Front. Med. 2025, 19(6): 1307−1310
https://doi.org/10.1007/s11684-025-1174-y

Clinical trial landscape of malignant peripheral nerve sheath tumors: challenges and opportunities

Guo Zhao[1,*], Yale Jiang[1,*], Jiaxiu Ma[2], Shuhang Wang (✉)[1], Ning Li (✉)[1]

[1]Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China; [2]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin 300020, China

© Higher Education Press 2025

Dear editor,

Malignant peripheral nerve sheath tumors (MPNSTs) are rare, aggressive sarcomas arising from peripheral nerves or pre-existing neurofibromas, accounting for approximately 5%–10% of all soft tissue sarcomas [1]. These tumors are notoriously heterogeneous: approximately 50% associated with neurofibromatosis type 1 (NF1), 40% occurring sporadically, and 10% linked to prior radiation exposure [2]. MPNSTs are characterized by rapid progression, high recurrence rates (30%–70%), and dismal 5-year survival rates (34%–50%), particularly in advanced or metastatic stages where therapeutic options are severely limited [3]. The clinical management of MPNSTs remains fraught with challenges. Complete surgical resection with negative margins is the cornerstone of treatment, yet anatomic constraints (e.g., spinal, cranial, or deep-seated tumors) often preclude radical excision, leading to frequent local recurrence and metastasis. Even in cases of successful R0 resection, patients face a high risk of rapid metastatic spread. Conventional chemotherapy, primarily anthracycline-based regimens, offers limited efficacy, with phase II trials revealing median progression-free survival (PFS) as low as 1.77 months in refractory or metastatic cases [4]. Similarly, radiotherapy provides marginal benefits for local control but fails to address systemic disease, underscoring the inadequacy of current multimodal approaches19. The molecular complexity of MPNSTs further complicates treatment.

Genomic studies have highlighted recurrent mutations in NF1, CDKN2A, SUZ12, and EED, along with dysregulated pathways such as RAS/MAPK, PI3K/AKT, and PRC2-mediated epigenetic silencing pathways [5]. Notably, recent multi-omics analyses have identified two distinct MPNST subtypes: SHH-activated (MPNST-G1) and WNT/β-catenin-driven (MPNST-G2), each harboring unique therapeutic vulnerabilities [6].

Despite these insights, no targeted therapies have achieved clinical validation, partly due to tumor heterogeneity and the lack of biomarkers to guide patient stratification [7]. Early-phase trials of agents like bromodomain and extraterminal (BET) inhibitors and histone deacetylase (HDAC) inhibitors have shown limited efficacy, with narrow therapeutic windows and rapid resistance emergence [7]. This bleak landscape underscores the critical need for innovative drug development. Preclinical breakthroughs, such as targeting the LSD1-HDAC1-CoREST (LHC) complex with bifunctional inhibitors like Corin, have demonstrated promising anti-tumor effects, including suppressed proliferation, induced apoptosis, and reduced invasiveness across MPNST models [8]. Similarly, strategies leveraging immune modulation, angiogenesis inhibitors, or combination therapies targeting parallel pathways (e.g., MEK and mTOR inhibitors) are gaining traction. Ongoing clinical trials emphasize the exploration of multimodal regimens and biomarker-driven approaches to overcome resistance mechanisms and improve outcomes [7]. In conclusion, MPNSTs represent a paradigm of unmet medical need in rare tumors. Thus, this study aims to visualize the clinical trial landscape of MPNSTs across the world to provide insight for researchers, clinicians, and pharmaceutical enterprise.

This study leverages the INFORMA Trialtrove database, a globally recognized repository of clinical trial data [9], to systematically analyze the therapeutic landscape of MPNSTs. By querying the database with

Received May 11, 2025; accepted August 14, 2025

Correspondence: Shuhang Wang, wangshuhang@cicams.ac.cn;
Ning Li, lining@cicams.ac.cn

*These authors contributed equally to this work.

Medical Subject Headings (MeSH) terminology and the keyword "MPNSTs," we identified 152 clinical trials specifically investigating this aggressive sarcoma. The curated dataset offers a multidimensional perspective on MPNST-focused studies, encompassing trial phases (Phase I to IV), current statuses (ongoing, completed, or terminated), and details of therapeutic strategies, including investigational drugs, combination regimens, targets, and mechanism of action. Through comprehensive metadata annotation, this analysis enables an in-depth assessment of both ongoing and completed interventions, revealing emerging trends in targeted therapies as well as novel immunotherapies. The synthesis of trial data not only informs future study designs but also holds translational potential to refine clinical protocols, optimize therapeutic combinations, and accelerate the development of precision medicine strategies for this malignancy.

In terms of trial phases, Phase II trials dominate the landscape (59%, 77 trials), followed by Phase I (17%, 23 trials) and Phase I/II (16%, 21 trials), with minimal representation in Phase IV (1%, 1 trial) (Fig. 1A). Trial status distribution shows 20% of trials are currently open (27 trials), while 13% are terminated (17 trials), 7% closed (9 trials), and 4% planned (5 trials) (Fig. 1B). Indications highlight that 65% of trials focus on pan-soft tissue sarcomas (85 trials), followed by advanced solid tumors (27 trials) and neurofibromatosis type 1-associated MPNSTs (11%, 14 trials), with smaller subsets addressing other patient cohorts (Fig. 1C). Current single chemotherapy still dominates the trials of MPNSTs, highlighting the unmet need of novel therapeutics. Regarding the combination therapy of MPNSTs, chemotherapy combination, chemotherapy + radiotherapy, and chemotherapy + targeted therapy are top 3 regimens (Fig. 1D). Chemotherapy remains a prominent therapeutic approach (15%, 10 trials), with DNA synthesis inhibitors (22 trials) and DNA inhibitors (24 trials) being the most common drug types (Fig. 1E). Targeted therapies prioritize kinases such as the Kinase Insert Domain Receptor (KIDR, 24 trials), fms related tyrosine 4 (19 trials), and fibroblast growth factor receptor 1/3 (FGFR1/3, 17 trials each) (Fig. 1F). Immunotherapy trials focus on PD-1/PD-L1 (15 trials)

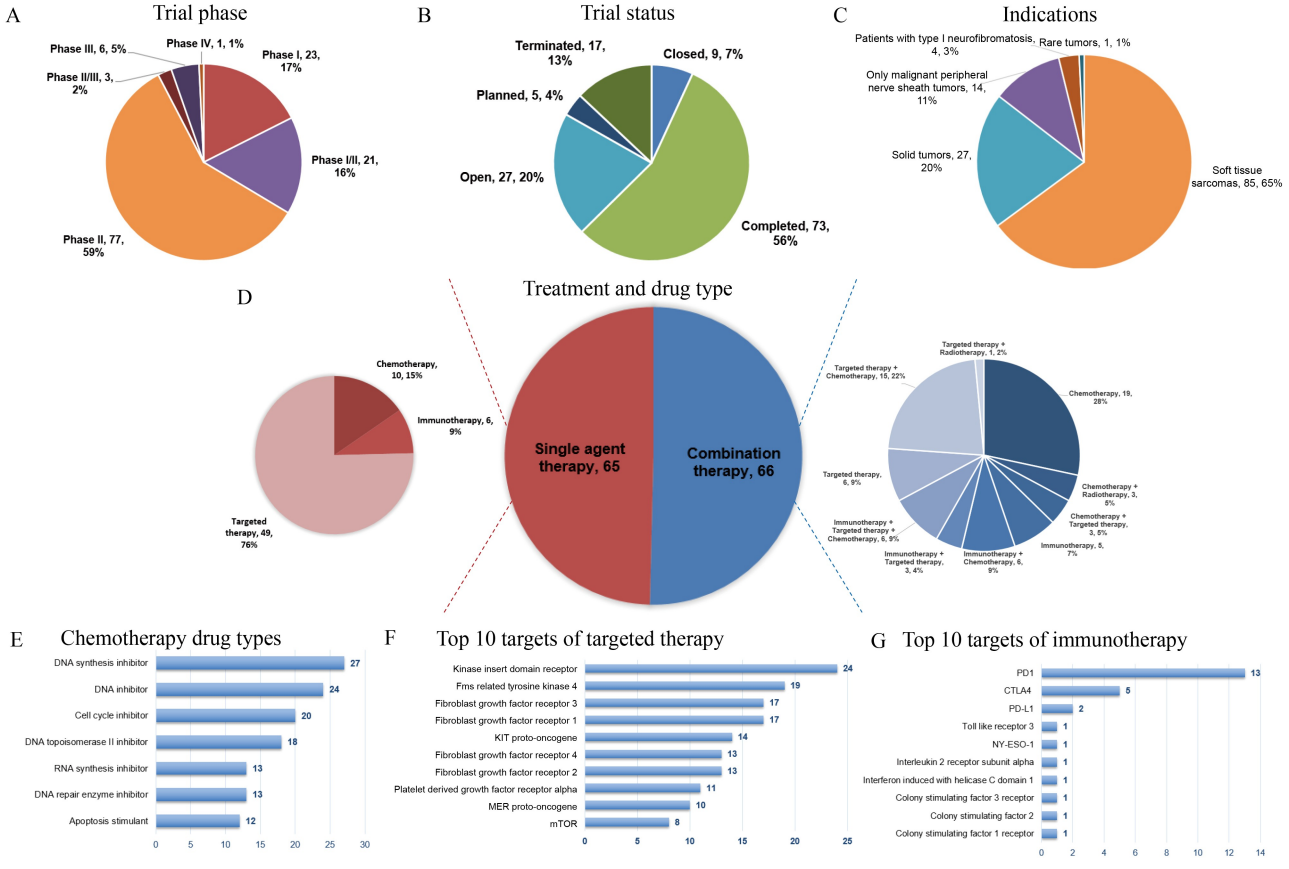

Fig. 1 Clinical trial landscape of all available therapies of MPNSTs worldwide. (A) Clinical trial phases. (B) Clinical trial status. (C) Clinical trial indications. (D) Treatment and drug types of MPNSTs. (E) chemotherapy drug types. (F) Top 10 most targeted proteins in MPNSTs. (G) Top 10 immunotherapy targets in MPNSTs. CTLA-4, cytotoxic T-lymphocyte associated protein 4; mTOR, mechanistic target of rapamycin; NY-ESO-1, New York esophageal squamous cell carcinoma-1; PD1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

and CTLA-4 (5 trials), though other immune targets like Toll-like receptor 3 or interleukin-related pathways show limited exploration (Fig. 1G). This analysis underscores a strong emphasis on early-phase trials and kinase-targeted strategies, while revealing gaps in biomarker-driven studies, late-phase validations, and tailored approaches for MPNSTs.

The development of novel therapies for MPNSTs represents a critical frontier in oncology, driven by the urgent need to address the dismal prognosis and therapeutic stagnation characterizing this aggressive rare tumor [10]. Current clinical trial data reveal a shifting landscape, with increasing emphasis on targeted therapies and immunotherapies, yet significant barriers impede their translation into clinical practice [11]. Targeted therapies focusing on dysregulated pathways such as RAS/MAPK, PI3K/AKT, and epigenetic modifiers (e.g., PRC2 complex) have shown preclinical promise, particularly agents inhibiting kinases like KIT, FGFR2/3, and PDGFR [12]. However, clinical validation remains sparse, as evidenced by the predominance of early-phase trials (59% Phase II) and the absence of the U.S. Food and Drug Administration (FDA)-approved targeted drugs. The heterogeneity of MPNSTs, compounded by divergent molecular subtypes (e.g., SHH-activated vs. WNT-driven), further complicates patient stratification and underscores the necessity for biomarker-driven trial designs. Immunotherapy, though less explored, holds transformative potential. PD-1/PD-L1 and CTLA-4 inhibitors dominate current efforts, yet their efficacy in MPNSTs remains modest, likely due to the tumor's immunosuppressive microenvironment and low mutational burden [13]. Emerging strategies, such as adoptive tumor infiltrating lymphocytes therapies or combinations with epigenetic modulators, aim to overcome these limitations but are hindered by small trial cohorts and inconsistent biomarker integration. Notably, the underrepresentation of NF1-associated MPNSTs in trials, a subgroup with distinct biology and poorer outcomes, highlights a critical gap in personalized therapeutic development.

The urgency for clinical translation is amplified by MPNSTs' rapid progression and resistance to conventional therapies. While preclinical breakthroughs, such as LSD1-HDAC dual inhibitors or MEK/mTOR combinations, demonstrate mechanistic synergy, their progression to late-phase trials is sluggish. Challenges such as drug toxicity, adaptive resistance, and inadequate funding for rare cancers further delay progress. To bridge this translational chasm, collaborative efforts must prioritize adaptive trial platforms, real-world data integration, and multidisciplinary approaches that align molecular insights with clinical needs, like genotyping-guided precision medicine for rare solid tumors in China [14]. Accelerating the development of precision therapies is not merely a scientific imperative but an ethical obligation to improve survival for patients facing this relentlessly fatal disease [15]. Besides, lumping MPNSTs with heterogeneous sarcomas dilutes statistical power and masks unique molecular drivers of MPNSTs (e.g., *NF1* loss, *SUZ12*/*PRC2* alterations). Dedicated trials focusing exclusively on MPNSTs, as opposed to pan-sarcoma basket trials, are essential to address the unmet needs of patients with MPNSTs.

Acknowledgements

This work was supported by the grant: the National Key Research and Development Program of China (No. 2023YFC2508500); and the National Natural Science Foundation of China (Nos. 82272951 and 82272953).

Compliance with ethics guidelines

Conflicts of interest Guo Zhao, Yale Jiang, Jiaxiu Ma, Shuhang Wang, and Ning Li declare no conflict of interest.

All authors have confirmed the publication. All primary data presented in this study are available from the corresponding author upon reasonable request. This manuscript is a database analysis study and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Data availability and compliance statement

The authors declare that the acquisition and subsequent use of all data presented in this manuscript comply fully with all relevant local, national, and international laws, regulations, ethical guidelines, and the terms of use associated with the original data sources.

The authors bear full legal responsibility for ensuring the legality of data acquisition and all subsequent uses.

References

1. Somatilaka BN, Sadek A, McKay RM, Le LQ. Malignant peripheral nerve sheath tumor: models, biology, and translation. Oncogene 2022; 41(17): 2405–2421
2. Korfhage J, Lombard DB. Malignant peripheral nerve sheath tumors: from epigenome to bedside. Mol Cancer Res 2019; 17(7): 1417–1428
3. Somaiah N, Paudyal B, Winkler RE, Van Tine BA, Hirbe AC. Malignant peripheral nerve sheath tumor, a heterogeneous, aggressive cancer with diverse biomarkers and no targeted standard of care: review of the literature and ongoing investigational agents. Target Oncol 2024; 19(5): 665–678
4. Akshintala S, Mallory NC, Lu Y, Ballman KV, Schuetze SM, Chugh R, Maki RG, Reinke DK, Widemann BC, Kim AR. Outcome of patients with malignant peripheral nerve sheath tumors

enrolled on sarcoma alliance for research through collaboration (SARC) phase II trials. Oncologist 2023; 28(5): 453–459

5. Cortes-Ciriano I, Steele CD, Piculell K, Al-Ibraheemi A, Eulo V, Bui MM, Chatzipli A, Dickson BC, Borcherding DC, Feber A, Galor A, Hart J, Jones KB, Jordan JT, Kim RH, Lindsay D, Miller C, Nishida Y, Proszek PZ, Serrano J, Sundby RT, Szymanski JJ, Ullrich NJ, Viskochil D, Wang X, Snuderl M, Park PJ, Flanagan AM, Hirbe AC, Pillay N, Miller DT. Genomic patterns of malignant peripheral nerve sheath tumor (MPNST) evolution correlate with clinical outcome and are detectable in cell-free DNA. Cancer Discov 2023; 13(3): 654–671
6. Suppiah S, Mansouri S, Mamatjan Y, Liu JC, Bhunia MM, Patil V, Rath P, Mehani B, Heir P, Bunda S, Velez-Reyes GL, Singh O, Ijad N, Pirouzmand N, Dalcourt T, Meng Y, Karimi S, Wei Q, Nassiri F, Pugh TJ, Bader GD, Aldape KD, Largaespada DA, Zadeh G. Multiplatform molecular profiling uncovers two subgroups of malignant peripheral nerve sheath tumors with distinct therapeutic vulnerabilities. Nat Commun 2023; 14(1): 2696
7. Yu Y, Wei C, Yue M, Zhang C, Wang Y, Wang Z. From benign neurofibromas to malignant peripheral nerve sheath tumors (MPNST): a gaming among multiple factors. Cell Oncol (Dordr) 2025; 48(4): 841–857
8. Soukar I, Fisher RJ, Bhagavatula S, Collard M, Cole PA, Alani RM. The CoREST complex is a therapeutic vulnerability in malignant peripheral nerve sheath tumors. Sci Rep 2025; 15(1): 10128
9. Stergiopoulos S, Getz KA, Blazynski C. Evaluating the completeness of ClinicalTrials. gov. Ther Innov Regul Sci 2019; 53(3): 307–317
10. Wang S, Ma P, Jiang N, Jiang Y, Yu Y, Fang Y, Miao H, Huang H, Tang Q, Cui D, Fang H, Zhang H, Fan Q, Wang Y, Liu G, Yu Z, Lei Q, Li N. Rare tumors: a blue ocean of investigation. Front Med 2023; 17(2): 220–230
11. Yao C, Zhou H, Dong Y, Alhaskawi A, Hasan Abdullah Ezzi S, Wang Z, Lai J, Goutham Kota V, Hasan Abdulla Hasan Abdulla M, Lu H. Malignant peripheral nerve sheath tumors: latest concepts in disease pathogenesis and clinical management. Cancers (Basel) 2023; 15(4): 1077
12. Voigt E, Quelle DE. FOXM1, MEK, and CDK4/6: new targets for malignant peripheral nerve sheath tumor therapy. Int J Mol Sci 2023; 24(17): 13596
13. Paudel SN, Hutzen B, Cripe TP. The quest for effective immunotherapies against malignant peripheral nerve sheath tumors: is there hope? Mol Ther Oncolytics 2023; 30: 227–237.
14. Wang S, Huang HY, Wu D, Fang H, Ying J, Bai Y, Yu Y, Fang Y, Jiang N, Sun C, Yu A, Fan Q, Xing S, Ni Y, Zhang W, Wu C, Ji X, Wang H, Guo Y, Tang Q, Wang Y, Tang Y, Li N. Platform study of genotyping-guided precision medicine for rare solid tumours: a study protocol for a phase II, non-randomised, 18-month, open-label, multiarm, single-centre clinical trial testing the safety and efficacy of multiple Chinese-approved targeted drugs and PD-1 inhibitors in the treatment of metastatic rare tumours. BMJ Open 2021; 11(6): e044543
15. Zheng R, Wang S, Zhao G, Wei W, Li N. Rare tumor list provide vast opportunities for novel drug development in China. Sci Bull (Beijing) 2025; 70(2): 132–134