according to the fusion gene type was reported from a post-hoc analysis, with a progression-free survival of 19·4 months for patients with EWSR1–NR4A3 fusion and 4·1 months (0·7–7·5) for patients with TAF15–NR4A3 fusion. These results raised some questions, including whether sunitinib should be approved due to its better response compared with pazopanib, and whether tumour shrinkage and duration of response are more practical than RECIST to assess response to treatment for these tumours. Nevertheless, the clear descriptions of the promising effectiveness by tumour shrinkage and intensive analysis of the comparison of effectiveness between fusion gene types are noteworthy as important references in treatment trials for rare fusion gene-related sarcomas. In addition, the VEGF and Notch pathway activation of the sensitive group in the transcriptional analysis provides desired information for patients who want to use pazopanib. The elucidation between *EWSR1* and the VEGF or Notch pathways is awaited for other *EWSR1*-related sarcomas.

In soft tissue sarcomas, several rare histological subtypes have specific fusion genes, including clear cell sarcoma (*EWSR1–ATF1*), synovial sarcoma (*SS18–SSX*), alveolar rhabdomyosarcoma (*PAX3*, *PAX7–FOXO1*), myxoid liposarcoma (*FUS–DDIT3*), Ewing family tumours (*EWSR1–FLI1*, *ERG*, *ETV*, and *FEV*), alveolar soft part sarcoma (*ASPL–TFE3*), inflammatory myofibroblastic tumour (*TMP3*, *TMP4–ALK*), infantile fibrosarcoma (*ETV6–NTRK3*), Ewing sarcoma-like small blue round cell tumour (*CIC–DUX4*), and solitary fibrous tumour (*NAB2–STAT6*).[8] Although these fusion genes were identified decades ago, the molecular mechanism is still not used as a drug development target. It might be appropriate to develop a driver gene-oriented or signalling pathway-oriented drug development for each rare sarcoma rather than a stale trial for soft tissue sarcomas in general. Similar to the approval of pembrolizumab for microsatellite instability-high tumours,[9] it might be necessary to investigate the oncogenetic signalling pathway of each rare entity and develop a new statistical strategy for clinical trials in these rare populations. Therefore, for specific entities, the first-line drug might change from doxorubicin to molecular targeted drugs.

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The necessity for rigour in rare disease study design

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In *The Lancet Oncology*, Maud Toulmonde and colleagues[1] report the results from the phase 2 DESMOPAZ trial. The study findings suggest that pazopanib at a daily dose of 800 mg could be considered a valid treatment option for patients who have progressive growth of a desmoid tumour.[1] The study was described as a non-comparative randomised trial. The treatment population was randomly assigned to receive pazopanib or a chemotherapy combination of methotrexate and vinblastine at a ratio of 2:1. Desmoid tumour, also called aggressive fibromatosis, is a rare disease that does not have metastatic potential, but can be invasive and lead to substantial morbidity. Unfortunately, desmoid tumour can recur even after a complete resection. Common reasons for systemic therapy include multiple recurrences, unresectable tumours, and treatment of a

rapidly growing intra-abdominal tumour. A hallmark of this tumour is its unpredictability.[2]

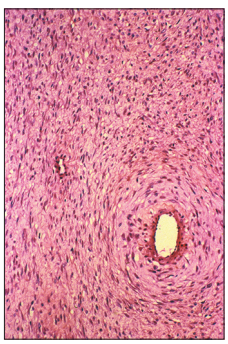
Strengths of the study include assessment of tumour shrinkage or progression in a uniform manner, collection of tumour specimens in a subset of patients for proteomic study, and inclusion of survival curves. However, aspects of the DESMOPAZ trial suggest that the conclusion that pazopanib could be considered a valid treatment option is premature.

The reference group of the non-comparative study was methotrexate and vinblastine and proportion of patients who had not progressed at a 6-month interval was chosen as the primary endpoint. The use of methotrexate and vinblastine as a reference treatment (as opposed to imatinib or sorafenib) was not fully justified, making it a curious choice given the known cytotoxic side effects (painful stomatitis) of this intravenous chemotherapy.[3] Despite the efficacy of tyrosine-kinase inhibitors (TKIs), the antitumour mechanisms of these drugs in desmoid tumour remain unclear.

The results clearly show the higher activity of pazopanib compared with methotrexate and vinblastine with a reported proportion of patients without progression at 6 months of 83·7% (95% CI 69·3–93·2) in the pazopanib group and 45·0% (23·1–68·5) in the methotrexate–vinblastine group. The detailed statistical plan required 80% or higher as a positive result. The 6-month progression-free survival in phase 2 studies of TKI's sorafenib and imatinib were 96% and 82%, but these latter data were not discussed in the current study.[4,5] In DESMOPAZ, pazopanib also had a higher progression-free survival at 12 months (86%) than did methotrexate and vinblastine (79%), but at 24 months methotrexate and vinblastine had a higher progression-free survival of 79% compared with 67% with pazopanib. Thus, there are different conclusions depending on the timepoint selected. Further, when compared with the ALLIANCE trial, a prospective randomised, controlled trial of sorafenib versus placebo, sorafenib has the highest progression-free survival at all three endpoints.[6] Would a log-rank assessment for pazopanib versus chemotherapy over the entire disease free survivorship reported have been even more informative?[7] Would a sensitivity analysis of non-progression at 6 months endpoint improve the generalisability and robustness?[8] Finally, neither best, nor overall response, nor 6 month non-progression correlated with overall survival as reported.

Should the French Sarcoma Group have considered that the dosage of pazopanib be reduced? Gounder and colleagues had already suggested a dose of sorafenib at 400 mg per day versus the approved dose of 800 mg.[4] In the ALLIANCE study, a randomised controlled, trial of sorafenib versus placebo, the dose selected was half the recommended dose at 400 mg per day and this TKI was clearly superior to placebo both in progression-free survival and the proportion of patients achieving a response.[6] Importantly, the proportion of patients who achieved a response to the placebo was 20%, which raises questions about use of response as a primary endpoint in these patients.

The concluding statement of this study is that pazopanib could be a valid treatment option for patients with progressive desmoid tumours. Despite the non-comparative study design, these findings when compared with other therapeutic options with higher progression-free survival at each time point or overall survival, challenge this claim. Perhaps a more useful comparison would be of pazopanib at 400 mg per day versus sorafenib at 400 mg per day to assess the long-term durability and clinical benefit. Unfortunately, financial backing for such a trial is highly unlikely outside of publicly funded trials. Going forward, more attention is clearly needed as to the appropriate clinical trial design in rare diseases such as desmoid tumours. The gold standard remains a randomised, controlled trial adequately powered to detect clinically meaningful endpoints of similarly efficacious therapies. In rare diseases, independent funding is badly needed to support the extent of collaboration needed to recruit the sufficiently large study population that rigorous inquiry requires.



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Management of high-risk endometrial cancer: are we there yet?

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Endometrial cancer is a diverse disease that includes varying stages and histologies. As a result, the design, completion, and interpretation of large randomised trials comparing adjuvant therapies for this disease, even when well conducted and well analysed, is problematic. This situation is especially true in the study of adjuvant therapy for advanced endometrial cancer, since many patients are diagnosed and treated surgically for early disease, with no indication for adjuvant treatment.

The PORTEC Study Group is to be commended for its work in refining the use of adjuvant therapy across various types of non-metastatic endometrial cancer. In the PORTEC-3 study, eligible patients included those with stages II and III and high-risk stage I endometrioid endometrial cancer and stages I–III serous and clear cell histologies.[1] With more than 650 women enrolled, the combination of systemic chemotherapy and radiotherapy was shown to improve outcomes compared with radiotherapy alone. For example, 5-year overall survival was 81·4% (95% CI 77·2–85·8) with chemoradiotherapy versus 76·1% (71·6–80·9) with radiotherapy alone (adjusted hazard ratio [HR] 0·70 [95% CI 0·51–0·97], p=0·034), and 5-year failure-free survival was 76·5% (95% CI 71·5–80·7) versus 69·1% (63·8–73·8; HR 0·70 [0·52–0·94], p=0·016). In the aftermath of these potentially practice-changing results, additional questions are raised.

First, do these findings apply broadly to all subgroups included in the study? In addition to the broad eligibility criteria of PORTEC-3 (ie, different tumour stages and histologies), many clinicopathological variables have prognostic significance, such as tumour grade, depth of myometrial invasion, patient age, lymphovascular space invasion (in the absence of positive lymph nodes), and the patient's general condition. Even within similar or identical subgroups, substantial differences exist among patients, such as extent of nodal dissection, which are potentially confounding variables.

Whether or not the results from PORTEC-3 are generally applicable across patient subgroups remains unknown. However, taking into account the statistical limitations of subgroup analyses, the therapeutic benefit of combined chemotherapy and radiotherapy (*vs* radiotherapy alone) appeared to remain confined to patients with stage III disease and those with serous carcinomas of all stages.

Second, is chemotherapy alone a sufficient form of adjuvant therapy? The Gynecologic Oncology Group (now NRG Oncology) did separate studies that overlap (in terms of patient eligibility) with PORTEC 3. In the NRG/GOG 249 study, investigators randomly assigned high-risk patients with stage I and II disease, including those with high-risk histologies, to chemotherapy plus vaginal cuff brachytherapy or pelvic radiotherapy with no chemotherapy. In the NRG/GOG 249 study, the chemotherapy plus vaginal cuff brachytherapy group did not show improved overall survival or relapse-free survival compared with the group that received pelvic radiotherapy alone. However, the incidence of nodal failure was significantly higher in the absence of pelvic radiation therapy, and acute toxicity was greater in the vaginal cuff brachytherapy group.[2] In the NRG/GOG 258 trial, patients with stage III–IVA uterine cancer were randomly assigned to received adjuvant chemotherapy alone or combined chemotherapy with pelvic radiotherapy (and para-aortic radiotherapy if nodal metastases were present). Although recurrence-free survival and overall survival were not improved with the combined therapy, nodal and vaginal failures were significantly lower when radiotherapy was given.[3]