personalised treatment for malignant pleural mesothelioma, with the potential to improve outcomes and enhance patients' quality of life.

In summary, the publication of these two promising studies is an important and encouraging advance for malignant pleural mesothelioma. ICIs have had an enormous impact on the treatment of other malignancies with poor prognoses, such as melanoma and non-small-cell lung cancer. They might do the same for malignant pleural mesothelioma in time; however, for now all efforts must be directed toward supporting definitive trials, for it is these that have the potential to transform the treatment landscape of malignant pleural mesothelioma.

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1 Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax* 2018; **73** (suppl 1): i1–30.
2 Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21:** 2636–44.
3 Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016; **387:** 1405–14.
4 Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol* 2019; published online Jan 16. http://dx.doi.org/10.1016/S1470-2045(18)30765-4.
5 Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet Respir Med* 2019; published online Jan 16. http://dx.doi.org/10.1016/S2213-2600(18)30420-X.
6 Ceresoli GL, Zucali PA, De Vincenzo F, et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer* 2011; **72:** 73–77.
7 Quispel-Janssen J, van der Noort V, de Vries JF, et al. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. *J Thoracic Oncol* 2018; **13:** 1569–76.
8 Calabrò L, Morra A, Giannarelli D, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. *Lancet Respir Med* 2018; **6:** 451–60.
9 Calabrò L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. *Lancet Respir Med* 2015; **3:** 301–09.
10 Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol* 2017; **18:** 1261–73.

More evidence for implant-based breast reconstruction


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The scarcity of randomised controlled trials is a key issue in surgical research. The dearth of trials results from several methodological challenges, and because of surgeons' reluctance to be involved in study design.[1] Nonetheless, experimental research is crucial to the generation of high-quality data to assess the effects of new procedures or devices before introducing them into standard practice. This insufficiency of high-level evidence becomes a paradox when dealing with implant-based breast reconstruction. Despite this technique being the most common surgical procedure for breast reconstruction worldwide, the number of patients involved in randomised trials is very low.[2]

In the iBRA study, Shelley Potter and colleagues investigated short-term outcomes of immediate implant-based breast reconstruction with or without mesh in a large prospective cohort of 2108 patients (2655 reconstructions) across 81 breast and plastic surgical units in the UK.[3] This study was designed to identify key questions and suitable outcomes to be investigated with adequate power in forthcoming randomised trials. Mesh-based reconstruction (1376 [65%] patients) was by far the most common method, followed by dermal sling implants (440 [21%] patients) and non-mesh submuscular or subfascial implants (181 [9%] patients). The results highlight that the proportion of patients with complications is far higher than proposed standards: nearly a tenth of patients had implant loss, almost a fifth were readmitted or re-operated for complications within 3 months, and a quarter needed treatment for infection.[3,4] Further, these levels of complications have not decreased since the 2008–09 UK National Mastectomy and Breast Reconstruction Audit (NMBRA).[5] In our opinion, these worrisome conclusions could be a direct consequence of the poor evidence available to inform choices about the best method of reconstruction to use, which generates unreliable and confusing information about indications, risk factors, and outcomes.

Although new trials are awaited, according to the findings of the iBRA cohort it is unlikely that they will be based on comparisons between two-stage and one-stage breast reconstruction. The latter has gained popularity (78% of patients in iBRA had a one-stage reconstruction planned), probably thanks to the generalised assistance of scaffolds (86% of biological meshes and 82% of synthetic devices were implanted in a one-stage procedure), which did not produce any significant difference in implant loss, infection, re-operation, or readmission. New research must further investigate the association between key short-term outcomes and risk factors as identified by the iBRA study. Infection, implant loss, readmissions, and re-operation were significantly associated with body-mass index (BMI) and smoking, whereas previous radiotherapy was a risk factor only for infection, and operative time only for re-operation.

The high incidence of infection shown by the iBRA findings is concerning, and we recommend analysis of this outcome according to antibacterial prophylaxis.

Despite the fact that all risk factors should be assessed in clinical practice to keep complications under control, we agree with Potter and colleagues that the inclusion criteria of further randomised trials should not be too restrictive. Eliminating subgroups from trials according to potential risk factors (ie, on the basis of BMI, smoking, previous radiotherapy, or duration of surgery) might prevent a conclusive and reliable investigation.

While the surgical community awaits newly designed trials, we wonder how these investigators' observations could be translated into safer clinical practice now, to bring the safety outcomes of implant-based reconstructions within the proposed standards. Potter and colleagues note the potential usefulness of a period of neoadjuvant medical treatment to allow patients to modify risk factors such as smoking and BMI before surgery. This assumption must be supported by data because some studies report that weight increase can be associated with chemotherapy.[6] We would suggest instead that pre-operative systemic treatment be used as an option to reduce the numbers of mastectomies.[7] Clearly, this approach might not reduce the relative number of complications, but it could affect the absolute number of sequelae.

It is interesting to notice that a Dutch trial,[8] by contrast with iBRA, concluded that two-stage reconstructions might be safer than one-stage techniques with acellular dermal matrix, and that one of the risk factors for complications is breast size.[9] For this reason, a robust oncoplastic assessment, including standard evaluation of breast morphology, glandular structure, and patterns of vascularity, should be done before selecting the most appropriate reconstructive technique.[10]

We applaud Potter and colleagues for preparing the ground for a future useful randomised controlled trial in implant-based breast reconstruction. These findings will hopefully clarify the status quo, and improve outcomes through a proper and evidence-based patient selection.

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1 Potter S, Mills N, Cawthorn S, Donovan J, Blazeby J. Time to be BRAVE: is educating surgeons the key to unlocking the potential of randomised clinical trials in surgery? A qualitative study. *Trials* 2014; **15:** 80.
2 Rocco N, Rispoli C, Moja L, et al. Different types of implants for reconstructive breast surgery. *Cochrane Database Syst Rev* 2016; **5:** CD010895.
3 Potter S, Conroy EJ, Cutress RI, et al. Short-term safety outcomes of immediate implant-based breast reconstruction with and without mesh after mastectomy (iBRA): a multicentre, prospective cohort study. *Lancet Oncol* 2019; published online Jan 9. http://dx.doi.org/10.1016/S1470-2045(18)30781-2.
4 Rainsbury D, Willett A. Oncoplastic breast reconstruction: guidelines for best practice: ABS and BAPRAS, 2012. http://www.bapras.org.uk/docs/default-source/commissioning-and-policy/final-oncoplastic-guidelines---healthcare-professionals.pdf?sfvrsn=0 (accessed Dec 28, 2018).
5 Jeevan R, Cromwell DA, Browne JP, et al. Findings of a national comparative audit of mastectomy and breast reconstruction surgery in England. *J Plast Reconstr Aesthet Surg* 2014; **67:** 1333–44.
6 Arpino G, De Angelis C, Buono G, et al. Metabolic and anthropometric changes in early breast cancer patients receiving adjuvant therapy. *Breast Cancer Res Treat* 2015; **154:** 127–32.
7 Criscitiello C, Curigliano G, Burstein HJ, et al. Breast conservation following neoadjuvant therapy for breast cancer in the modern era: are we losing the opportunity? *Eur J Surg Oncol* 2016; **42:** 1780–86.
8 Dikmans RE, Negenborn VL, Bouman MB, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *Lancet Oncol* 2017; **18:** 251–58.
9 Negenborn VL, Dikmans REG, Bouman MB, et al. Predictors of complications after direct-to-implant breast reconstruction with an acellular dermal matrix from a multicentre randomized clinical trial. *Br J Surg* 2018; **105:** 1305–12.
10 Catanuto G, Dumitru D, Rancati A, Rocco N, Nava MB. Quality of life after breast reconstruction—the BRIOS study. *Lancet Oncol* 2018; **19:** e578.