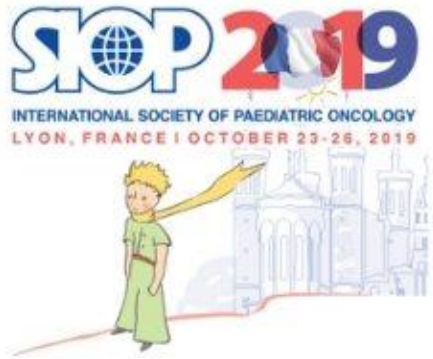
NAXITAMAB-BASED CHEMOIMMUNOTHERAPY FOR RESISTANT HIGH-RISK NEUROBLASTOMA: INTERIM RESULTS OF HITS (Humanized 3F8, Irinotecan, Temozolomide and Sargramostim) STUDY (Clinicaltrials.gov NCT03189706)

Shakeel Modak[1], B. Kushner[1], M. Flores[2], V. Santa-Maria[2], M. Garraus[2], E. Basu[1], S. Roberts[1], A. Castaneda[2], M. Gorostegui[2], N.K. Cheung[1], Jaume Mora[2]

Department of Pediatrics[1] Memorial Sloan Kettering Cancer Center, New York, USA
Department of Oncology, Hospital Sant Joan de Deu, Barcelona, Spain



modaks@mskcc.org

Relevant Disclosures

- MSK has institutional financial interests related to this research in the form of intellectual property rights and equity interests in Y-mAbs Therapeutics, the company licensing the intellectual property from MSK.

- Nai-Kong. Cheung reports receiving commercial research grants from Y-mAbs Therapeutics, Inc. holding ownership interest/equity in Y-mAbs Therapeutics. Nai-Kong Cheung is the inventor of issued patents licensed by MSK to Y-mAbs Therapeutics.

- Shakeel Modak reports consulting for YmAbs Therapeutics.

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Background

- Immunotherapy with anti-GD2 MoAbs has improved outcomes in patients with high-risk NB
- Immunotherapy alone is relatively ineffective in patients with chemoresistant soft tissue and high-burden NB
- Chemoimmunotherapy with dinutuximab/irinotecan/temozolomide/GMCSF yields responses in ~50% of chemoresistant NB*
- Anti-GD2 antibodies differ in their in vitro and in vivo properties

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**Mody etal Lancet Oncology 2017*

Comparison of anti-GD2 antibodies in clinical use

	Killing Mechanism					Affinity	Pharmacokinetics	
	NK-ADCC	PMN-ADCC	ADCP	CMC	CDCC	Fold	Cmax	Half-life
mouse 3F8	+	+	+	+++	+++	10x	high	short
hu3F8 (naxitamab)	++	++	++	++	++	10x	high	intermed
ch14.18 (dinutuximab)	++	++	++	+	+	1x	low	long
hu14.18-K322A	+++	+++	++	-	-	1x	low	long

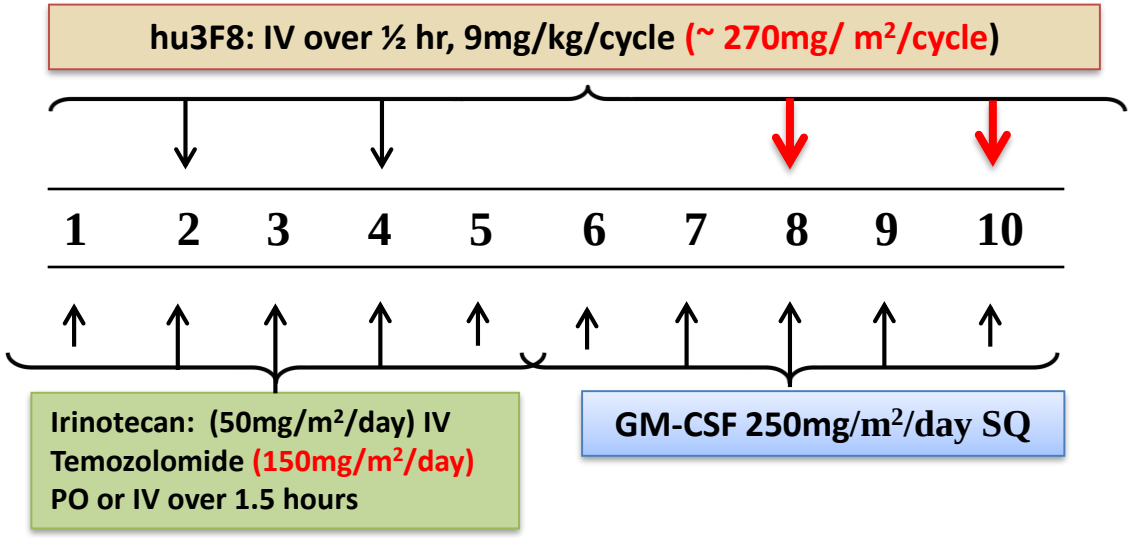
ADCC: Antibody dependent cell mediated cytotoxicity
CMC: Complement mediated cytotoxicity

ADCP: Antibody dependent cell mediated phagocytosis
CDCC: Complement dependent cell mediated cytotoxicity

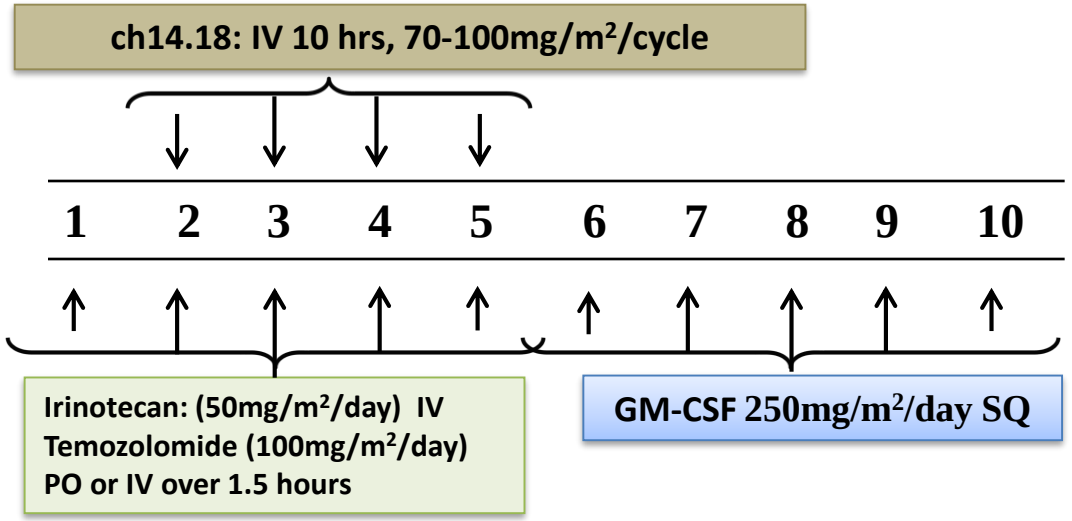
Data provided by Dr Nai-Kong V. Cheung

Chemoimmunotherapy: Differences between COG ANBL1221 and HITS

- Higher dose of temozolomide
- Higher dose of MoAb
- Hu3F8 given during and after chemotherapy
- 30-60 minute infusion of hu3F8
- Out-patient treatment



HITS



ANBL1221

Lancet Oncol 2017; 18:845 (commentary)

Salient Eligibility Criteria

- Measurable or evaluable disease

- Chemoresistant neuroblastoma
  - ***Primary refractory***: no remission after induction chemotherapy
  - ***Relapse/progressive disease***: relapse after achieving CR or progression after never achieving remission

- Prior anti-GD2 MoAb and/or irinotecan permitted

- Platelet count >30,000

- HAHA negative if previous MoAb exposure

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Protocol Design

- Initial pilot study at MSKCC converted to phase II after 7 patients enrolled (will be included in analysis); Favorable response rate of 35% after 4 cycles
- Primary endpoint: Response rate (CR+PR) assessed by INRC
- Patients treated at Hospital Sant Joan de Deu on compassionate basis following all protocol requirements except for research studies
- Response after 2 cycles and after 4 cycles reported in this ***interim*** report (Aug 2019)

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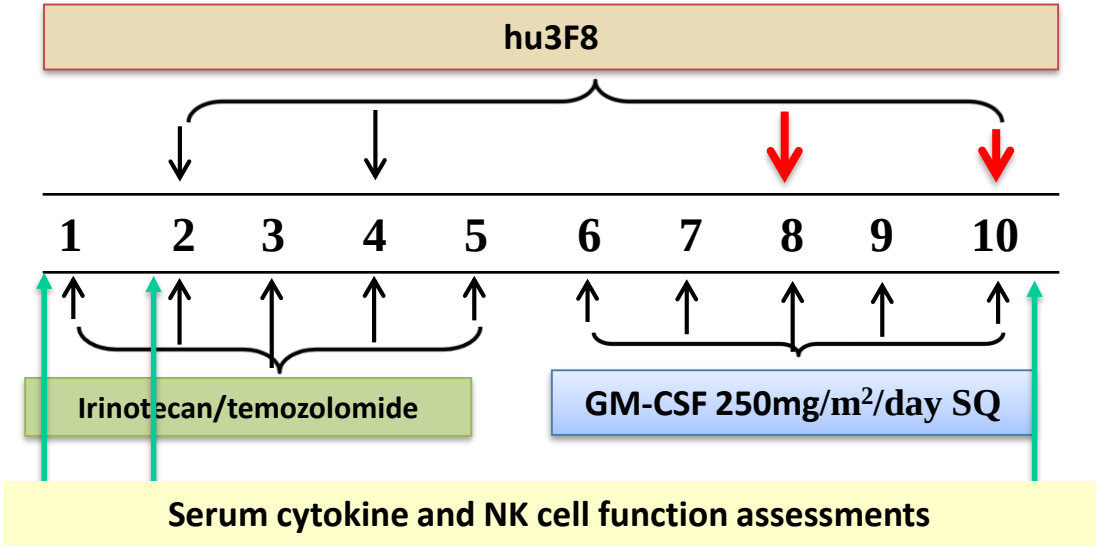
Mechanistic Hypothesis

- Enhancement of MoAb-based immunotherapy by chemotherapy ***counterintuitive***: chemotherapy could impair functioning of immune effector cells
- Chemotherapy could lead to “inflammatory state” leading to enhanced effector function
- Chemotherapy leads to release of cytokines and enhanced NK, neutrophil and macrophage function



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Preliminary report: Patient Characteristics

	MSK	SJD	Total
Total treated	33	32	**65**
Total cycles given	98	159	**257**
MYCN amplification	2	3	5 (7%)
Median number of prior relapses/PD	2 (0-8)	1 (0-4)	**2 (0-8)**
Prior status: Primary refractory Relapse	2 31	6 26	8 (12%) 57 (88%)
Stage at diagnosis: M <M	2 31	1 31	3 62
Stage at chemoimmunotherapy: M	33	32	65
Prior irinotecan/temozolomide	23	17	**40 (65%)**
Prior anti-GD2 MoAb: naxitamab dinutuximab	15 10	11 11	**26 (40%)** **21 (32%)**

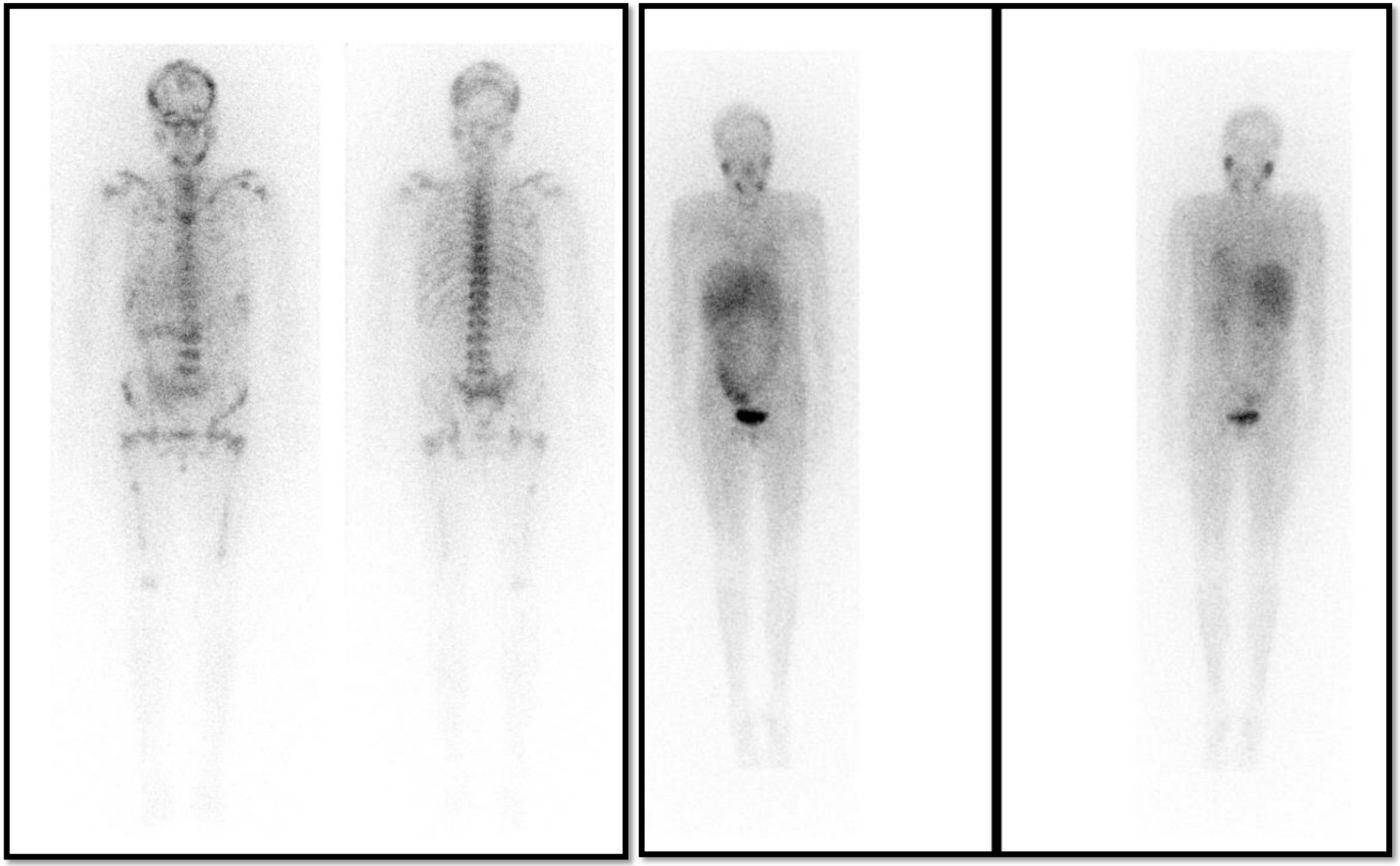
> Grade 2 Related Toxicities (MSK)

	Grade 3	Grade 4
Clinical Toxicities (n=24 evaluable)		
Urticaria	2 (9%)	0
Febrile neutropenia	3 (13%)	0
Hypotension	2 (9%)	0
Stridor	2 (9%)	0
Laboratory Toxicities (n=32 evaluable)		
ALT	4 (12%)	0
AST	2 (6%)	0
Anemia	20 (63%)	0
Lymphopenia	9 (28%)	19 (59%)
Neutropenia	9 (28%)	11 (34%)
Thrombocytopenia	8 (25%)	11 (34%)
Hypokalemia (diarrhea-related)	3 (9%)	7 (22%)

Preliminary report: INRC responses after 2 cycles

	MSK	SJD	Total
Total evaluable	24	32	56
Overall			**34%**
CR	4	7	11
PR	2	6	8
MR	1	0	1
SD	6	12	18
PD	11	7	18
Compartment-specific			
Soft tissue	2/14	6/16	**8/30 (27%)**
MIBG osteomedullary	5/23	17/28	**22/51 (43%)**
BM histology	13/17	1/3	**14/20 (70%)**

MIBG: Complete remission after two cycles



3/2018

5/2018

Sub-group response after 2 cycles

	MSK	SJD	Total
Total evaluable	24	32	56
MYCN amp	0/2	1/3	1/5
Primary refractory	0/2	2/6	2/8
Relapse/PD	6/22	5/26	11/48
Prior hu3F8	4/15	7/11	**11/26 (42%)**
Prior dinutuximab	2/10	5/11	**7/21 (33%)**
Prior I/T	4/23	7/17	**11/40 (27%)**

Preliminary report: Best Response after 4 cycles

	MSK	SJD	Total
Total evaluable	24	32	56
Overall			**39%**
CR	5	8	13
PR	2	7	9
MR	1	0	1
SD	5	10	15
PD	11	7	18

Durability/improvement of response: Response after 4 cycles

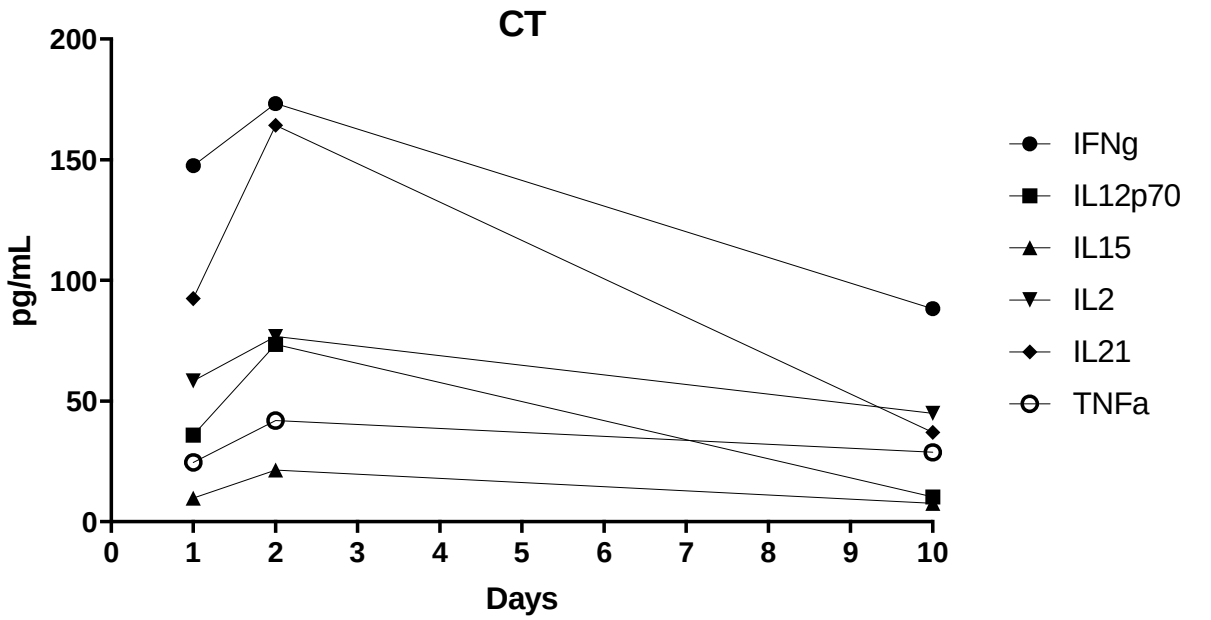
	MSK	SJD	Total
No. of pts receiving ≥4 cycles	10	21	31
Continued CR	3/3	7/7	10/10
Continued PR	1/1	5/5	6/6
Improved responses after 4 cycles compared to 2	2/7	2/9	**4/16 (25%)**

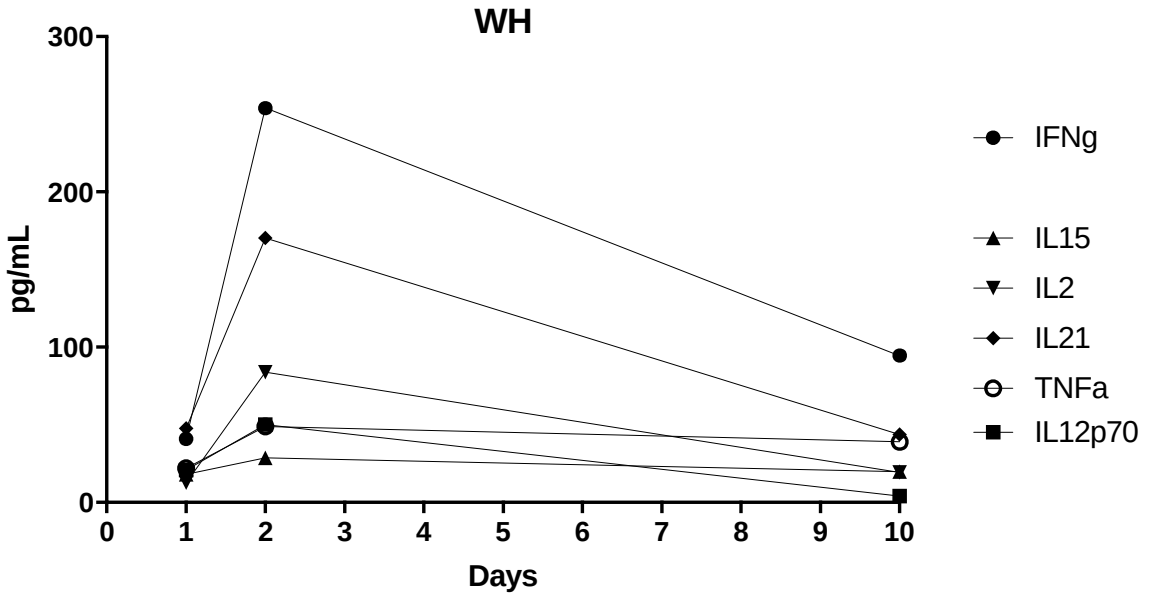
HITS vs ANBL 1221 B

	HITS (interim)	ANBL1221 B
Total reported	56	17
Primary refractory	**8 (14%)**	**8 (47%)**
Relapse/PD	**48 (86%)**	**9 (53%)**
Pts with >1 relapse	**22 (39%)**	**0**
Prior I/T	**40 (71%)**	**0**
CR+PR	22 (39%)	9 (53%)
Responses in soft tissue (measurable disease)	8/30 (27%)	3/10 (30%)

Similar response rates; more resistant disease in HITS cohort

Mechanistic Hypothesis: very preliminary data





JB le Luduec, Soo Park, Kathy Hsu *October 2019*

Conclusions and Future Directions

- Chemoimmunotherapy on the HITS protocol is associated with major responses in soft tissue and osteomedullary disease
- Responses were observed in patients who had previously received individual components of HITS chemoimmunotherapy
- Treatment was administered out-patient and was well tolerated with a low incidence of febrile neutropenia
- Most patients who had ongoing/durable responses had objective evidence of disease response after two cycles

- *Complete phase II*
- *Combinations with other chemotherapy regimens could be considered*
- *Incorporation into upfront therapy (Furman etal CCR 2019)*

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