase II Study of  
Interleukin-21 (IL-21) in Patients  
With Metastatic or Recurrent  
Melanoma:  
IND 189**

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# Phase II Study IL-21: IND 189

## Study Design:

- Multi-centre phase II open label single arm study with test of higher doses in initial cohorts

## Key Eligibility

- Previously untreated metastatic or recurrent melanoma
- Patients with bulky disease (individual lesion  $\geq$  5cm) and those with brain metastases were *excluded*
- Other standard eligibility criteria

## Primary Endpoints:

- Objective response and early progression

## Secondary Endpoints:

- Response duration, toxicity, pharmacokinetics, immunogenicity, correlative studies in serum/tumour

# IND 189 Study Design

## Part A:

IL-21 days: 1-5

15-19

29-33

50 ug x 3 weeks:  
3 subjects, 2 DLTS

Dose reduced

Safety eval ↑

30 ug x 3 wks:  
30 subjects enrolled

## Part B:

IL-21 days: 1-5

15-19

50 ug x 2 wks:  
7 subjects, 4 DLTS

Part B terminated

Safety eval ↑

# Patient Characteristics

		# Patients
No. enrolled		40
No. with baseline data		40
No. evaluable for toxicity/response		40/39
Median age (range)		56 (25-85)
Gender	Female	16
	Male	24
ECOG PS	0	31
	1	9
Prior Therapy	Adj. immunotherapy	17
	Radiotherapy	7
No. disease sites	1	6
	2	16
	3	9
	4 or more	9
Sites of disease	Subcut/nodes	9/25
	Lung	32
	Liver	14
	Bone	3

# Summary of Adverse Events (AEs)

- Most common AEs were fatigue, rash, fever, myalgia, anorexia, chills, and nausea
- *Grade 3 rash*
  - 3 of 30 (10%) at 30µg/kg
  - 4 of 10 (40%) at 50µg/kg
- *9 serious adverse events (SAEs) were reported:*
  - 4 were possibly, probably or definitely related
    - One Infection with grade 4 neutropenia (50 µg/kg dose)
    - Two with Grade 4 liver enzyme elevation (one at 30 µg/kg with progressive liver metastases, one at 50 µg/kg)
    - One second malignancy: AML (30 µg/kg - 11 mo after last dose)

# Results

## *Objective Response*

	Schedule A		Schedule B	TOTAL	%	Median mo. (range)
Dose level	50 ug	30ug	50ug			
CR	0	0	0	0	0	
<b>PR</b>	<b>1</b>	<b>6</b>	<b>2</b>	<b>9*</b>	<b>22.5%</b>	<b>5.0 (3.1 -16.8)</b>
SD	2	11	3	16	40%	5.3 (2.2 - 8.8)
PD	0	12	2	14	35%	
Ineval	0	1	0	1	2.5%	
Total	3	30	7	40		

\*For evaluable patients ORR 9/39 or 23.1%

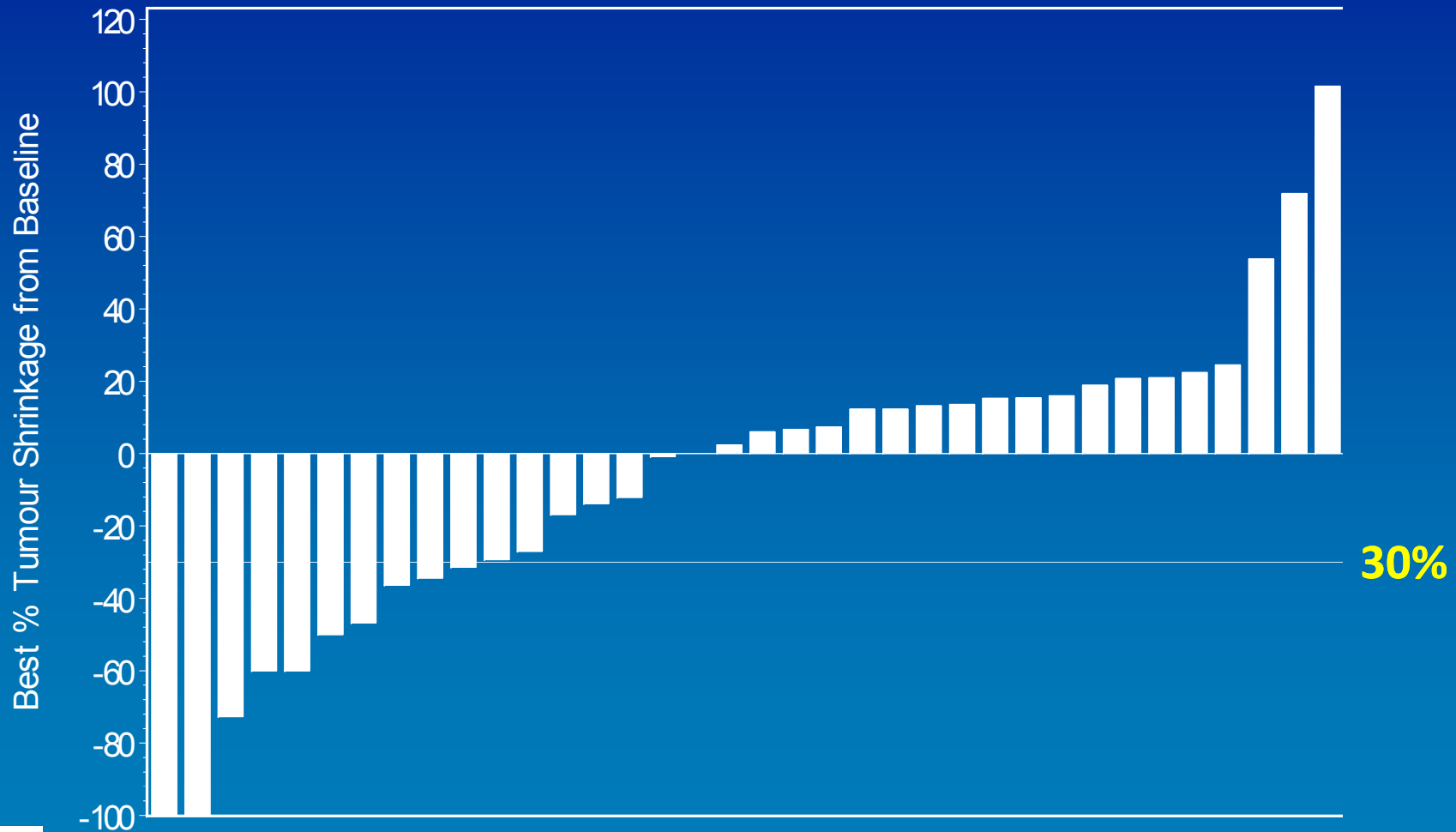
# II-21 Responders

## Sites of Response

- 9 patients with PRs:

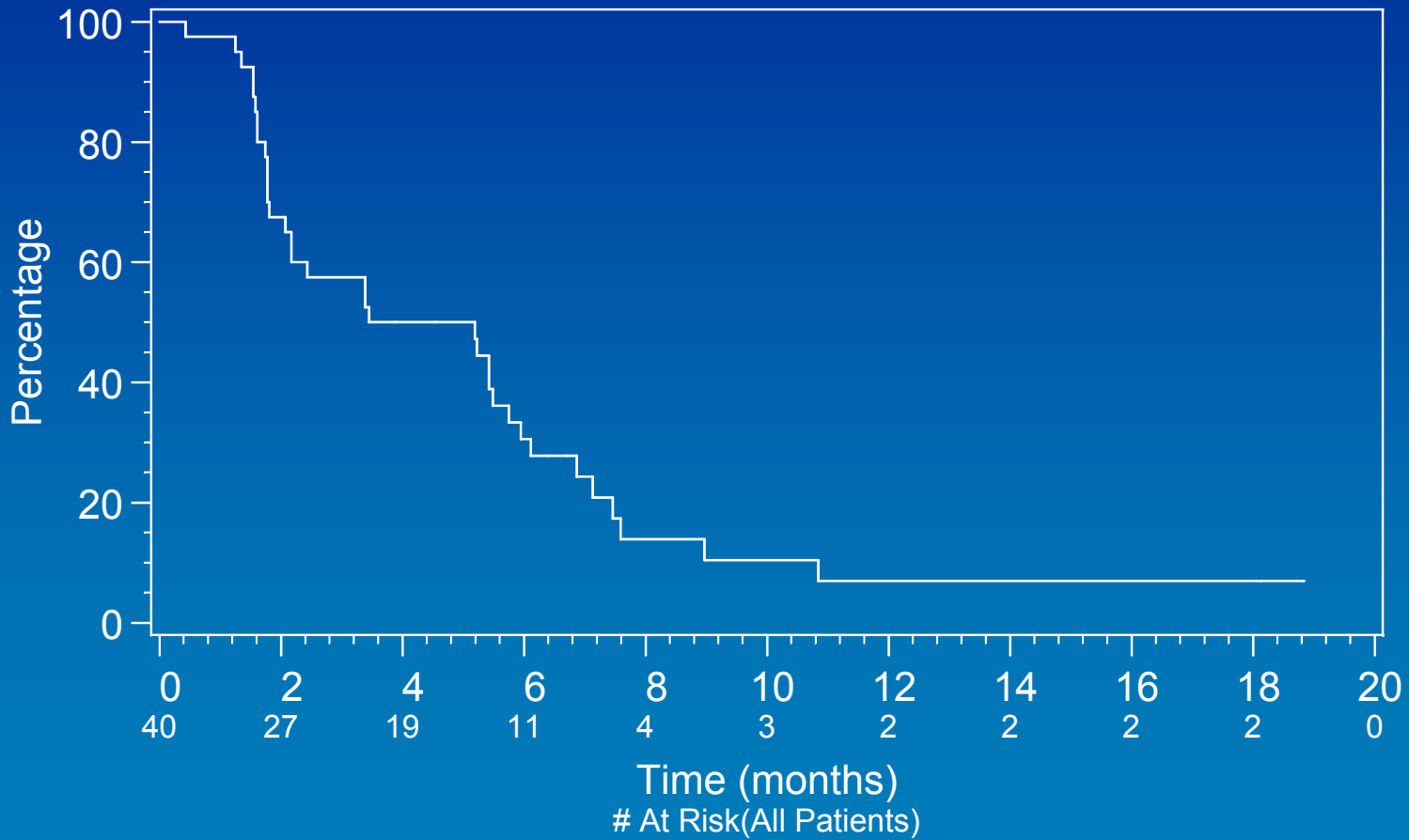
Sites of Disease	# of pts
Liver	4
lung	5
Nodes	4
Omentum	1
Pelvis	1
skin	1
spleen	1
Subcutaneous soft tissue	4

# Maximum Percent Tumor Shrinkage from Baseline



# Progression Free Survival

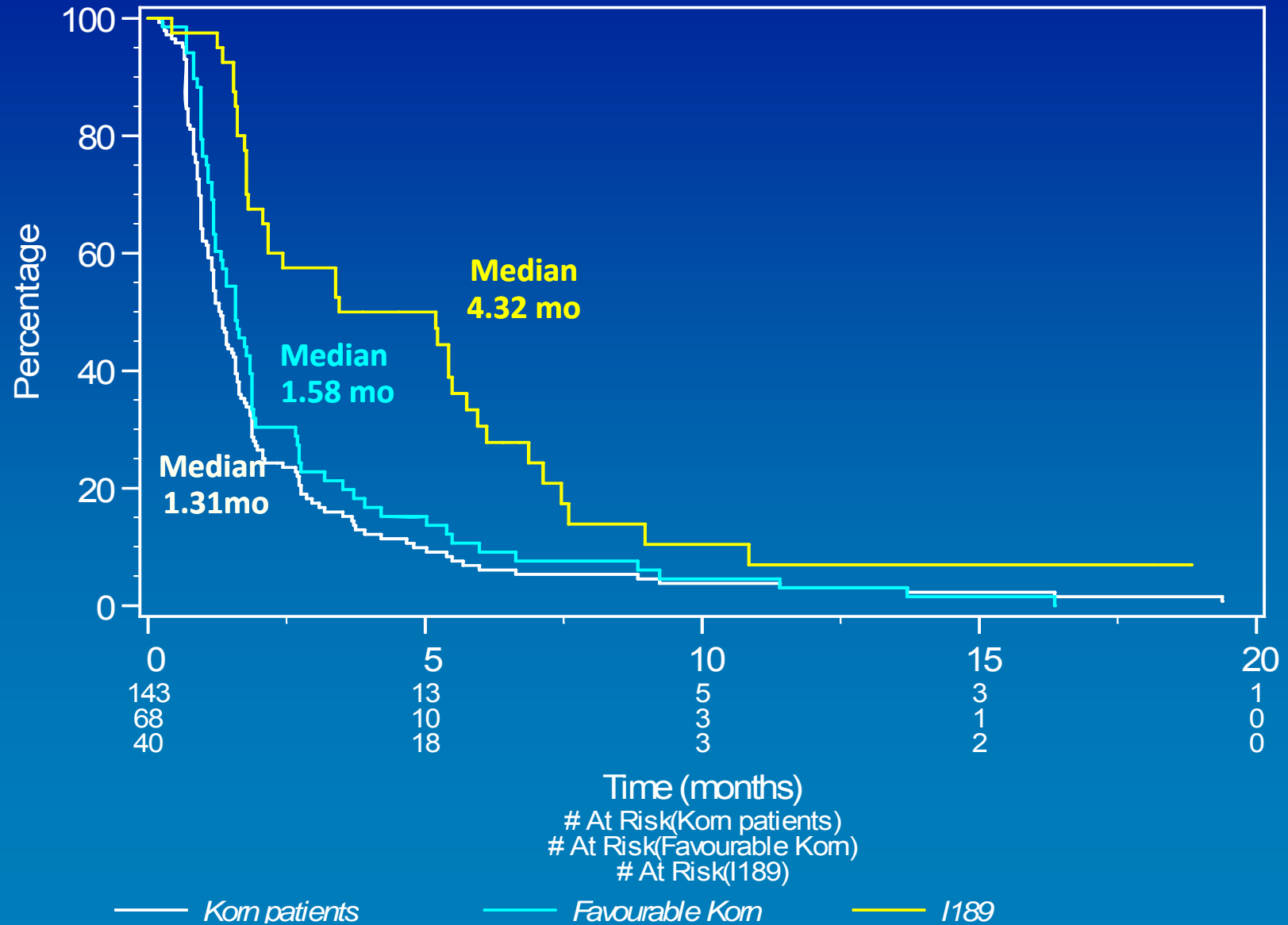
Median PFS: 4.32 mo (95% CI 2.17, 5.75)



# Benchmarking of PFS

- *Korn et al* (J Clin Oncol 2008 26(4): 527): Meta-analysis of cooperative group phase II melanoma trials to identify benchmarks for future phase II melanoma trials
- NCIC CTG contributed 143 patients from all historical phase II melanoma trials to Korn analysis, 68 of which matched IND.189 entry criteria
- IND.189 PFS benchmarked against PFS from historical data

# PFS of IND.189 and NCIC CTG Korn Data



# Progression Free at 6 months

Patient Group	Observed Progression Free at 6 months	Expected Progression Free at 6 months*
IND 189	27.8 %	16.7%
Korn (n=143)	6.1 %	14.5%
Korn Favourable (n=68)	9.1 %	14.9 %

- Observed PFS at 6 months was compared to expected PFS based on the benchmark equations provided by Korn et al.
- PFS for patients treated with IL-21 is higher than expected, even though the observed PFS for NCIC studies is slightly lower than expected
- The improved PFS for IND 189 cannot fully be explained by prognostic factors identified in the Korn analysis

(\*) the expected % of progression free at 6 months was calculated using:  
(% of patients with ECOG PS of 0 \* 18.0%) + (% of patients with ECOG PS of 1 \* 12.3%) + (% of patients with ECOG PS of 2 \* 7.4%) + (% of patients with missing ECOG PS \* 15.0%)  
Korn et al (J Clin Oncol 2008 26(4): 527)

## Multivariate Analysis of PFS

Variable	No of patients	Adjusted HR	P-value
<b>Trial</b>			<b>0.0206</b>
NCIC CTG Phase II	68	1.000	
IND 189	40	0.594	
<b>Age</b>	108	0.973	<b>0.0006</b>
<b>Sex</b>			NS
Female	42	1.000	
Male	66	0.863	
<b>Performance Status</b>			<b>0.0031</b>
0	64	1.000	
1	41	1.426	
2	3	8.017	
<b>Site of Disease</b>			NS
Liver= No	74	1.000	
Liver= Yes	34	0.759	
<b>Number of Sites</b>			NS
1	28	1.000	
2	36	0.726	
3	23	0.956	
4 or more	21	1.059	

- Multivariate analysis of PFS for IL-21 treated pts and historical group adjusted for prognostic factors

- Age, PS and IL-21 trial treatment were significant predictors of PFS

# Correlative and Biomarker Studies

- Archival melanoma tissue was evaluated for:
  - IL21 receptor expression (IHC)
  - Bcl2 expression (IHC)
  - BRAF (V600E) mutational analysis
  - Ulceration
- Serum was evaluated for:
  - VEGF baseline levels
  - Serum CD25
- None showed any relationship with Response, SD or PD

## e.g. BRAF Mutation by Best Response

Result	CR	PR	SD	PD	IN	Total
Mutation present	0	3	7	4	0	14
No mutation detected	0	5	7	9	1	22
Inconclusive	0	1	1	1	0	3

# Conclusions

- IL-21 administered at 30ug/kg daily x 5, wks 1, 3 and 5 q 8 wks is well tolerated
- IL-21 is biologically active with an overall RR of 22% in first line metastatic melanoma patients
  - Responses were seen in all sites of disease
- A median PFS of 4.3 months was observed
- Patients are being followed for survival
- A Phase II randomized controlled trial is planned to confirm results

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