Editorial Commentary

Future directions for the molecular therapy of rhabdomyosarcoma: how do we detect and investigate new, appropriate target mutations and populations?

Kenji Nakano

Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Correspondence to: Dr. Kenji Nakano, MD, PhD. Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Tokyo 135-8550, Japan. Email: kenji.nakano@jfcr.or.jp.

Comment on: Gupta AA, Xue W, Harrison DJ, *et al*. Addition of temsirolimus to chemotherapy in children, adolescents, and young adults with intermediate-risk rhabdomyosarcoma (ARST1431): a randomised, open-label, phase 3 trial from the Children's Oncology Group. Lancet Oncol 2024;25:912-21.

Keywords: Rhabdomyosarcoma; mammalian target of rapamycin inhibitor (mTOR inhibitor); temsirolimus; *FOXO1* fusion

Submitted Dec 24, 2024. Accepted for publication Apr 02, 2025. Published online Apr 27, 2025.
doi: 10.21037/tp-2024-605
View this article at: https://dx.doi.org/10.21037/tp-2024-605

The results of the phase III trial ARST1431 evaluating the efficacy and safety of adding temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, to the standard chemotherapy for pediatric-to-young adult patients with rhabdomyosarcoma were reported in 2024 by Gupta *et al.* (1). That trial evaluate the efficacy and safety of the addition of temsirolimus to multimodal therapy for intermediate-risk rhabdomyosarcoma patients. The multimodal therapy was comprised of alternating VAC/VI chemotherapy, i.e., VAC (vincristine, actinomycin-D, and cyclophosphamide) and VI (vincristine and irinotecan) plus definitive radiotherapy with or without sequential maintenance therapy by vinorelbine and oral cyclophosphamide. The trial's primary endpoint, i.e., the 3-year event-free survival (EFS) rate, did not differ significantly between the patients treated with or without temsirolimus [66.8%, 95% confidence interval (CI): 57.5–76.2% in the tensirolimus group and 64.8%, 95% CI: 55.5–74.1% in the without-temsirolimus group; hazard ratio (HR) 0.86, 95% CI: 0.58–1.26, log-rank P=0.44].

The investigational history of temsirolimus treatment for rhabdomyosarcoma

Temsirolimus, which was initially approved for the treatment of renal cell carcinoma (RCC) in adult malignancies (2), is administered intravenously and is one of the molecular targeted drugs whose investigation in relation to pediatric malignancies (including rhabdomyosarcoma) has been ongoing for many years. A preclinical study revealed the inhibition of rhabdomyosarcoma xenograft cell growth by temsirolimus (3), and this result was the rationale for planning and performing rhabdomyosarcoma clinical trials. In a phase II trial of temsirolimus monotherapy, only one of the 16 enrolled patients with rhabdomyosarcoma achieved disease stabilization by week 12, and no objective response was observed (4). However, in the randomized phase II ARST0921 trial that evaluated the efficacy of temsirolimus or the anti-VEGF antibody bevacizumab in combination with cytotoxic chemotherapy (vinorelbine and cyclophosphamide) administered to patients with recurrent rhabdomyosarcoma, the temsirolimus combination cohort (n=38) showed a 65% 6-month EFS rate (95% CI: 44–79%) and a 47% objective response rate (95% CI: 31.5–63.2%), which was superior to the efficacy in the bevacizumab combination cohort (5). The phase III ARST1431 trial's study design (1) was based on this result.

Due to the lack of information about the tolerability of temsirolimus combined with the standard induction chemotherapy regimen for rhabdomyosarcoma (i.e., alternating VAC/VI), the safety of this treatment was evaluated using the cases of the first 10 patients enrolled in the ARST1431 trial as the feasibility phase, and based on

the analysis results the temsirolimus combination with an alternating VAC/VI regimen was regarded as tolerable (6). As noted above, the result of the ARST1431 trial was negative, indicating that the strategy of adding temsirolimus to standard treatment does not provide a clinical benefit for intermediate-risk rhabdomyosarcoma patients.

Next step: How do we detect the appropriate targets for the appropriate patients?

In light of these investigational pathways and temsirolimus clinical trial results, what should we do in the future to develop molecularly targeted drugs for rhabdomyosarcoma? The ARST1431 trial applied a new strategy for rhabdomyosarcoma investigations; *FOXO1* fusion gene was used in the trial's patient enrollment and risk stratification. Until recently, clinical trials for individuals with newly diagnosed rhabdomyosarcoma were designed for patients at their respective prognostic risk levels: in low-risk groups, minimizing invasiveness and late toxicity while preserving curative potential could be the treatment goal, and in intermediate/high risk groups, more intensive treatment or the incorporation of new drugs for improving the response and prognoses could be applied (7).

The past risk classifications were based on the primary site of disease, the patients' age, cellular morphology, and/or immunostaining results. More detailed pathological features have recently become available, making the risk and prognosis classifications more detailed, objective, and accurate (8). The application of the *FOXO1* fusion gene as an assessment tool in the ARST1431 trial is part of this trend and is expected to improve the accuracy of identifying patients in need of novel therapies, i.e., those with poor prognoses.

However, the detection of a poor-prognosis patient population does not necessarily mean that molecularly targeted therapies, including mTOR inhibitors, are effective therapeutic targets. For adult malignancies, many molecular targeted drugs targeting the PI3K/mTOR/Akt signaling pathway have been investigated and approved, including temsirolimus treatment for RCC as noted above. Before the early 2010's, the clinical trials of these targeted drugs included patients with specific tumor origins regardless of the molecular profile, e.g., everolimus for RCC (9), hormone receptor-positive breast cancer (10), and neuroendocrine tumors (11), but specific mutations such as the PI3K inhibitor alpelisib were later detected and then required for clinical trial enrollment (12).

Concerning adult soft tissue sarcomas, the mTOR inhibitor nab-sirolimus was approved for perivascular epithelioid cell tumor (PEComa) by the U.S. Food and Drug Administration based on the results of a phase II trial (AMPECT) in which the overall response rate was 38.7%, the median progression-free survival was 10.6 months, and the median overall survival was 53.1 months (13,14). PEComas are known to be related to the genetic alterations of the tuberous sclerosis complex (TSC), which is an autosomal dominant genetic disease due to losses of *TSC1* (9q34) or *TSC2* (16p13.3) genes which seem to have a role in the regulation of the PI3K/mTOR/Akt pathway, which could be an appropriate target for mTOR inhibitors (15).

Another challenge is that the current identification of such mutations is not yet sufficient to predict the efficacy of molecularly targeted therapies. Regarding mTOR inhibitors, a histology-agnostic clinical trial of everolimus that enrolled patients with any type of solid tumor with *TSC1*/*TSC2* or mTOR mutations did not show clinical benefits (16). Aside from mTOR inhibitors, there have been rhabdomyosarcoma clinical trials of molecular targeted drugs that explored biomarkers of target mutations such as an insulin-like growth factor-1 receptor (IGF-1R) inhibitor (biomarker: IGF-1R expression by immunohistochemistry) (17) and an anaplastic lymphoma kinase (ALK) inhibitor to ALK and/or MET alteration (18), but these trials did not obtain evidence of clinical benefits.

With the recent proliferation of whole gene panel testing, more knowledge has been attained regarding genetic mutations in rhabdomyosarcoma than ever before. Many potential new prognostic factors and therapeutic targets are observed in rhabdomyosarcoma, e.g., *TP53*, a well-known tumor suppressor gene that is mutated in many solid tumors, and the fusion gene *MYOD1-LR122R*, which has shown potential as a new poor prognostic factor in addition to *FOXO1* (19,20). There are also some known targetable mutations such as BRAF and fibroblast growth factor receptor (FGFR) have been observed in rhabdomyosarcoma patients even though extremely low rates (19,20); for these mutations, tumor agnostic targeting treatments have been investigated and/or approved to adult malignancies (21,22), so rhabdomyosarcoma patients with BRAF/FGFR mutations might benefit from receiving targeted therapies. The *FOXO1* fusion gene, introduced as a new prognostic factor as mentioned above, is not merely a prognostic factor. The details of the cell proliferation signaling pathway involving this fusion gene are becoming clear, and proteins that can be targeted in the pathway

and drugs that are candidates for targeted therapy are also emerging (20).

The future development of therapeutics for rhabdomyosarcoma is likely to focus more closely on the relationship between patients' genetic abnormalities and the therapeutic targets for those abnormalities. In these cases, the design of clinical trials that focus on individual cases (e.g., small number single-arm and/or n-of-1 trials rather than large randomized controlled trials such as the ARST1431) should be considered as precision medicine due to (I) the rarity of rhabdomyosarcoma, (II) the difficulty in collecting a large number of cases with each genetic mutation, and (III) the ethical difficulties involved in setting up a control arm (especially a placebo group) due to the large proportion of children with this cancer (23). Furthermore, in seeking regulatory approval, it is necessary to establish a causal relationship of a candidate target gene mutation to the development and progression of rhabdomyosarcoma by preclinical studies and consider how to ensure the cost of developing, supplying, operating, and maintaining a therapeutic agent.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Pediatrics*. The article has undergone external peer review.

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-2024-605/prf

Funding: None.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-2024-605/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Gupta AA, Xue W, Harrison DJ, et al. Addition of temsirolimus to chemotherapy in children, adolescents, and young adults with intermediate-risk rhabdomyosarcoma (ARST1431): a randomised, open-label, phase 3 trial from the Children's Oncology Group. Lancet Oncol 2024;25:912-21.
2. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-81.
3. Wan X, Shen N, Mendoza A, et al. CCI-779 inhibits rhabdomyosarcoma xenograft growth by an antiangiogenic mechanism linked to the targeting of mTOR/Hif-1alpha/VEGF signaling. Neoplasia 2006;8:394-401.
4. Geoerger B, Kieran MW, Grupp S, et al. Phase II trial of temsirolimus in children with high-grade glioma, neuroblastoma and rhabdomyosarcoma. Eur J Cancer 2012;48:253-62.
5. Mascarenhas L, Chi YY, Hingorani P, et al. Randomized Phase II Trial of Bevacizumab or Temsirolimus in Combination With Chemotherapy for First Relapse Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol 2019;37:2866-74.
6. Oberoi S, Qumseya A, Xue W, et al. Feasibility of combining temsirolimus to vincristine, dactinomycin, cyclophosphamide, and vincristine and irinotecan chemotherapy for children with intermediate-risk rhabdomyosarcoma: A report from Children's Oncology Group. Pediatr Blood Cancer 2023. [Epub ahead of print]. doi: 10.1002/pbc.30436.
7. Pappo AS, Dirksen U. Rhabdomyosarcoma, Ewing Sarcoma, and Other Round Cell Sarcomas. J Clin Oncol 2018;36:168-79.
8. Haduong JH, Heske CM, Allen-Rhoades W, et al. An update on rhabdomyosarcoma risk stratification and the rationale for current and future Children's Oncology Group clinical trials. Pediatr Blood Cancer 2022;69:e29511.

9. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.
10. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968-77.
11. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9.
12. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2019;380:1929-40.
13. Wagner AJ, Ravi V, Riedel RF, et al. nab-Sirolimus for Patients With Malignant Perivascular Epithelioid Cell Tumors. J Clin Oncol 2021;39:3660-70.
14. Wagner AJ, Ravi V, Riedel RF, et al. Phase II Trial of nab-Sirolimus in Patients With Advanced Malignant Perivascular Epithelioid Cell Tumors (AMPECT): Long-Term Efficacy and Safety Update. J Clin Oncol 2024;42:1472-6.
15. Martignoni G, Pea M, Reghellin D, et al. PEComas: the past, the present and the future. Virchows Arch 2008;452:119-32.
16. Adib E, Klonowska K, Giannikou K, et al. Phase II Clinical Trial of Everolimus in a Pan-Cancer Cohort of Patients with mTOR Pathway Alterations. Clin Cancer Res 2021;27:3845-53.
17. Schwartz GK, Tap WD, Qin LX, et al. Cixutumumab and temsirolimus for patients with bone and soft-tissue sarcoma: a multicentre, open-label, phase 2 trial. Lancet Oncol 2013;14:371-82.
18. Schöffski P, Wozniak A, Leahy MG, et al. The tyrosine kinase inhibitor crizotinib does not have clinically meaningful activity in heavily pre-treated patients with advanced alveolar rhabdomyosarcoma with FOXO rearrangement: European Organisation for Research and Treatment of Cancer phase 2 trial 90101 'CREATE'. Eur J Cancer 2018;94:156-67.
19. Shern JF, Selfe J, Izquierdo E, et al. Genomic Classification and Clinical Outcome in Rhabdomyosarcoma: A Report From an International Consortium. J Clin Oncol 2021;39:2859-71.
20. Hettmer S, Linardic CM, Kelsey A, et al. Molecular testing of rhabdomyosarcoma in clinical trials to improve risk stratification and outcome: A consensus view from European paediatric Soft tissue sarcoma Study Group, Children's Oncology Group and Cooperative Weichteilsarkom-Studiengruppe. Eur J Cancer 2022;172:367-86.
21. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. Nat Med 2023;29:1103-12.
22. Pant S, Schuler M, Iyer G, et al. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): an international, single-arm, phase 2 study. Lancet Oncol 2023;24:925-35.
23. Kyr M, Svobodnik A, Stepanova R, et al. N-of-1 Trials in Pediatric Oncology: From a Population-Based Approach to Personalized Medicine-A Review. Cancers (Basel) 2021;13:5428.

Cite this article as: Nakano K. Future directions for the molecular therapy of rhabdomyosarcoma: how do we detect and investigate new, appropriate target mutations and populations? Transl Pediatr 2025;14(4):769-772. doi: 10.21037/tp-2024-605