A Phase I Clinical Trial of EMD 273063 (hu14.18-IL2) in the Treatment of Children with Refractory/Recurrent Neuroblastoma and Melanoma: A Study of the Children's Oncology Group

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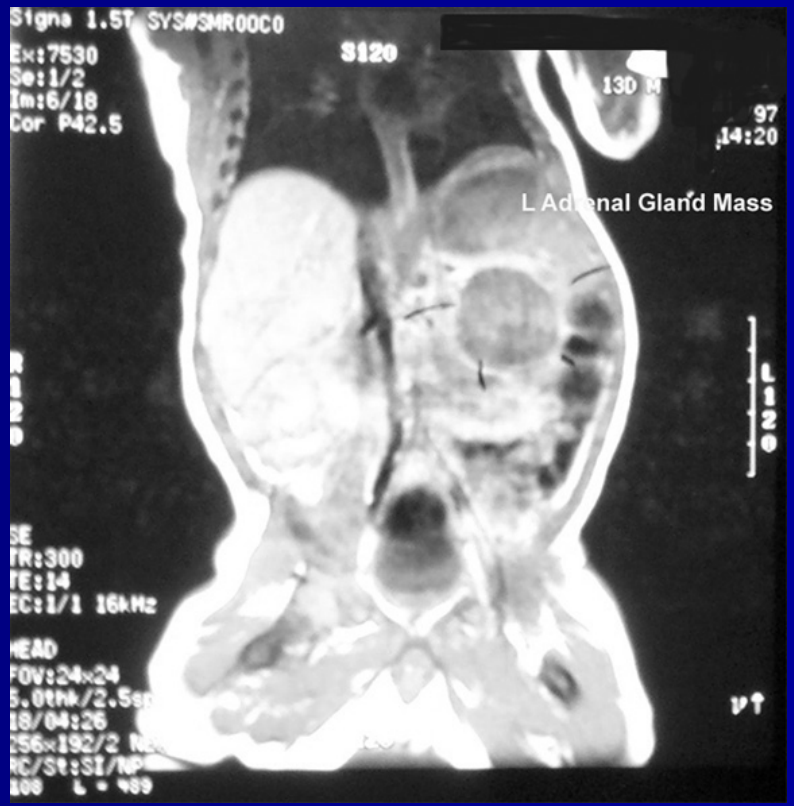
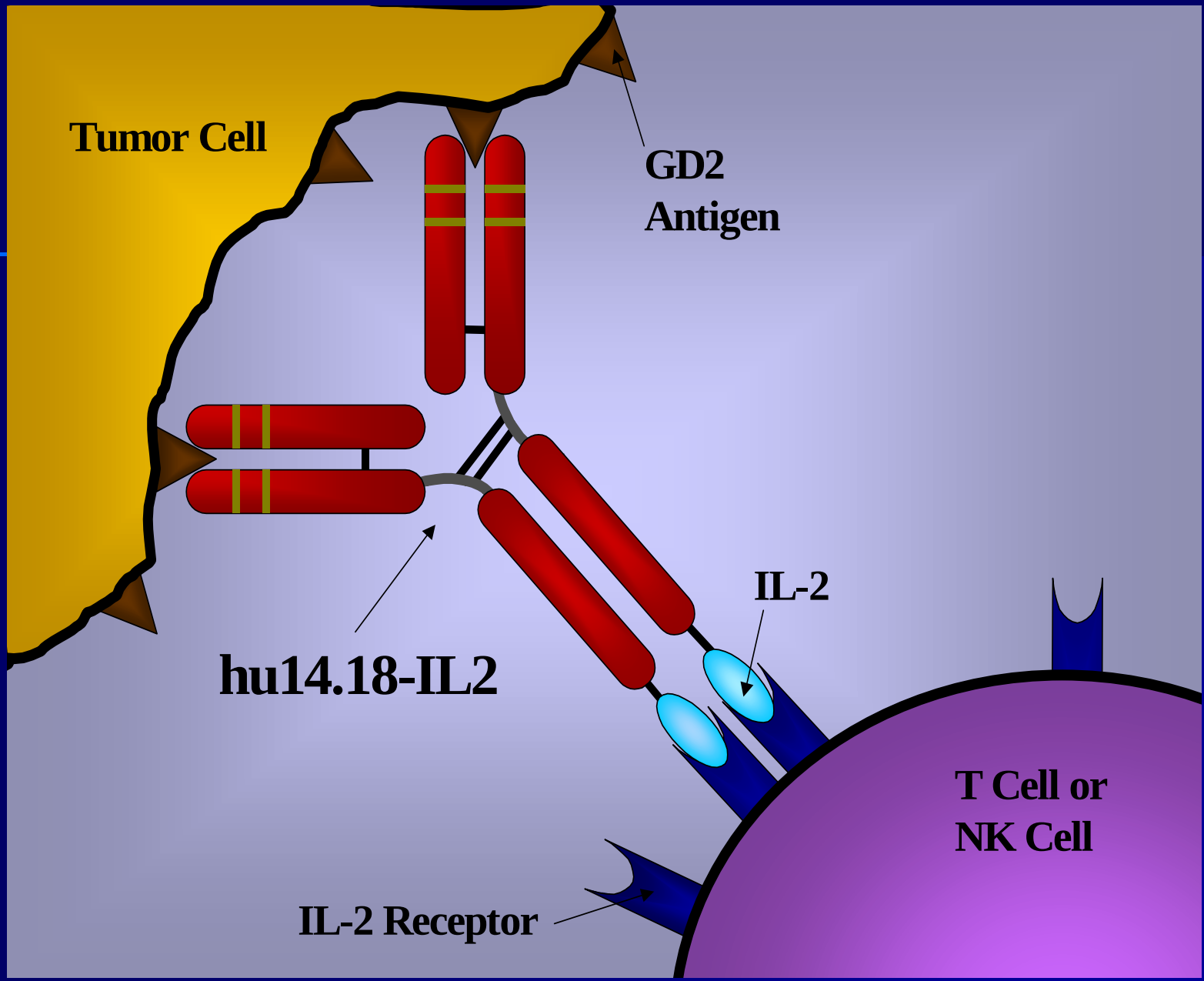
General Overview of Pediatric Neuroblastoma

- Second most common solid tumor in childhood
- Responsible for 15% of childhood deaths due to malignancy



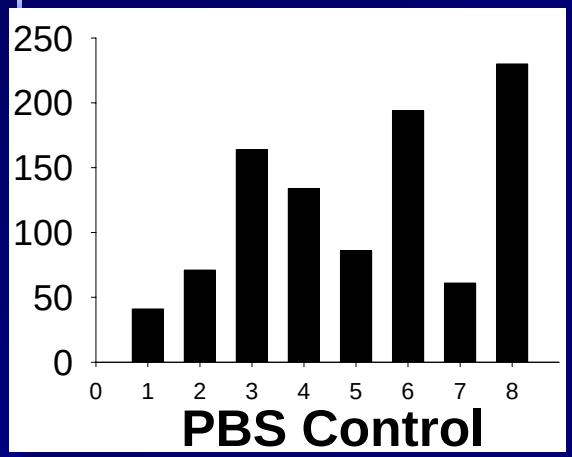

Tumor Cell
GD2
Antigen
hu14.18-IL2
IL-2
T Cell or
NK Cell
IL-2 Receptor

Efficacy of ch14.18-IL2 Immunocytokine against Murine Neuroblastoma Liver Metastases

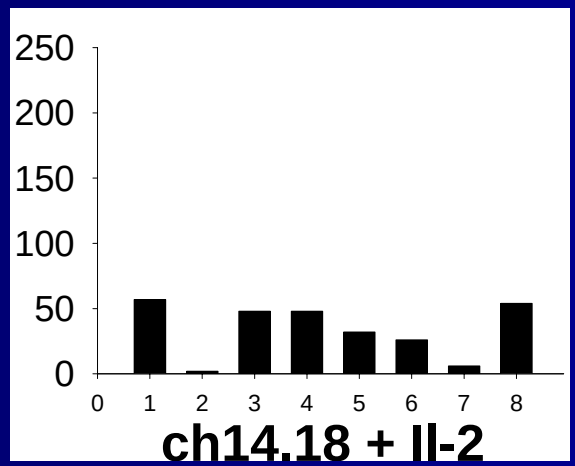
Lode et al: *J. Natl. Cancer Inst.* 89:1586, 1997

# of Liver Mets

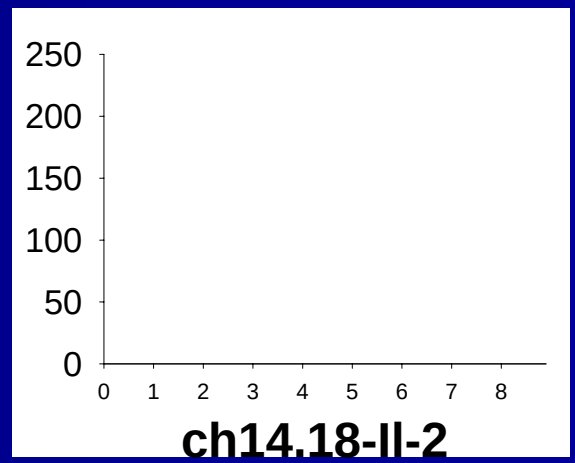
123 ± 69

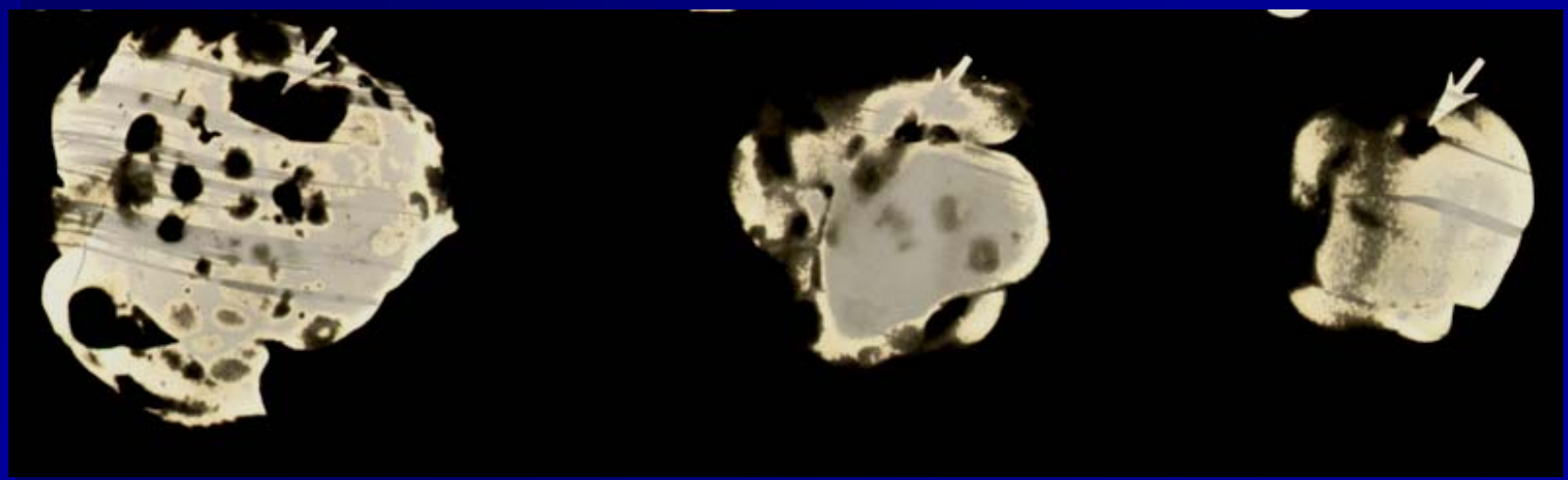


34 ± 21

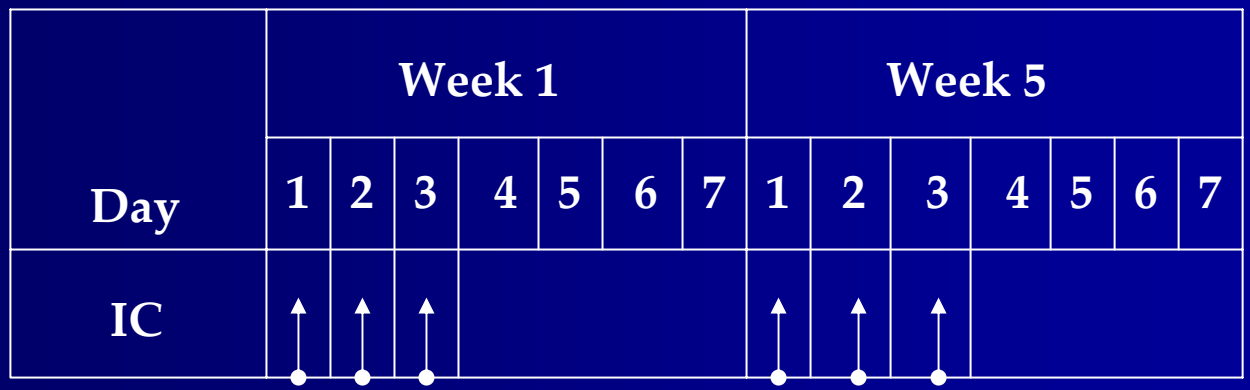


0 ± 0





Treatment Schema



IC= Immunocytokine (hu14.18-IL2) given as 4 hour infusion on 3 consecutive days

Each eligible patient had disease evaluation on day 1, week 5. If stable or responsive disease were eligible for further courses of therapy.

28 patients treated within the Children's Oncology Group

Dose-Limiting Toxicities

MTD = 12 mg/m²/day

Dose (mg/m²/day)	Total Patients	Dose Limiting Toxicity *Course 1* (number of patients)	Dose Limiting Toxicity *Courses 2-4* (number of patients)
2	6	Neutropenia (1)	Hematuria (1)
4	3	None	None
6	3	None	None
8	3	None	Hypotension (1)
10	3	None	None
12	6	Allergic Reaction (1)	Thrombocytopenia/Hypotension (1), Rash (1), Blurred vision (1)
14.4	3	Delayed Neutropenia and Leukopenia (1)	None

Grade 3 Clinical Toxicities observed in 76 total courses of therapy

Pain	19
Neuropathic	4
Abdominal	3
Muscular	5
Bone	2
Head	2
Other	3
Fever	12
Vascular Leak	4
Hypotension	4

Skin Reaction	2
Colitis	1
Nausea	1
Hypoxia	1
Blurred Vision	1
Hematuria	1

* Numbers represent number of courses out of 76

Grade 3 Laboratory Toxicities observed in 76 total courses of therapy

Hematologic

ANC	8*
Platelets	6**
Hemoglobin	6
Lymphocyte	5
WBC	5

Hepatic

AST	5
ALT	4
Bilirubin	1
GGT	1

Other

Albumin	2
Calcium	1
Phosphate	1

* Three grade 4 ANC included

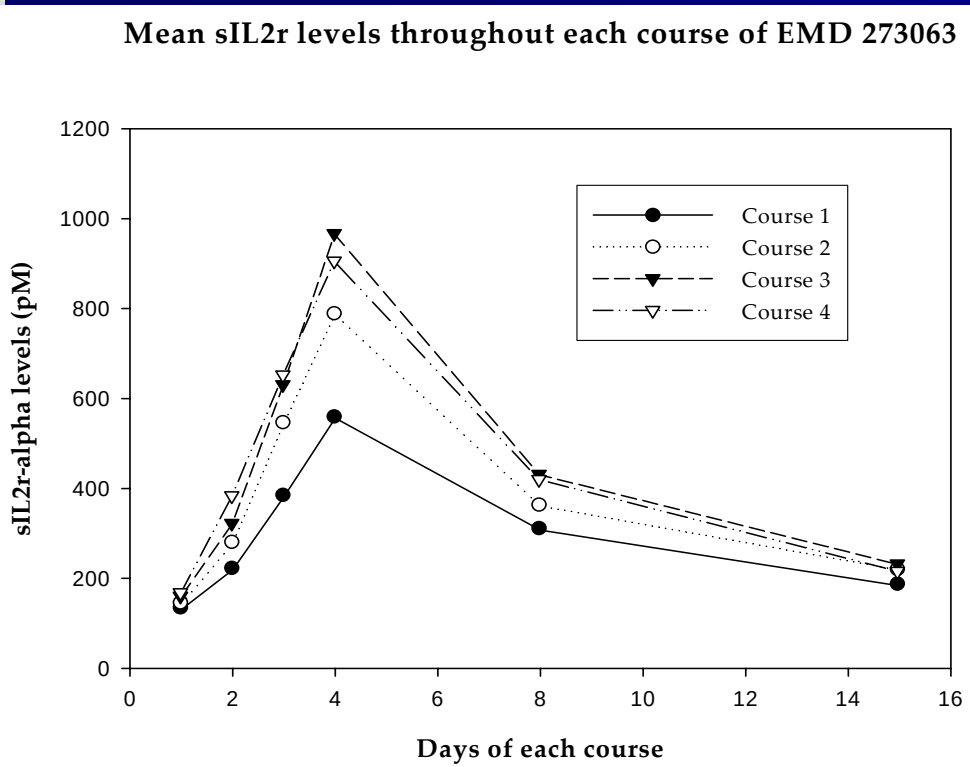
** One grade 4 platelets included

Pharmacokinetics (Cs 1, d1)

Half Life of hu14.18-IL2 is 3.15 hours

Dose $mg/m^2/day$	**Peak Conc** ng/mL	**AUC** ng/mL*h
2	840	5200
4	1800	11000
6	2100	13000
8	3300	22000
10	3200	21000
12	6400	36000
14.4	7300	45000
p- value	***0.0096***	***<0.001***

Immune Modulation



There is a significant dose, day and course effect each with a p-value of <0.001.

Anti-tumor Response

- 18 patients with progressive disease
- 10 patients with stable disease
- ***No true measurable responses***
- 3 patients show clinical suggestion of anti-tumor activity

Dose: 2 mg/m^2/day Best Response: Stable Disease Complete Remission after 4HPR 7 days (remains in CR~ 2 years later)
Dose: 2 mg/m^2/day Best Response: Prog disease Decrease in ICC (24516 OS to 144 after course 1)
Dose: 14.4 mg/m^2/day Best Response: Prog disease Improving histology despite progressing bulky disease

Conclusions

- For pediatric patients with refractory/recurrent neuroblastoma, a dose, schedule and MTD (with acceptable toxicity) have been determined
- Hu 14.18-IL2 induces immune activation in vivo
- Possible evidence of anti-tumor activity

Future Directions

- ANBL0322: Phase II COG Trial in Pediatric patients with Neuroblastoma
- Phase II Trial of Hu14.18-IL2 (EMD 273063) in Adults with Advanced Melanoma
- Combining IC with conventional modalities

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