2024 ESMO SARCOMA AND RARE CANCERS
Annual Congress

RESULTS FROM A PHASE 2 PART 1 TRIAL OF MECBOTAMAB VEDOTIN (BA3011), A CAB-AXL-ADC, IN PATIENTS WITH ADVANCED REFRACTORY SARCOMA

Seth M. Pollack, Anthony P. Conley, William Tap, Chueh-Chuan Yen, John Charlson, Lara E. Davis, Anna Chalmers, Mihaela Druta, Elizabeth T. Loggers, Jaspreet Grewal, Gerald Falchook, Brian Schulte, Thomas Yau, AeRang Kim, Herbert H. Loong, Suzanne George, Bhuvana Setty, Leo Mascarenhas, Gregory M. Cote, Breelyn Wilky

Presented by Seth M. Pollack

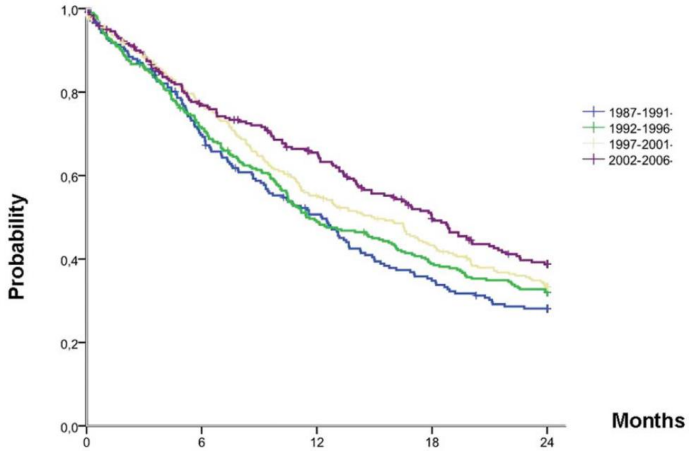
DECLARATION OF INTERESTS

Seth M. Pollack

Advisory and consulting fees from Adaptimmune, Bayer, Boehringer Ingelheim, Deciphera, Rain Therapeutics, and SpringWorks

SARCOMAS REMAIN DIFFICULT TO TREAT

Limited improvements in overall survival over time for metastatic soft tissue sarcomas[1]



Patients at risk	0	6 months	12 months	18 months	24 months
1987–1991	203	141	99	68	54
1992–1996	285	203	137	108	89
1997–2001	280	213	150	115	87
2002–2006	238	179	147	106	80

Few agents have efficacy in the treatment of osteosarcoma[2]

Selected Phase II Trials in Osteosarcoma[2]

Study	No. of Patients	Agent	Response	Years Study Open
A09713	10	Topotecan	No responses	1995–1998
ADVL0122	12	Imatinib	No responses	2002–2004
ADVL0421	13	Oxaliplatin	No responses	2004–2006
ADVL0524	11	Ixabepilone	No responses	2006–2007
CCG-0962	23	Docetaxel	1 PR, 1 CR, 2 NE, 19 with no response	1997–2001
EORTC phase II	15	Iproplatin	1 SD, 14 with no response	1997–1998
P9761	10	Irinotecan	9 with no response, 1 NE	1999–2005
P9963	16	Rebeccamycin	No responses	2000–2003
Phase II ridaforolimus	NR	Ridaforolimus	2 PR (total no. of patients NR)	2004–2005

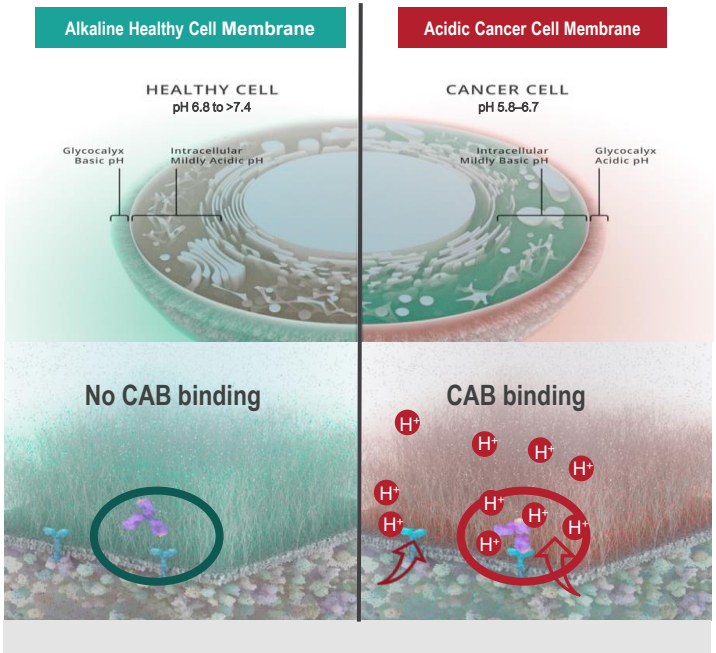
- **The historical use of radiographic response as the primary endpoint in osteosarcoma phase II trials has made it difficult to achieve PR[2]**

1. Italiano A, Mathoulin-Pelissier S, Cesne AL, et al. *Cancer*. 2011;117(5):1049-1054. 2. Isakoff MS, Bielack SS, Meltzer P, Gorlick R. *J Clin Oncol*. 2015;33(27):3029-3035.
Abbreviations: ADVL, Children's Oncology Group Developmental Therapeutic committee; CCG, Children's Cancer Group; CR, complete response; EORTC, European Organisation for the Research and Treatment of Cancer; NE, not evaluable; NR, not reported; PR, partial response; SD, stable disease.

CONDITIONALLY ACTIVE BIOLOGIC (CAB) TECHNOLOGY

Selective and targeted to widen the therapeutic index

- Acidic pH (5.8–6.7) at the cancer cell surface unveils binding sites that are shielded at normal pH (6.8 to >7.4)
- CAB antibodies (BioAtla Inc.) bind only to these unveiled sites on cancer cells in the tumor microenvironment[1]
- Not masked or caged, thus differentiating CABs from prodrugs that require irreversible enzymatic cleavage
- CABs have the potential for increased efficacy with improved safety relative to traditional antibodies

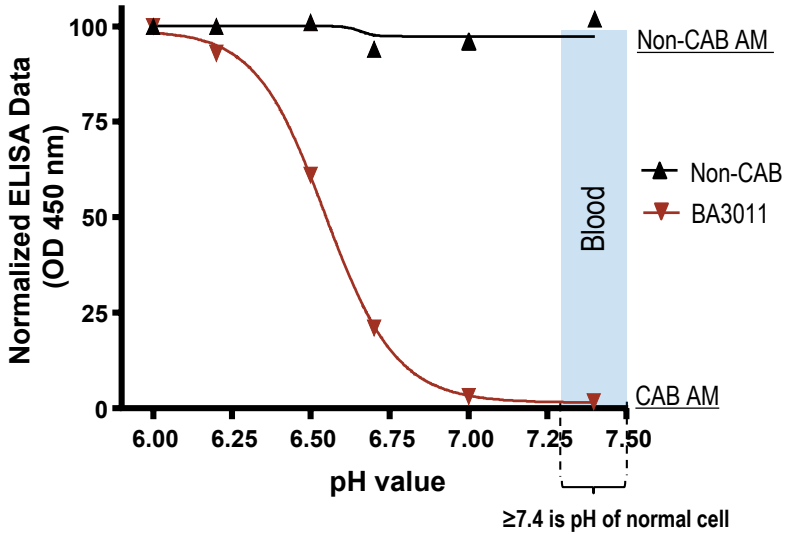


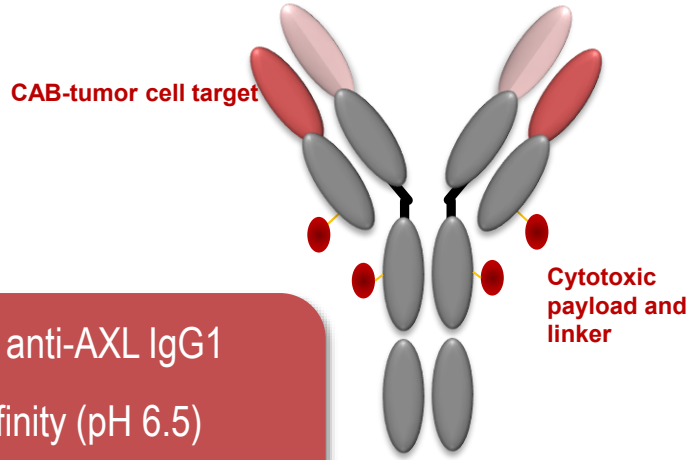
1. Chang HW, Frey G, Liu H, Xing C, Steinman L, Boyle WJ, Short JM. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

MECBOTAMAB VEDOTIN (BA3011): A CAB-AXL-ADC

AXL is expressed in a variety of tumor types, with overexpression associated with metastasis, tumor resistance to chemotherapy, and poor prognosis[1,2]

CAB-AXL-ADC pH binding inflection point adjusted for tumor microenvironment selectivity





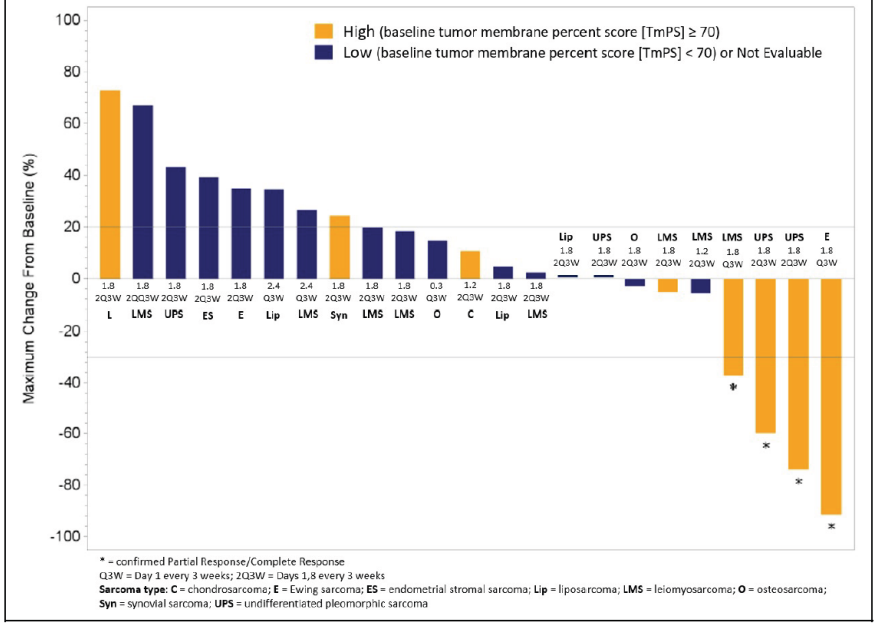
- Humanized anti-AXL IgG1
- ~100 pM affinity (pH 6.5)
- VC-MMAE linker and payload
- DAR 4
- Epitope in Ig loop region

1. Gay CM, Balaji K, Byers LA. *Br J Cancer*. 2017;116(4):415-423. 2. Zhang G, Wang M, Zhao H, Cui W. *Oncol Lett*. 2018;15(3):2726-2734.
Abbreviations: ADC, antibody-drug conjugate; AM, affinity matched; CAB, conditionally active biologic; DAR, drug antibody ratio; ELISA, enzyme linked immunosorbent assay; Ig, immunoglobulin; OD, optical density; VC-MMAE, valine-citrulline monomethylauristatin E.

CAB-AXL-ADC: PHASE 1 RESULTS

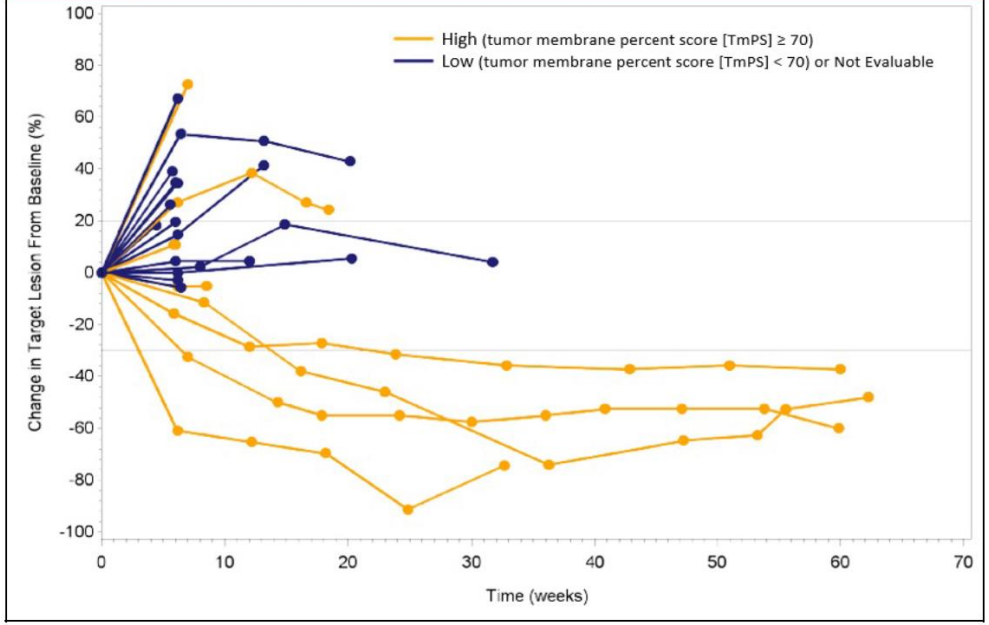
Durable responses observed among patients with UPS, LMS, and Ewing sarcoma; prospective, phase 2, single-arm UPS trial presently enrolling with data to be reported separately

Figure 2. Percent Change in Sum of Target Lesions (Best Response) by AXL TmPS Category – Evaluable Sarcoma Patients in Phase 1 at All Doses Tested



* = confirmed Partial Response/Complete Response
Q3W = Day 1 every 3 weeks; 2Q3W = Days 1,8 every 3 weeks
Sarcoma type: C = chondrosarcoma; **E** = Ewing sarcoma; **ES** = endometrial stromal sarcoma; **Lip** = liposarcoma; **LMS** = leiomyosarcoma; **O** = osteosarcoma; **Syn** = synovial sarcoma; **UPS** = undifferentiated pleomorphic sarcoma

Figure 3. Percent Change in Sum of Target Lesions by Visit and AXL TmPS Category – Evaluable Sarcoma Patients in Phase 1 at All Doses Tested

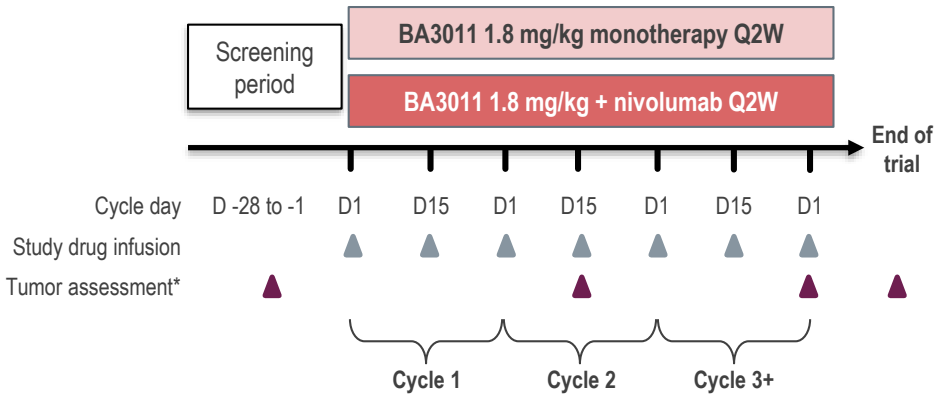


1. Wilky B, Druta M, Ahnert JR, et al. Poster presented at: Connective Tissue Oncology Society Annual Meeting; November 10-13, 2021.
Abbreviations: ADC, antibody-drug conjugate; AM, affinity matched; CAB, conditionally active biologic; LMS, leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma.

PHASE 2 PART 1 OPEN-LABEL STUDY DESIGN

Inclusion criteria

- ≥12 years of age
- AXL-expressing† locally advanced, unresectable, or metastatic sarcoma
- Measurable disease by RECIST v1.1
- Received ≥1 regimen containing anthracycline and ≤3 prior lines of approved systemic therapy for histologic subtypes that typically receive chemotherapy‡



Endpoints

- DCR (objective response or stable disease for ≥12 weeks)
- Number of responders (complete or partial)
- PFS rate at week 12
- TEAEs

†Tumor membrane percent score ≥50%.
‡Prior chemotherapy was not required for histologic subtypes that do not typically receive chemotherapy.
*Tumor assessment by CT or MRI every 6 weeks from C1D1 until 12 weeks, then every 8 weeks up to 1 year, then every 12 weeks thereafter.
Abbreviations: C, cycle; CT, computed tomography; D, day; DCR, disease control rate; MRI, magnetic resonance imaging; PFS, progression-free survival; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; v, version.

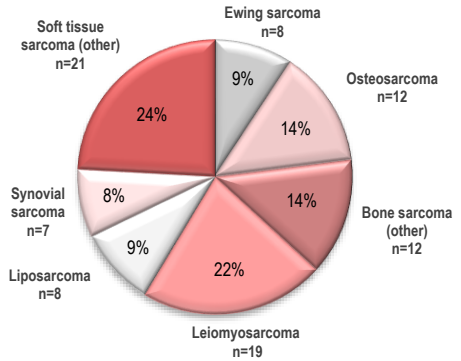
DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	BA3011 monotherapy (n=87)	BA3011 + nivolumab (n=26)
Age, y, mean (SD)		
Overall	51.5 (17.2)	55.3 (12.8)
12–17	3 (3.4)	0
18–65	65 (74.7)	21 (80.8)
>65	19 (21.8)	5 (19.2)
Gender, n (%)		
Male	44 (50.6)	6 (23.1)
Female	43 (49.4)	20 (76.9)
ECOG performance, n (%)		
0	38 (43.7)	12 (46.2)
1	48 (55.2)	14 (53.8)
Number of prior systemic therapies for metastatic disease, n (%)*		
1	19 (21.8)	5 (19.2)
2	27 (31.0)	11 (42.3)
3	23 (26.4)	7 (26.9)
≥4	14 (16.1)	3 (11.5)

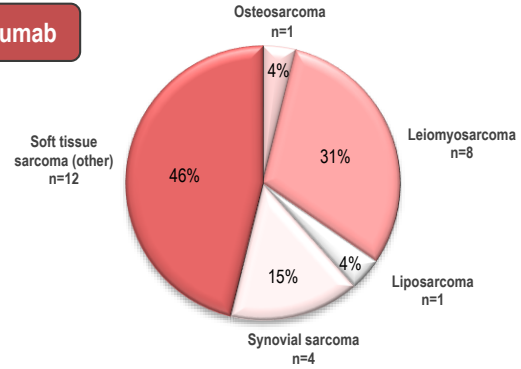
*Four patients had missing data in the BA3011 monotherapy cohort.
Data cutoff date: November 27, 2023.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Sarcoma subtypes enrolled (excluding UPS)

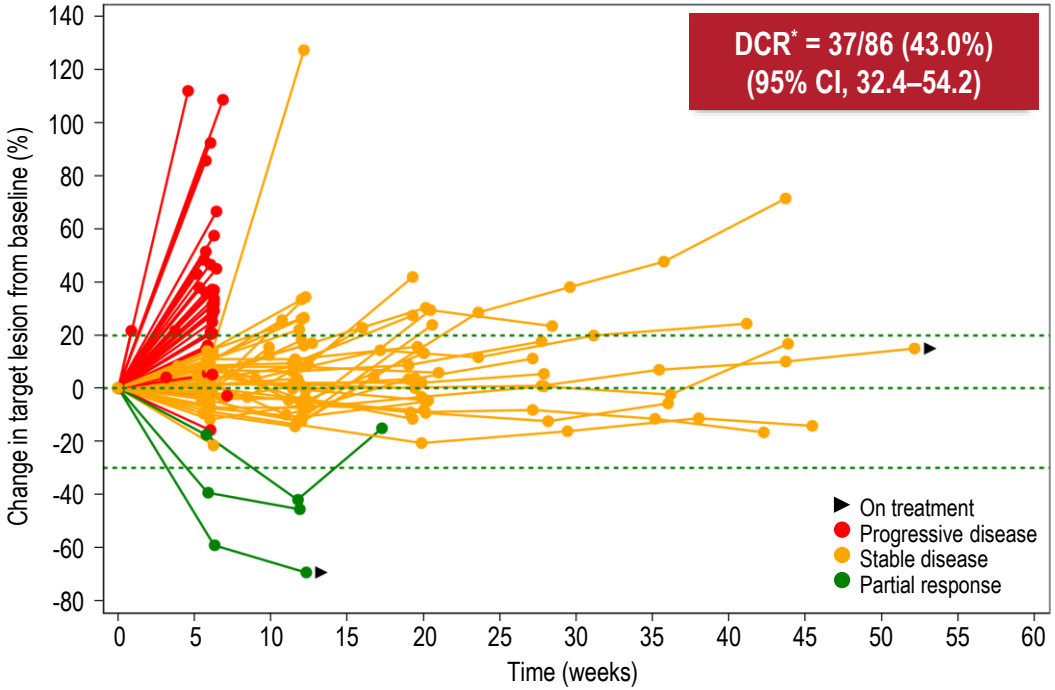
BA3011 monotherapy



BA3011 + nivolumab



BA3011 MONOTHERAPY ANTITUMOR ACTIVITY

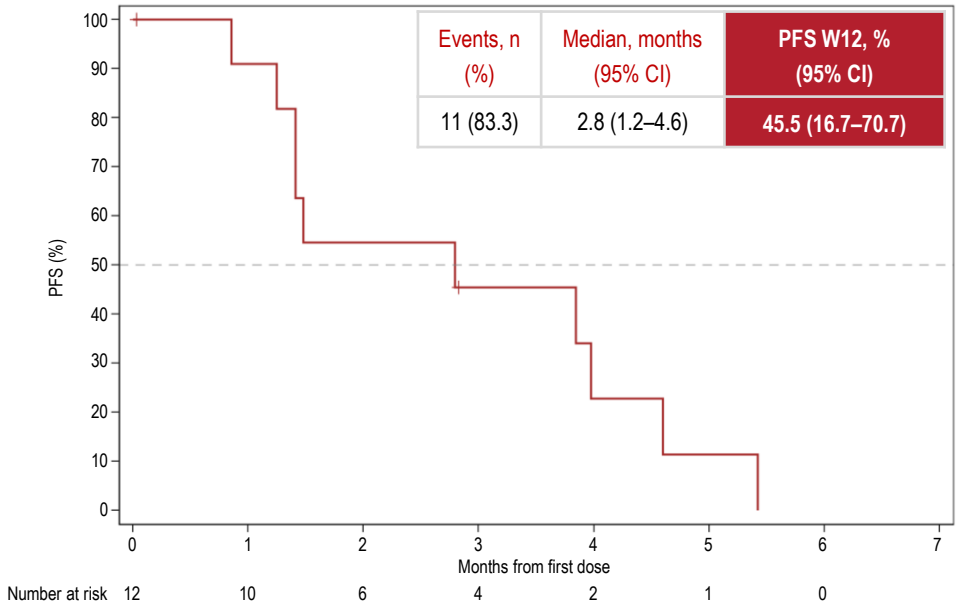


- Disease control observed regardless of AXL expression
- Confirmed partial responses observed among osteosarcoma patients (n=2)

*DCR defined as objective response or stable disease for ≥12 weeks; 1 patient lost to follow-up was not efficacy-evaluable.
Data cutoff date: November 27, 2023.
Abbreviation: DCR, disease control rate.

OSTEOSARCOMA PHASE 2 PFS

BA3011 monotherapy



- Week 12 PFS of 45.5% exceeds COG threshold (40%) for establishing an “agent of interest” for additional development[1]
- 2 out of 11 efficacy-evaluable patients with osteosarcoma achieved confirmed partial response

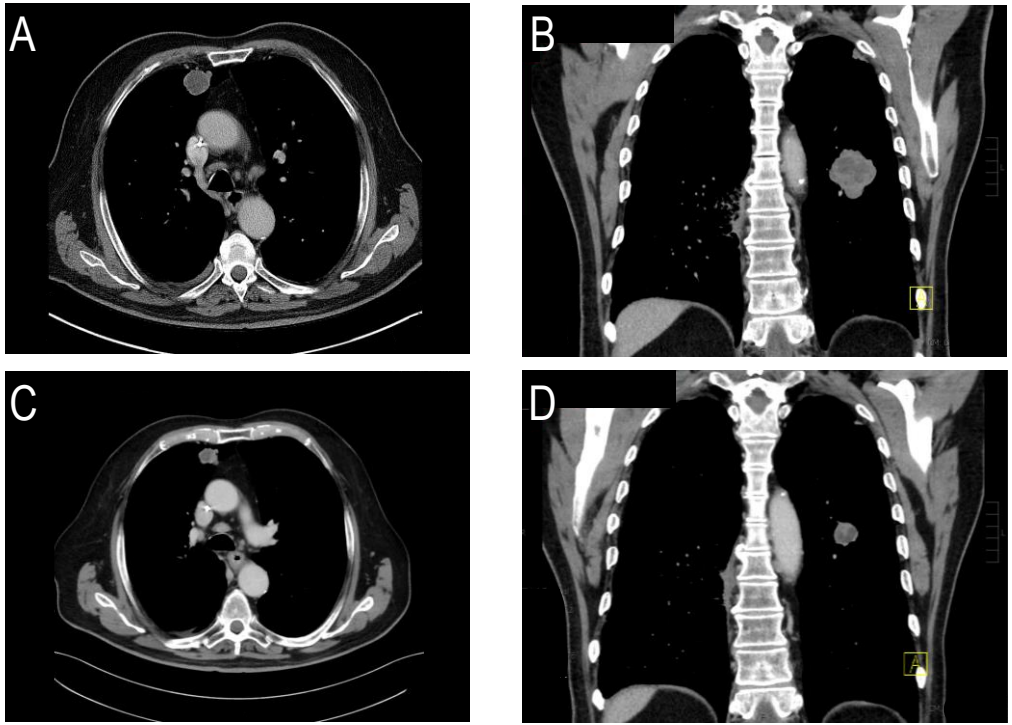
1. Lagmay JP, Krailo MD, Dang H, et al. *J Clin Oncol*. 2016;34(25):3031-3038.
Data cutoff date: November 27, 2023.
Abbreviations: COG, Children’s Oncology Group; PFS, progression-free survival; W, week.

OSTEOSARCOMA RESPONSE TO BA3011 MONOTHERAPY

83-year-old man previously treated with liposomal doxorubicin and cabozantinib

Baseline chest CT with contrast (June 26, 2023)

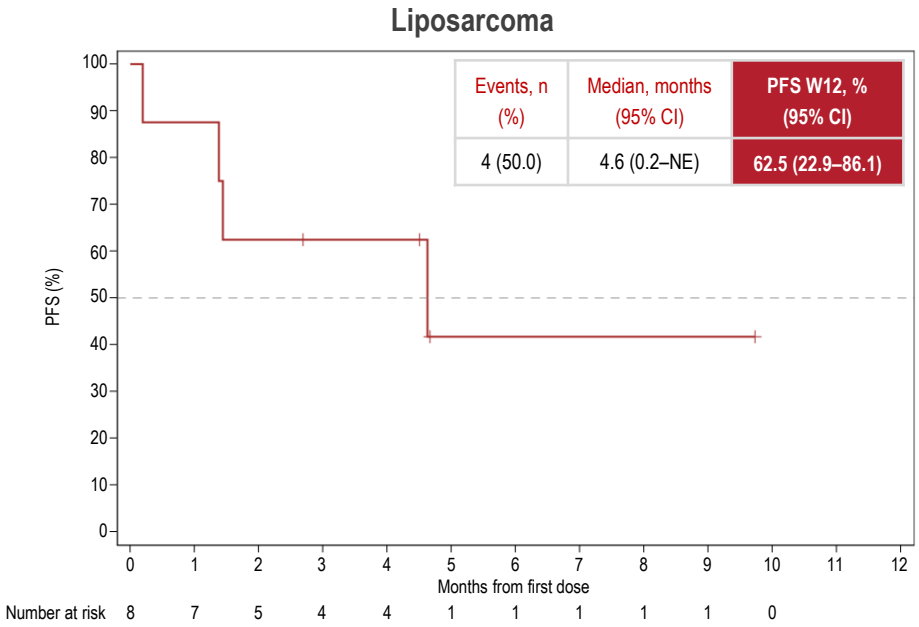
Follow-up chest CT with contrast (August 14, 2023)

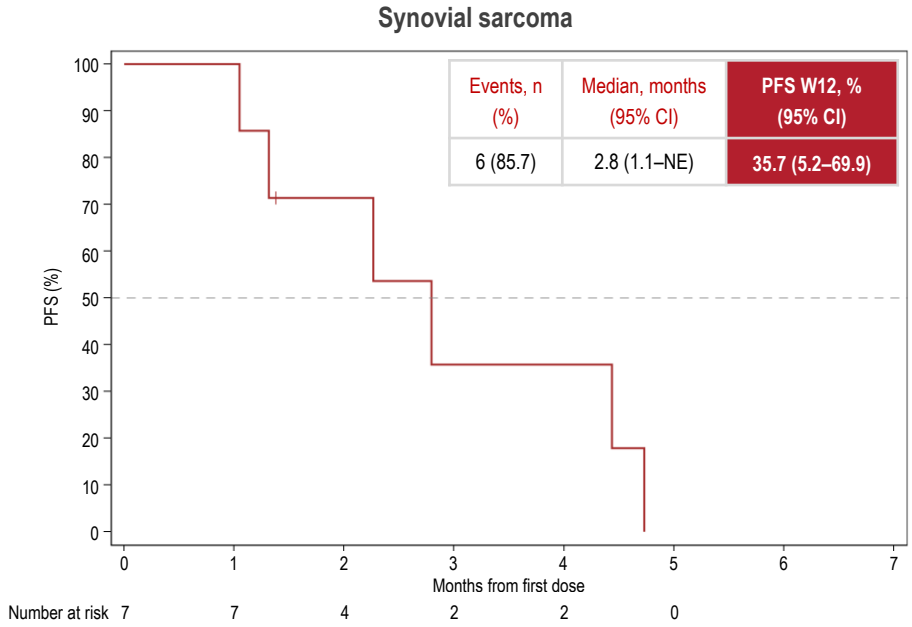


Data cutoff date: November 27, 2023.
Abbreviation: CT, computed tomography.

LIPOSARCOMA AND SYNOVIAL SARCOMA PHASE 2 PFS

BA3011 monotherapy



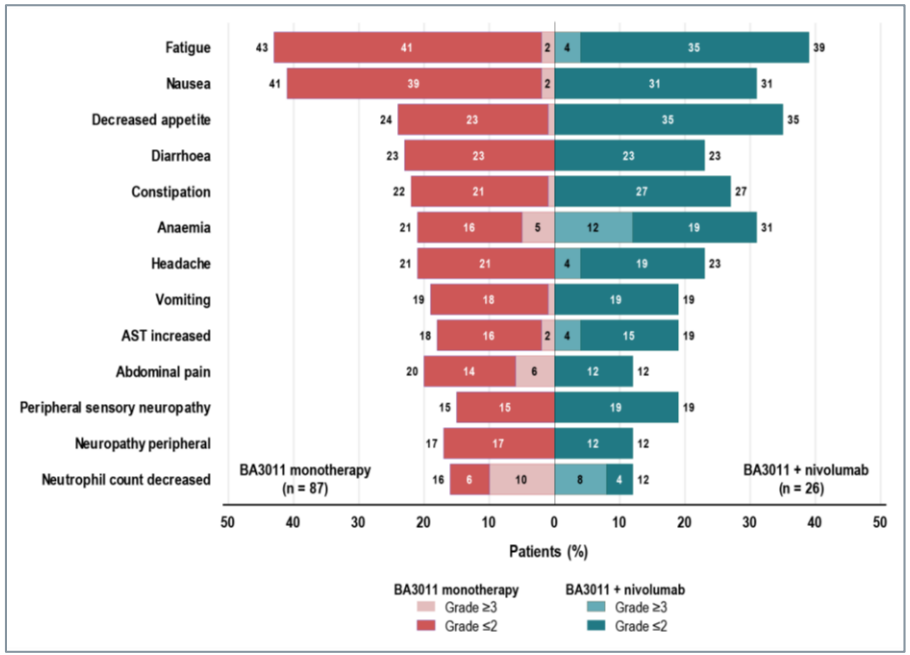


Data cutoff date: November 27, 2023.
Abbreviations: NE, not evaluable; PFS, progression-free survival; W, week.

SAFETY SUMMARY

Broadly well tolerated; most events low-grade and reversible

Most frequent TEAEs (≥15% of patients)



Summary of TEAEs

Characteristic, n (%)	BA3011 monotherapy (n=87)	BA3011 + nivolumab (n=26)
Any TEAE	85 (97.7)	24 (92.3)
Related TEAEs with CTCAE grade 3 or 4*	26 (29.9)	11 (42.3)
Related serious TEAEs*	4 (4.6)	6 (23.1)
Related TEAEs leading to death*	0	0
Related TEAEs leading to treatment discontinuation*	7 (8.0)	1 (3.8)

*As assessed by the investigator. Missing responses were counted as related.

Related TEAEs of Special Interest

Characteristic, n (%)	BA3011 monotherapy (n=87)		BA3011 + nivolumab (n=26)	
	All grades	Grades 3–4	All grades	Grades 3–4
Peripheral neuropathy	27 (31.0)	0	7 (26.9)	0
Neutropenia	18 (20.7)	14 (16.1)	5 (19.2)	4 (15.4)
Abnormal liver function tests	14 (16.1)	3 (3.4)	3 (11.5)	1 (3.8)
Hyperglycemia	3 (3.4)	1 (1.1)	1 (3.8)	0

Data cutoff date: November 27, 2023.
Abbreviations: AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Every-other-week delivery of an AXL-targeted ADC, mecbotamab vedotin, attained disease control in 43% of patients with treatment-refractory sarcomas
- Treatment responses were observed among patients with osteosarcoma (2 PRs; week 12 PFS rate = 45.5%) and undifferentiated pleomorphic sarcoma (UPS; reported previously)[1]
- Toxicity was manageable and few high-grade related TEAEs were observed
  - Very few related TEAEs led to treatment discontinuation
- Data observed thus far justifies further evaluation of mecbotamab vedotin, particularly among patients with osteosarcoma and UPS; a Phase 2 registrational study is ongoing (NCT03425279)

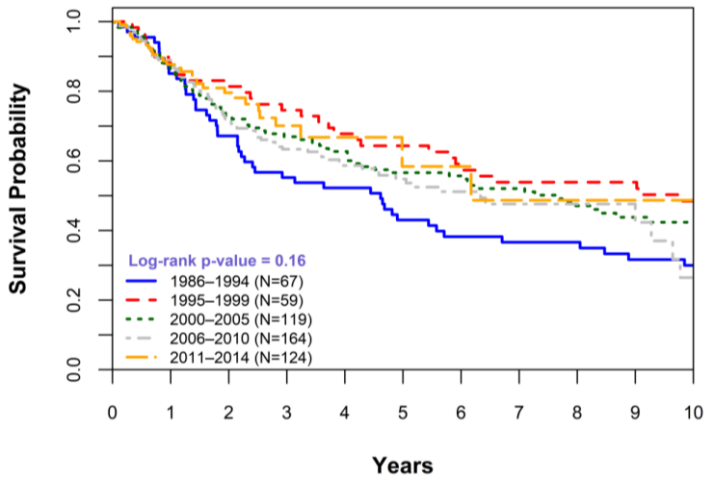
1. Wilky B, Druta M, Ahnert JR, et al. Poster presented at: Connective Tissue Oncology Society Annual Meeting; November 10-13, 2021.
Abbreviations: ADC, antibody-drug conjugate; PFS, progression-free survival; PR, partial response; TEAE, treatment-emergent adverse event.

THANK YOU

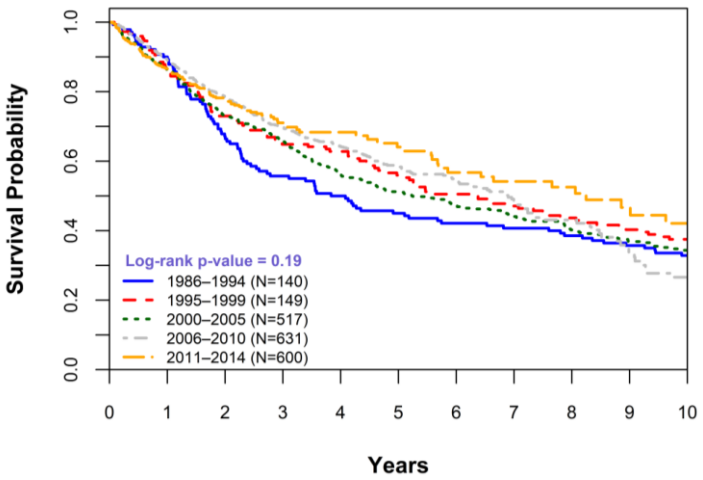
SARCOMAS REMAIN DIFFICULT TO TREAT

Limited improvements in overall survival over time for bone and soft tissue sarcomas[1]

Kaplan–Meier survival curves by year of diagnosis for patients with bone sarcomas at a tertiary cancer center



Kaplan–Meier survival curves by year of diagnosis for patients with soft tissue sarcomas at a tertiary cancer center



1. Stricker E, Reed DR, Schabath MB, Sok P, Scheurer ME, Lupo PJ. *Cancers (Basel).* 2023; 15(2):514.