Targeting TGF-β Signaling in the Tumor Microenvironment as an Effective Therapy in Osteosarcoma

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Disclosures

- Discussion of investigational drug use
  - TEW-7197, Vactosertib, MedPacto

Immunotherapy and Osteosarcoma (OS)

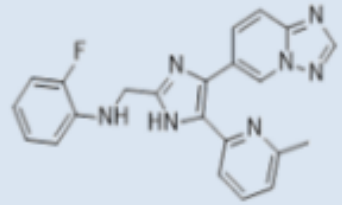
- Promising approach to overcome limitation of conventional treatments
- Achieves good therapeutic effects in other malignancies
- OS has immunosuppressive tumor microenvironment that can be modulated to improve immune responsiveness
    - Challenges to using immunotherapy exist
        - Lack validated biomarkers for predicting responses to immunotherapy
    - Inconsistent clinical efficacy of immunotherapy in OS due to tumor heterogeneity, immune evasion mechanisms, and insufficient immune infiltration

Han Z, Chen G and Wang D (2025) Emerging immunotherapies in osteosarcoma: from checkpoint blockade to cellular therapies. *Front. Immunol.* 16:1579822. doi: 10.3389/fimmu.2025.1579822

Vactosertib (TEW-7197, MedPacto)

- Small molecule inhibitor against Type 1 TGF-β receptor (ALK 5)
- Orally available
- Transient, low-grade toxicities
- Has 10 times the potency (IC50=11nM) of previous ALK5 inhibitors

TGF-βR1/ALK 5 Inhibitor

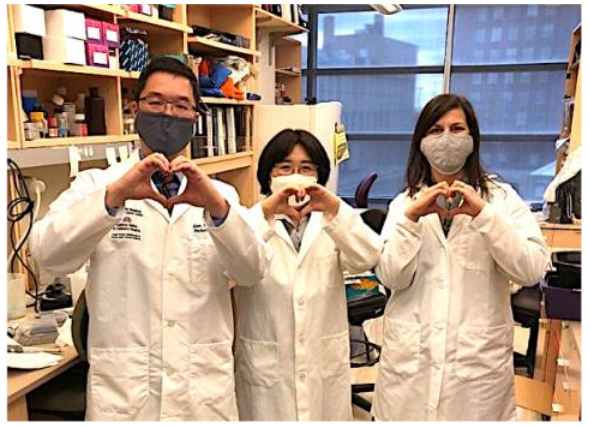


Tumor Associated Macrophages

- Tumor associated macrophages are a dominant immune cell in OS
  - Secrete high levels of immunosuppressive cytokines, including TGF-β
    - Recruits and induces immune-suppressive myeloid and regulatory T cells
    - TGF-β1 signaling pathway in myeloid cells has been found to be required for tumor metastasis

Preclinical Data Review

- Vactosertib inhibits murine osteosarcoma cell growth *in vitro* and *in vivo*
- Tumor incidence and volume in mice treated with vactosertib decreased than compared to mice treated with vehicle
- Survival was improved in mice treated with vactosertib compared to mice treated with vehicle
- Vactosertib had efficacy in immune competent syngeneic Balc/C mice starting treatment with vactosertib 4 weeks after tumor inoculation when pulmonary disease was evident



Targeting TGF-β in the tumor microenvironment of OS may reduce or ameliorate disease

- Vactosertib may address unmet clinical need by targeting TGF-β signaling pathway

FDA's expedite programs

- **Orphan Drug Designation** (08/2021)
- **Rare Pediatric Drug Designation** (09/2022)
- **Fast Track Designation** (01/2023)
- **Orphan Medical Product (EMA)** (07/2023)

Crucial role of TGF-β in OS

Transforming Growth Factor-β Signaling Plays a Pivotal Role in the Interplay Between Osteosarcoma Cells and Their Microenvironment

Franck Verrecchia and Françoise Rédini*

Front Oncol. 2018 Apr 30;8:133.

Transforming growth factor β signaling in myeloid cells is required for tumor metastasis

Yanli Pang[1,4], Sudheer Kumar Gara[1], Bhagelu R. Achyut[1], Zhaoyang Li[1], Hannah H. Yan[1], Chi-Ping Day[1], Jonathan M. Weiss[2], Giorgio Trinchieri[2], John C. Morris[3], and Li Yang[1,*]

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TGF-β Signaling in Bone Remodeling and Osteosarcoma Progression

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TGF-β is critical to OS development

- **Immune suppressive molecule in the tumor microenvironment**
- **Increased in serum of patients with OS**
- **Associated with lung mets**

Study Design for MP-VAC-209 (Phase 1b ongoing, Phase 2)

- NCT05588648, Phase 1b is nearing completion

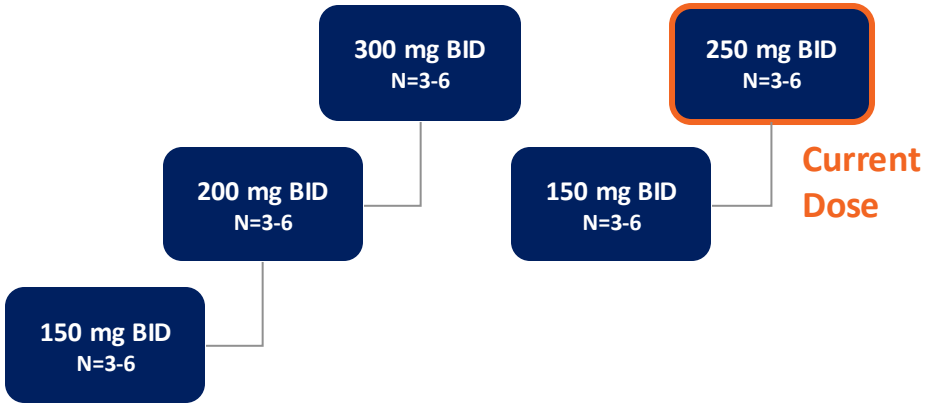
Key Eligibility Criteria

- Age ≥12 years
- Confirmed histologic verification of Osteosarcoma
- Progressed, relapsed or became refractory to conventional therapy

Phase 1b

Adult cohort
18+ years old

Adolescent cohort
12-to <18 years old



Phase 2a

Adult and Adolescents

RP2D
N=42

Total of 42 evaluable patients including patients in Phase 1 treated at the same dose

Endpoints

- Primary: Safety, Tolerability
- Secondary: OS, ORR, PFS, DOR, TTR, TTP
- Exploratory: Biomarker (c-Myc etc)

Individual Subject Data by Prognostic Factors (Phase 1b)

ORR = 36.4% (4/11)

Subject	Sex/Age	Primary	Disease Duration (years)	Prior line	Metastasis	LDH ALP	Tumor Size (mm)	Status	BOR	OS	PFS
Adult – Vactosertib 150 mg BID											
108-001	M/35	Femur	15.6	-	Lung, Pleura, Abdomen wall	**176** 132	110	EOT – PD EOS – Study closing	PD	6.3+	1.6
202-001	M/30	Femur	6.1	6th line: CPA/VP-16	Bone, Lung	**378** 391	238.6	EOT - Withdrawal EOS - Death	PD	5.4	1.8
202-002	F/31	Femur	3.6	7th line: ICE	Skin, Muscle, H&N, lung, Brain	**162** 121	64.9	EOT - PD EOS – Withdrawal	PD	4.0+	1.1
Adult – Vactosertib 200 mg BID											
108-003	M/35	Chest	4.8	-	Lung, Pleura, Liver, Muscle, Bone	**366** 942	126	EOT - PD EOS – Death	PD	2.4	1.2
201-001	M/26	Humerus	5.6	2nd line: ICE	Muscle, Bone, Pleura	**256** 125	32.8	Ongoing	PR (-31.1%)	16.6+	13.8+
201-002	F/31	Pelvis	4.5	4th line: GD	Bone	**154** 65	50	Ongoing	PR (-47.2%)	16.6+	13.8+
Adult – Vactosertib 300 mg BID											
201-003	M/56	Femur	8.0	3rd line: IE	Bone	**175** 87	41.9	Ongoing	PR (-51.1%)	7.4+	5.5+
201-004	M/40	Pelvis	3.0	3rd line: ICE/GD	Bone, Lung	**140** 138	94	EOT – Death EOS - Death	-	2.0	2.0
202-003	M/19	Femur	4.1	4th line: Sorafenib	Bone	**172** 169	109	EOT – PD EOS - Ongoing	PD	1.9+	1.7
Adolescent – Vactosertib 150 mg BID											
202-004	F/16	Femur	4.7	11th line: CPA	Bone, Mediastinum, Lung	**162** 168	241.2	EOT – PD EOS - Ongoing	PD	1.9+	1.8
202-005	F/17	Femur	4.7	4th line: ICE	Bone	**103** 295	23	Ongoing	PR (-65.2%)	1.0+	TBD

[Abbreviation] CPA, Cyclophosphamide; GD, Gemcitabine + D[illegible]oposide; IE, Ifosfamide + Etoposide; VP-16, Etoposide ; UPS, Undifferentiated Pleomorphic Sarcoma

Cumulated AE Listing (1/2)

Data as of 19-May-2025

Subject	Age Group	Dose	AE Term	Start Date	End Date	Causal Relationship	Action Taken	DLT	SAE	Outcome	Maximum Severity
108-001	Adult	150mg BID	Vomiting	20-Nov-23	25-Nov-23	Not related	Dose not changed	No	No	Recovered/Resolved	GRADE 1
108-001	Adult	150mg BID	Nausea	05-Nov-23	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 1
108-001	Adult	150mg BID	Dyspnea	06-Nov-23	10-Nov-23	Not related	Dose not changed	No	No	Recovered/Resolved	GRADE 1
108-001	Adult	150mg BID	Pain in extremity right shoulder	02-Dec-23	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2
108-001	Adult	150mg BID	Tumor pain right side abdomen	02-Dec-23	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2
108-001	Adult	150mg BID	Cough	29-Oct-23	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2
108-003	Adult	200mg BID	Fatigue	25-Jan-24	Ongoing	Related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 1
108-003	Adult	200mg BID	Anemia	24-Jan-24	17-Mar-24	Related	Dose not changed	No	No	Recovered/Resolved	GRADE 3
108-003	Adult	200mg BID	Spinal cord compression	28-Feb-24	Ongoing	Not related	Drug withdrawn	No	No	Not recovered/Not resolved	GRADE 3
108-003	Adult	200mg BID	Urinary retention	28-Feb-24	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2
108-003	Adult	200mg BID	Constipation	01-Mar-24	13-Mar-24	Not related	Dose not changed	No	No	Recovered/Resolved	GRADE 2
108-003	Adult	200mg BID	Systemic inflammatory response syndrome	12-Mar-24	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 3
108-003	Adult	200mg BID	Scrotal swelling	12-Mar-24	Ongoing	Not related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2

Cumulated AE Listing (2/2)

Data as of 19-May-2025

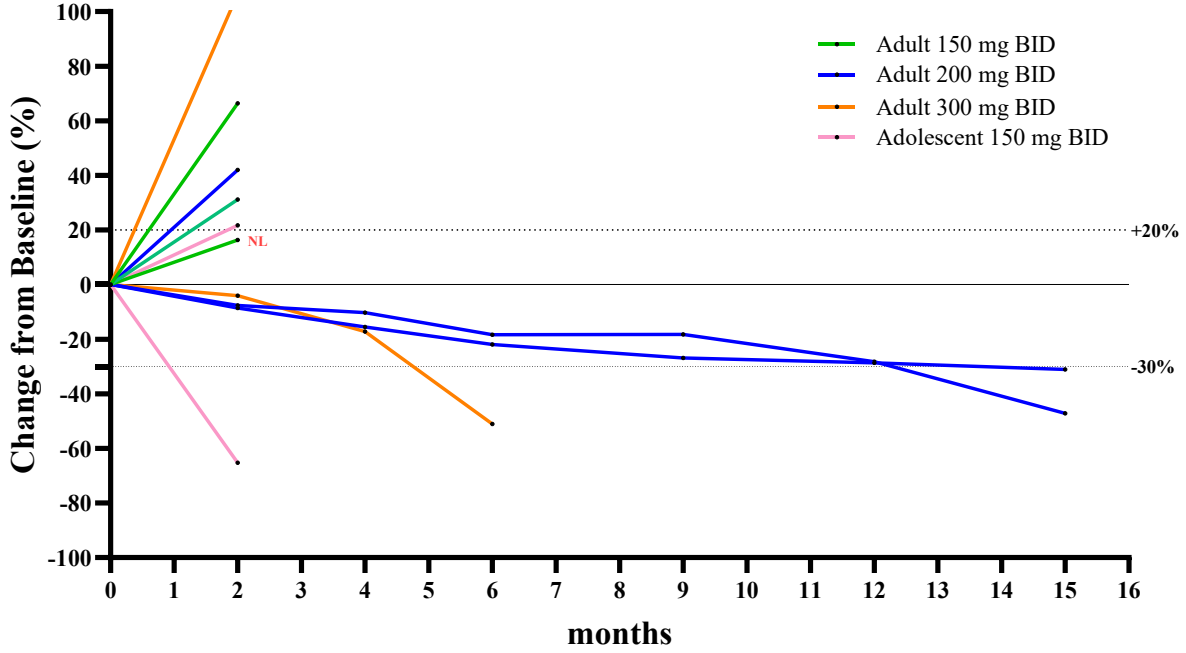
Subject	Age Group	Dose	AE Term	Start Date	End Date	Causal Relationship	Action Taken	DLT	SAE	Outcome	Maximum Severity
201-002	Adult	200mg BID	Enterocolitis	10-Jun-24	14-Jun-24	Not related	Dose not Changed	No	Yes	Recovered/Resolved	GRADE 3
201-004	Adult	300mg BID	Tumor hemorrhage	21-Nov-24	Ongoing	Not related	Dose not Changed	No	Yes	Not Recovered/Not Resolved	GRADE 3
202-001	Adult	150mg BID	Anemia	14-Nov-23	11-Jan-24	Related	Dose not changed	No	No	Recovered/Resolved	GRADE 3
202-001	Adult	150mg BID	Hypophosphatemia	23-Oct-23	Ongoing	Not related	Dose not changed	No	No	Recovering/Resolving	GRADE 2
202-001	Adult	150mg BID	Urinary tract infection	23-Oct-23	28-Nov-23	Not related	Dose not changed	No	No	Recovered/Resolved	GRADE 3
202-002	Adult	150mg BID	Dizziness	28-Oct-23	28-Oct-23	Not related	Not Applicable	No	No	Recovered/Resolved	GRADE 1
202-002	Adult	150mg BID	Fatigue	04-Nov-23	Ongoing	Related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2
202-002	Adult	150mg BID	Vomiting	04-Nov-23	Ongoing	Related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 1
202-002	Adult	150mg BID	Nausea	04-Nov-23	Ongoing	Related	Dose not changed	No	No	Not recovered/Not resolved	GRADE 2
202-002	Adult	150mg BID	Headache	28-Oct-23	Ongoing	Related	Not Applicable	No	No	Not recovered/Not resolved	GRADE 2
202-003	Adult	300mg BID	Fever	08-Nov-24	11-Nov-24	Related	Dose not changed	No	Yes	Recovered/Resolved	GRADE 3
202-004	Adolescent	150mg BID	Hypotension	18-Feb-25	18-Feb-25	Not related	Dose not changed	No	No	Recovered/Resolved	GRADE 1
202-005	Adolescent	150mg BID	Maculopapular rash	22-Feb-25	22-Feb-25	Related	Dose not changed	No	No	Recovered/Resolved	GRADE 1

[Note] No DLT observed. No significant risk observed.

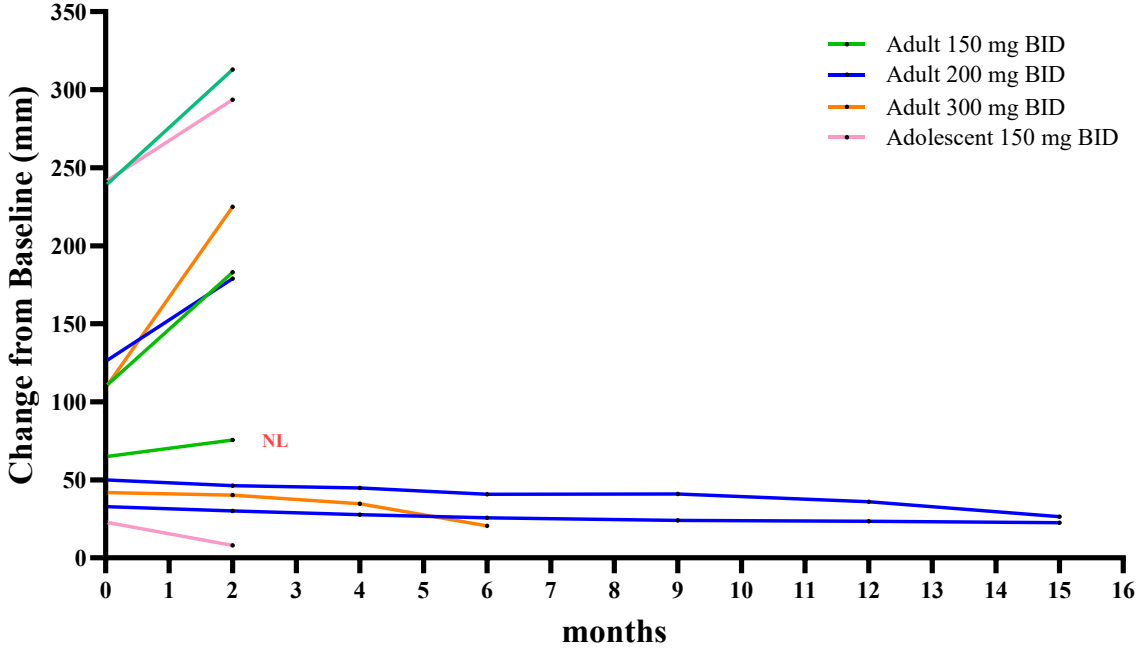
Change from Baseline in Tumor Burden (Phase 1b)

- Vactosertib thus far may be effective in patients with smaller tumors

Change in Size (%)



Change in Size (mm)



Rationale for a Phase 2 maintenance clinical trial

- Risk of relapse and death for osteosarcoma patients with metastatic or relapsed disease having achieved remission is still unacceptably high
- Vactosertib
  - Oral agent
  - Tolerated well, which makes it ideal for a maintenance regimen
- **Patients with minimal residual disease may benefit most**

Risk Factor (≥2 high-risk factors)		
Metastatic at diagnosis (M1a)	**HR 2.34 (95% CI 1.95 to 2.81)**	**Smeland et al., 2019 (EURAMOS-1)**
<90% necrosis	**HR 2.13 (95% CI 1.76 to 2.58)**	**Smeland et al., 2019 (EURAMOS-1)**
1) Primary tumor site (Axial)	HR 1.29 (95% CI 0.86 to 1.95)	Smeland et al., 2019 (EURAMOS-1)
2) ≥18 age	HR 1.53 (95% CI 1.17 to 1.99)	Smeland et al., 2019 (EURAMOS-1)
3) 1st relapse <18 months	RR 1.65 (95% CI 1.23 to 2.20)	Kempf-Bielack et al., J Clin Oncol. 2005

[Note] Tumor size, AJCC 8th T3 not included, Zhang et al., BMC Cancer 2023

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