Sequential Therapy with Brentuximab Vedotin in Newly Diagnosed Patients with Systemic Anaplastic Large Cell Lymphoma

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The European Society for Medical Oncology Congress
28 September–2 October 2012
Vienna, Austria

Disclosures for Michelle Fanale, MD

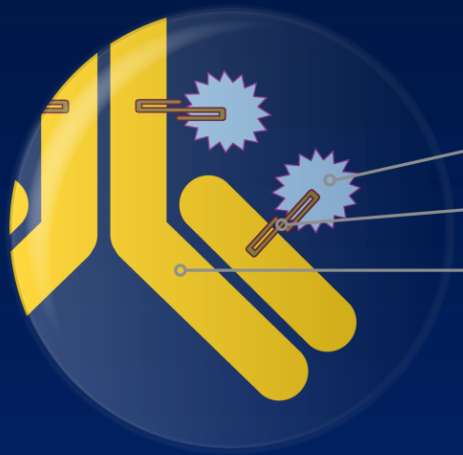
Research Support, P.I.	Seattle Genetics, Inc.
Employee	None
Consultant	Seattle Genetics, Inc.
Stockholder	None
Speakers Bureau	None
Advisory Board	Seattle Genetics, Inc.
Other	None

Background

- Systemic anaplastic large cell lymphoma (sALCL) is an aggressive subtype of mature T- and NK-cell lymphoma characterized by high-level expression of CD30[a]
- Most sALCL patients achieve remission with multi-agent frontline treatment (ORR 76–88%); however approximately half will relapse (5-year FFS 36–60%)[b]
- In a pivotal phase 2 study in relapsed or refractory sALCL patients, brentuximab vedotin (ADCETRIS®) induced durable remissions in 86% of patients (CR, 57%)[c]

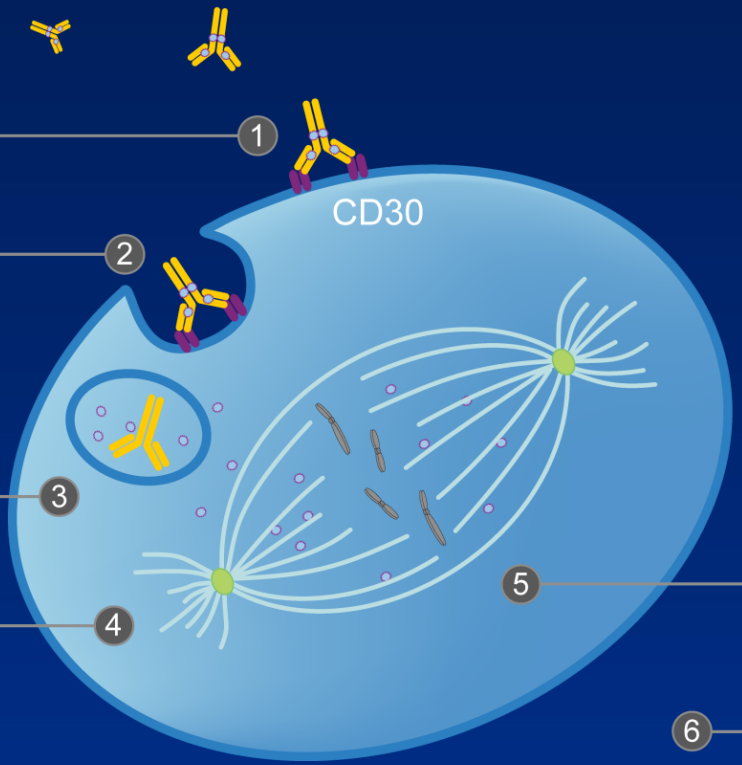
a Vose et al, 2008
b Savage et al, 2008
c Pro et al, 2012

Brentuximab Vedotin Mechanism of Action



Brentuximab vedotin antibody-drug conjugate (ADC)

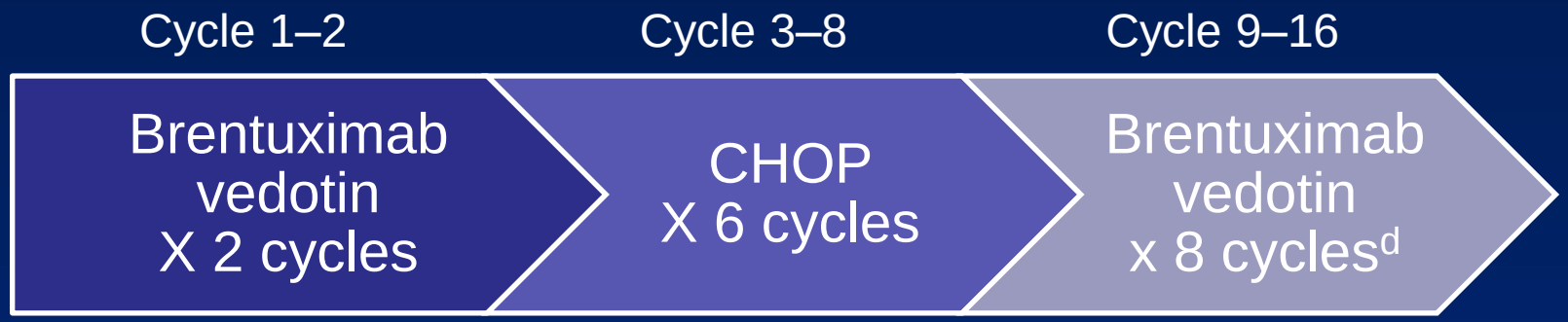
- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody



1. Brentuximab vedotin binds to CD30
2. Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

Phase 1, Multicenter, Open-Label Study of Brentuximab Vedotin as Frontline Treatment[a]

- Arm 1 of a 3-arm study[b]
  - Brentuximab vedotin (1.8 mg/kg) in sequence with CHOP[c]



- Arm 1 objectives
  - Primary: Safety and tolerability
  - Secondary: Investigator assessment of response (per Cheson 2007)

a Data are preliminary
b Arms 2 and 3 investigated combination therapy with brentuximab vedotin and CHP (CHOP without vincristine)
c Each treatment cycle = 3 weeks
d Patients who achieve a PR or CR after completion of induction therapy (end of Cycle 8) are eligible to continue brentuximab vedotin

Demographics and Baseline Characteristics

	N=13
Age[a]	62 (23–81)
Gender	9 M / 4 F
ECOG status, n	
0–1	11
2	2
ALK status[b], n	3 positive/10 negative
Disease stage[c], n	
I/II	5
III/IV	7
IPI score, n	
0–1	5
2–3	5
4–5	3

a Median (range)
b ALK-positive patients must have IPI score ≥2
c Disease stage for 1 patient is missing

Adverse Events

Preferred Term*	Total N=13 n (%)
Nausea	10 (77)
Peripheral sensory neuropathy	10 (77)
Vomiting	7 (54)
Constipation	6 (46)
Fatigue	6 (46)
Alopecia	5 (38)
Dyspnea	5 (38)
Myalgia	5 (38)
Peripheral edema	5 (38)
Oral pain	4 (31)
Pyrexia	4 (31)

* Occurring in ≥30% of total patients, regardless of severity or relationship to therapy

Adverse Events ≥ Grade 3

	Cycle of first onset			
	Brentuximab vedotin	CHOP	Brentuximab vedotin	
	Cycle 1–2	Cycle 3–8	Cycle 9–16	Total N=13
Preferred term[a]	N=13	N=13	N=11	n (%)
Any event[b], n	4	2	1	7 (54)
Anemia	1	1	--	2 (15)
Constipation	1	1	--	2 (15)
Fatigue	1	--	1	2 (15)
Febrile neutropenia	--	2	--	2 (15)
Peripheral Sensory Neuropathy	--	2	--	2 (15)

a Occurring in ≥10% of total patients, regardless of relationship to therapy
b Not subject to ≥10% incidence cutoff

Peripheral Neuropathy (PN) Events[a]

	Cycle of first onset			
	Brentuximab vedotin	CHOP	Brentuximab vedotin	
	Cycle 1–2	Cycle 3–8	Cycle 9–16	Total N=13
	N=13	N=13	N=11	n (%)
Treatment-emergent PN any event, n	5	5	1	11 (85)[b]
Peripheral sensory neuropathy	5	5	--	10 (77)
Muscular weakness	--	--	2	2 (15)
Peripheral motor neuropathy	--	1	--	1 (8)

a Events analyzed using Standardized MedDRA Queries (SMQs)
b 10 of 11 patients with any treatment-emergent PN (SMQ analysis) experienced resolution or some improvement in symptoms

Dose Modifications and Discontinuations Brentuximab Vedotin and Vincristine

	Brentuximab vedotin			Vincristine
Dose modification or discontinuation due to AE	Cycles 1–2 N=13	Cycles 9–16 N=11	Total N=13 n (%)	Cycles 3–8 N=13 n (%)
Dose reductions, n	--	4	4 (31%)[a]	7 (54%)
Dose delays, n	1	4	4 (31%)[b]	3 (23%)
Discontinuations, n	--	1	1 (8%)	--

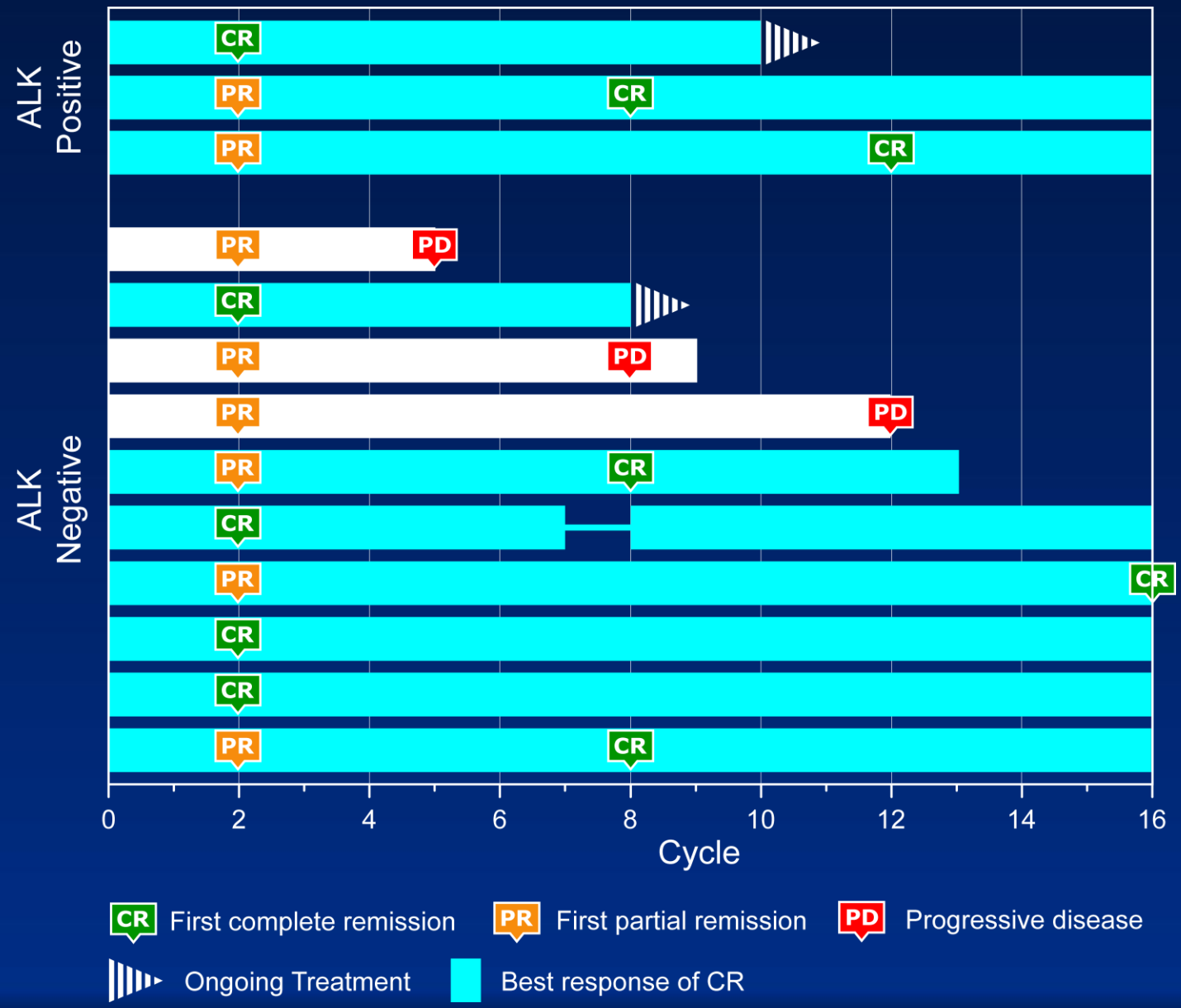
a 18 of 94 doses (19%) reduced in 4 patients
b One patient experienced a dose delay during both dosing periods

Preliminary Response Results

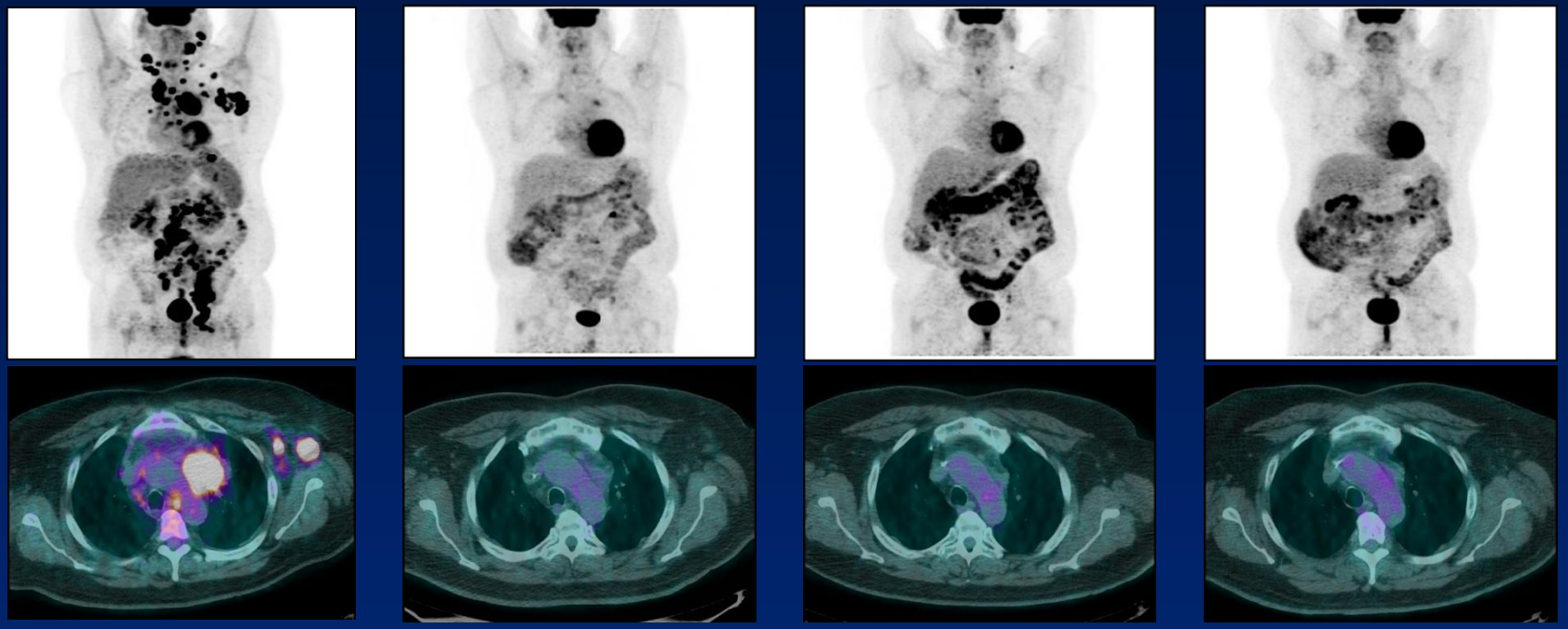
	End-Cycle Assessment			
	Brentuximab vedotin	CHOP	Brentuximab vedotin	
	Cycle 2	Cycle 8	Cycle 12	Cycle 16
Response	N=13	N=12	N=9	N=5
ORR, n (%)	13 (100)	11 (92)	8 (89)	5 (100)
CR	5 (38)	8 (67)	7 (78)	5 (100)
PR	8 (62)	3 (25)	1 (11)	--
PD, n (%)	--	1 (8)*	1 (11)	--

* One additional patient had progressive disease after 6 cycles of CHOP; this was captured as an end of treatment assessment and is not reflected in this summary

Initial Responses by Cycle



Case study: 60 YO Male, ALK+ sALCL, Conversion to CR with Continued Single-Agent Brentuximab Vedotin Therapy



Baseline | Cycle 2 - PR | Cycle 8 - PR | Cycle 12 – CR*

- Stage IV at diagnosis, IPI score 3
- B symptoms resolved after first brentuximab vedotin dose
- Vincristine dose reduced by 50% at Cycle 5 due to peripheral sensory neuropathy
- PET negative at end of Cycle 12 scan

* Patient continued single-agent brentuximab vedotin treatment and CR maintained at end of Cycle 16

Preliminary Conclusions

- Adverse events associated with sequential brentuximab vedotin and CHOP treatment were manageable
  - Adverse events with an incidence ≥40% included nausea, peripheral sensory neuropathy, vomiting, constipation, and fatigue
- Sequential brentuximab vedotin showed efficacy in the frontline treatment of sALCL
  - ORR = 100% (38%, CR) after 2 cycles of brentuximab vedotin monotherapy
  - ORR = 92% (67%, CR) after 8 cycles of sequential brentuximab vedotin and CHOP therapy
  - Responses were generally maintained in patients treated with single-agent brentuximab vedotin following CHOP (7/9 CR at Cycle 12; 5/5 CR at Cycle 16)
- Enrollment in the brentuximab vedotin + CHP arms is complete and data are forthcoming
- A phase 3 trial comparing frontline treatment with brentuximab vedotin + CHP versus CHOP alone is planned for patients with sALCL and other CD30-positive mature T-cell lymphomas

Acknowledgements

- With gratitude to our patients and their families
- Thank you to our investigators:
  - Dr Ranjana Advani
  - Dr Nancy L Bartlett
  - Dr Robert Chen
  - Dr Andrew Davies
  - Dr Michelle Fanale
  - Dr Andres Forero-Torres
  - Dr Steven Horwitz
  - Dr Tim Illidge
  - Dr Barbara Pro
  - Dr Andrei Shustov
- Clinical trial sponsors:
  - Seattle Genetics, Inc.
  - Millennium Pharmaceuticals, Inc.