until proven otherwise, we should assume that not detecting these cancers by mammographic screening leads to harm.

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I declare no competing interests.

1 Saadatmand S, Geuzinge HA, Rutgers EJT, et al. MRI versus mammography for breast cancer screening in women with familial risk (FaMRIsc): a multicentre, randomised, controlled trial. *Lancet Oncol* 2019; published online June 17. http://dx.doi.org/10.1016/S1470-2045(19)30275-X.

2 Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004; **351:** 427–37.

3 Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* 2005; **365:** 1769–78.

4 Warner E, Plewes DB, Hill KA, et al. Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 2004; **292:** 1317–25.

5 Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* 2005; **23:** 8469–76.

6 Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental breast MR imaging screening of women with average risk of breast cancer. *Radiology* 2017; **283:** 361–70.

7 Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018; **379:** 111–21.

Nanoparticle augmentation of radiotherapy in sarcoma

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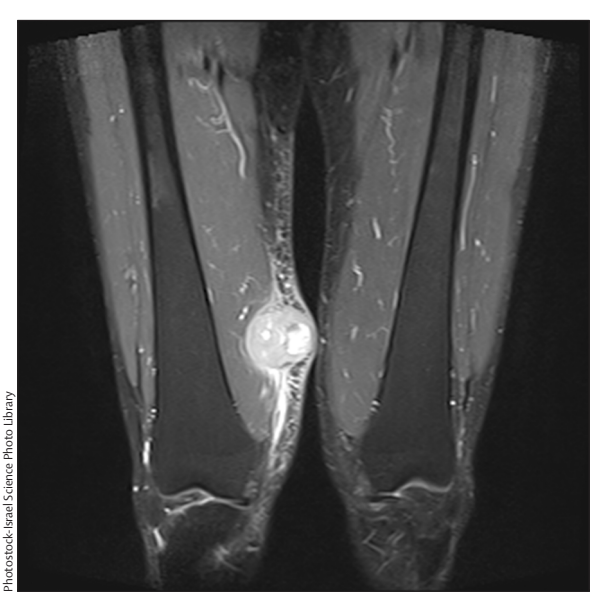
Soft-tissue sarcomas represent a heterogeneous group of mesenchymal tumours that have classically been defined by their tissue of origin. In the past few years, high-throughput efforts have characterised the genomic and epigenomic landscape of these malignancies, uncovering molecular mechanisms that underlie diverse biological properties and clinical behaviours.[1] However, despite this more comprehensive understanding, surgical resection remains the cornerstone of treatment for nearly all subtypes of extremity soft-tissue sarcoma. Whereas limb-sparing surgery alone has been associated with unacceptable levels of local recurrence,[2] surgery plus neoadjuvant or adjuvant radiotherapy has become the dominant approach for improving local control, largely obviating the need for amputation when gross negative resection margins can be achieved.[3] With the utility of radiotherapy well established, more recent efforts have focused on augmentation strategies to achieve optimal oncological outcomes in soft-tissue sarcoma of the extremities.



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In *The Lancet Oncology*, in a non-blinded, multicentre, randomised, controlled, phase 2–3 trial (Act.In.Sarc), Sylvie Bonvalot and colleagues tested a first-in-class nanoparticle, NBTXR3, as a radiotherapy enhancer for patients with non-metastatic, locally advanced soft-tissue sarcoma of the extremity or trunk wall.[4] NBTXR3 comprises a negatively charged phosphate coating, which permits uptake by tumour cells, and a core of inert, crystalline hafnium oxide (HfO_2), which is activated by external-beam radiotherapy to generate oxygen free radicals and augment the cell destruction induced by radiotherapy alone.[4] Previously, radioenhancement with NBTXR3 was shown by means of in-vitro cell line models and in-vivo tumour xenografts;[5] in their previous phase 1 trial, Bonvalot and colleagues showed its clinical activity in human patients,[6] providing equipoise for this subsequent randomised phase 2–3 trial.

Patients in this study were randomly assigned to receive either preoperative external-beam radiotherapy alone or following the administration of intratumoral NBTXR3. Patients in both groups received either intensity-modulated radiotherapy or 3D conformal radiotherapy to a dose of 50 Gy, followed

by surgery 4–8 weeks after completion of radiotherapy. The primary endpoint was pathological complete response, and secondary endpoints included safety, objective response, histological evaluation, negative resection margin prevalence, and limb amputation prevalence. In total, 180 patients were enrolled and randomly assigned, of whom 176 were included in this interim analysis reported at a median follow-up of 9·7 months (IQR 0·2–28·9). In the intention-to-treat analysis, the proportion of patients who achieved a pathological complete response was 16% (14 of 87) in the NBTXR3 experimental group and 8% (seven of 89) in the radiotherapy alone control group (p=0·044). Patients receiving NBTXR3 also had improved prevalence of R0 resection and histological tumour necrosis. Notably, although these parameters appeared to come at the expense of greater adverse events in the experimental group, there were negligible differences in adverse events related to radiation, and grade 3–4 events related to NBTXR3 injection were uncommon (eg, pain and ecchymosis in approximately 4%). Interestingly, despite an improved number of pathological complete responses with NBTXR3, no differences were observed between the treatment groups in the proportion of patients achieving an objective response on MRI according to RECIST criteria. This finding suggests that standard radiographic studies might not capture these specific tumour changes on treatment, and that novel radiomic strategies might be needed to detect real-time treatment responses.[7]

The long-term results of this study will be available after April, 2020, and in addition to final safety data, the authors will report results for local and distant recurrence. These data will be necessary to interpret whether the activity of NBTXR3 translates to improvements in meaningful clinical outcomes. The two previous randomised trials evaluating the addition of radiotherapy to limb-sparing surgery for soft-tissue sarcoma of the extremities both showed superior local control with radiotherapy—especially in patients with high-grade tumours—without parallel improvements in overall survival.[8,9] Owing to challenges in recruiting patients with soft-tissue sarcoma into clinical trials, because of the relative rarity of these tumours (and in the USA, because many patients are not treated at regional hight-volume centres), previous randomised studies have not had sufficient power to clearly show that improved local control naturally leads to a survival benefit, leaving experts in the area to make this extrapolation and to continue using local recurrence as a surrogate endpoint for survival.[10] Given these realities, randomised trials assessing modifications to radiotherapy will be unlikely to have adequate power to detect overall survival differences, and the sarcoma community will therefore need to continue relying on these surrogate markers, which the authors have wisely selected as outcomes in their final analysis.

During the past three decades, the addition of radiotherapy has facilitated a limb-sparing approach for extremity soft-tissue sarcoma. Clearly, however, additional strategies are needed to further minimise local recurrence and ultimately establish an overall survival benefit. In this well-designed trial, the authors show the promising efficacy of a novel nanoparticle that augments radiotherapy in a tumour-specific manner. The final results will be telling as to whether the addition of NBTXR3 can also improve local and distance recurrence, the established surrogates that reflect clinically meaningful outcomes in this complex disease.

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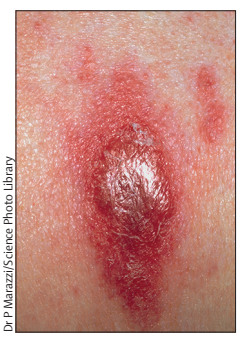
1 Cancer Genome Atlas Research Network. Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. *Cell* 2017; **171:** 950–65.
2 Cahlon O, Brennan MF, Jia X, Qin LX, Singer S, Alektiar KM. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limb-sparing surgery without adjuvant radiation. *Ann Surg* 2012; **255:** 343–47.
3 Haas RL, Gronchi A, van de Sande MAJ, et al. Perioperative management of extremity soft tissue sarcomas. *J Clin Oncol* 2018; **36:** 118–24.
4 Bonvalot S, Rutkowski PL, Thariat J, et al. NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft tissue sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial. *Lancet Oncol* 2019; published online July 8. http://dx.doi.org/10.1016/S1470-2045(19)30326-2.
5 Pottier A, Borghi E, Levy L. New use of metals as nanosized radioenhancers. *Anticancer Res* 2014; **34:** 443–53.
6 Bonvalot S, Le Pechoux C, De Baere T, et al. First-in-human study testing a new radioenhancer using nanoparticles (NBTXR3) activated by radiation therapy in patients with locally advanced soft tissue sarcomas. *Clin Cancer Res* 2017; **23:** 908–17.
7 Messiou C, Bonvalot S, Gronchi A, et al. Evaluation of response after pre-operative radiotherapy in soft tissue sarcomas; the European Organisation for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and Imaging Group recommendations for radiological examination and reporting with an emphasis on magnetic resonance imaging. *Eur J Cancer* 2016; **56**: 37–44.

8 Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol* 1996; **14:** 859–68.
9 Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998; **16:** 197–203.
10 Zer A, Prince RM, Amir E, Abdul Razak A. Evolution of randomized trials in advanced/metastatic soft tissue sarcoma: end point selection, surrogacy, and quality of reporting. *J Clin Oncol* 2016; **34:** 1469–75.

Anti-KIR3DL2 therapy in the treatment of Sézary syndrome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In *The Lancet Oncology*, Bagot and colleagues[1] present the results of an international, multicentre, open-label, phase 1 study evaluating IPH4102 in patients with relapsed or refractory cutaneous T-cell lymphoma. IPH4102 is a humanised, first-in-class, monoclonal antibody that targets KIR3DL2, a cell surface protein widely expressed in cutaneous T-cell lymphoma, and predominantly in its leukaemic form, Sézary syndrome. The binding of the drug with the target induces antibody-dependent cell cytotoxicity and phagocytosis.[2]

The study was composed of two parts (a dose-escalation and cohort expansion) with different inclusion criteria. Eligible patients for the dose-escalation stage had relapsed or refractory cutaneous T-cell lymphoma of stage IB or higher after at least two previous systemic therapies, and with at least 5% of skin-infiltrating mononuclear cells or phenotypically aberrant circulating T-cells expressing KIR3DL2. However, KIR3DL2 expression was not an inclusion criterion for cohort expansion, which included patients in two disease subsets, Sézary syndrome or mycosis fungoides, with evidence of large-cell transformation. The choice of Sézary syndrome is related to the finding that KIR3DL2 is expressed in more than 85% of patients with Sézary syndrome, whereas its expression in mycosis fungoides is more heterogeneous.[3] All patients in the cohort expansion received a flat intravenous dose of 750 mg IPH4102.

The key messages of this study are the favourable safety profile of the drug (primary endpoint), coupled with potentially relevant clinical activity. Most common adverse events were grade 1 or 2 (peripheral oedema in 12 [27%] of 44 patients; and fatigue in nine [20%] patients). Six grade 3 or 4 treatment-related adverse events were described, of which three were grade 3 lymphopenia. One death due to hepatitis occurred in a patient 6 weeks after treatment discontinuation due to progression in association with human herpe svirus 6B liver infection. With regard to clinical activity, the treatment induced substantial responses in 35 patients with Sézary syndrome; 15 (43% [95% CI 28·0–59·1]) achieved a global overall response, the proportion who achieved an overall response in the blood was 19 (56%) of 34, and median response duration was 13·8 months (IQR 7·2–not reached).

Sézary syndrome represents the erythrodermic and leukaemic variant in the spectrum of cutaneous lymphomas, accounting for 2% of all cases, with a poor prognosis and a disease-specific survival of 36% at 5 years.[4] The treatment of Sézary syndrome remains a challenge in terms of responses to treatment, response duration, side-effects, and impairment of the quality of life; thus, these patients have a high clinical need for effective treatments.

According to the European Organisation for Research and Treatment of Cancer guidelines,[5] first-line treatments for Sézary syndrome are extracorporeal photochemotherapy alone or in combination, low-dose methotrexate, and chlorambucil plus prednisone, and second-line approaches include chemotherapy (gemcitabine and pegylated liposomal doxorubicin), alemtuzumab, and allotransplant. Allogeneic stem-cell transplantation represents the only therapy with curative intent in cutaneous T-cell lymphoma, although it is associated with relevant treatment-related morbidity and mortality and warrants a careful patient selection.

The retrospective multicentre analysis of 853 advanced-phase patients with Sézary syndrome or mycosis fungoides done by the Cutaneous Lymphoma International Consortium[6] highlighted that these patients have a great heterogeneity of treatment approaches (more than 20 different therapeutic methods with 36% of patients receiving four or more treatment lines). Extracorporeal photochemotherapy alone or in combination with immune modulators or retinoids was the most frequent treatment in erythrodermic cutaneous T-cell lymphoma and patients with Sézary syndrome. Chemotherapy as first line treatment was found to be associated with a significantly increased risk of death or