the predictions of standard quantum theory, no matter how many dimensions are assigned to the real spaces.

Renou and co-workers put forward a measurable quantity whose value can distinguish between the real and complex frameworks — and this quantity has now been measured[2,3]. In two experimental papers, the value of this key quantity (or, in one case, a closely related quantity[3]) was found to conflict strongly with the real-number framework. Both experimental groups used binary quantum objects, 'qubits', as prescribed by Renou *et al.*, but the actual physical systems were quite different: superconducting qubits in one case[2] and photons in the other[3].

As Renou *et al.* point out, their work does not imply that the empirical content of quantum theory cannot be captured by a model that uses only real numbers[8,9]. Indeed, in 1960, Ernst Stueckelberg presented precisely this kind of model[10]. There is no contradiction here. A representation of a composite system using Stueckelberg's formulation is not based on the real tensor product — rather, it is based on a real-number encoding of the complex tensor product. So even though there are no imaginary numbers in Stueckelberg's theory, the structure of complex-number arithmetic is still present.

The complex numbers are special in another way. In the two-site electron example, the 4D real space allows too many possibilities — more than can actually be measured — and so the theory needs to be restricted. In standard quantum theory, by contrast, there is a perfect match between the structure of the abstract space and the physics that can be observed.

For some quantum physicists, Renou and colleagues' work will raise a long-standing question anew: why is the world structured such that complex numbers have a fundamental role? In the century since quantum theory was first developed, many answers to this question have been proposed. The current findings provide a concrete counterexample to the most natural real-number analogue of quantum theory, thereby strengthening the evidence that the complex structure is essential. Conceivably, a deeper explanation of this intriguing feature of the physical world is still waiting to be discovered.

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1. Renou, M.-O. *et al. Nature* **600**, 625–629 (2021).
2. Chen, M.-C. *et al. Phys. Rev. Lett.* (in the press); preprint at https://arxiv.org/abs/2103.08123
3. Li, Z.-D. *et al. Phys. Rev. Lett.* (in the press).
4. Schrödinger, E. *Math. Proc. Camb. Phil. Soc.* **31**, 555–563 (1935).
5. Pál, K. F. & Vértesi, T. *Phys. Rev. A* **77**, 042105 (2008).
6. McKague, M., Mosca, M. & Gisin, N. *Phys. Rev. Lett.* **102**, 020505 (2009).
7. Moroder, T., Bancal, J.-D., Liang, Y.-C., Hofmann, M. & Gühne, O. *Phys. Rev. Lett.* **111**, 030501 (2013).
8. Dyson, F. J. *J. Math. Phys.* **3**, 1199–1215 (1962).
9. Boaz, J. C. *Found. Phys.* **42**, 819–855 (2012).
10. Stueckelberg, E. C. G. *Helv. Phys. Acta* **33**, 727–752 (1960).

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Medical research

Stomach cancer gets a triple punch of therapy

Myriam Chalabi

Harnessing immune cells to target tumours is a growing trend. The results of a clinical trial combining such treatment with other standard therapies for gastric cancer have altered medical practice — and more changes are to come. **See p.727**

Gastric cancer is a highly aggressive disease. Janjigian *et al.*[1] present clinical data on page 727 that point to a way to improve outcomes for people who have this type of tumour.

Expression of the protein HER2 is found in approximately 20% of gastric cancers. For people who have such a HER2-positive tumour, the use of an antibody (a drug called trastuzumab) that blocks HER2 function improves outcomes when given with chemotherapy. The combination of immunotherapy (a treatment called immune-checkpoint blockade that stimulates an antitumour immune response) with chemotherapy is beneficial for those people whose gastric tumours lack HER2 expression[2]. But what if immunotherapy were combined with trastuzumab and chemotherapy (Fig. 1)? Could that improve outcomes for people with a HER2-positive gastric cancer that has spread elsewhere in the body? Janjigian and colleagues investigated these clinically relevant questions.

HER2 belongs to a family of transmembrane receptors called tyrosine kinases, and it mediates cell proliferation and development. In several types of human cancer, tumour-promoting (oncogenic) mutations have been found in the gene that encodes HER2, and these mutations are associated with aggressive tumours that have a high potential to spread to other locations in the body (metastatic tumours). Trastuzumab blocks HER2-mediated signalling, inhibiting both the downstream pathways and the cell cycle.

Another important mechanism of action of trastuzumab is its ability also to bind to the Fc receptor of immune cells — especially those of natural killer cells. This leads to the activation and subsequent recruitment of other types of immune cell in addition to natural killer cells. Trastuzumab was first introduced in the clinic for the treatment of HER2-positive breast cancer, and although it is effective in some cases when used alone[3], there is a better (synergistic) response when the treatment is combined with chemotherapy[4]. In people with HER2-positive gastric cancer, the addition of trastuzumab treatment to chemotherapy improves survival compared with the use of chemotherapy alone[5].

The combination of immune-checkpoint blockade (which targets the protein PD-1) and chemotherapy became a standard-of-care treatment (a therapy that is routinely used) in the United States in 2021, because it increases the length of survival for people with metastatic gastric cancers[2]. This therapeutic effect seems to be strongest in individuals whose tumour and immune cells express the protein PD-L1. PD-1 has an inhibitory effect on the immune system through its interaction with PD-L1, and, therefore, PD-1 blockade leads to the activation of immune cells (called cytotoxic T cells) that can kill cancer cells. Preclinical animal studies[6] have shown that trastuzumab treatment leads to an increase in the levels of cytotoxic T cells, which can subsequently be stimulated by PD-1 blockade, leading to an improved response if antibodies targeting HER2 and antibodies blocking PD-1 are combined.

Janjigian and colleagues conducted a phase III randomized, double-blind clinical trial. This focused on people with previously untreated HER-2-positive cancers of the stomach or gastro-oesophageal junction (the site at which the oesophagus meets the stomach) that were metastatic or not amenable to surgical treatment (unresectable). The participants received either a PD-1-blocking antibody (called pembrolizumab) or a placebo, together with trastuzumab and the treating physician's choice of one of two standard-of-care chemotherapy regimens.

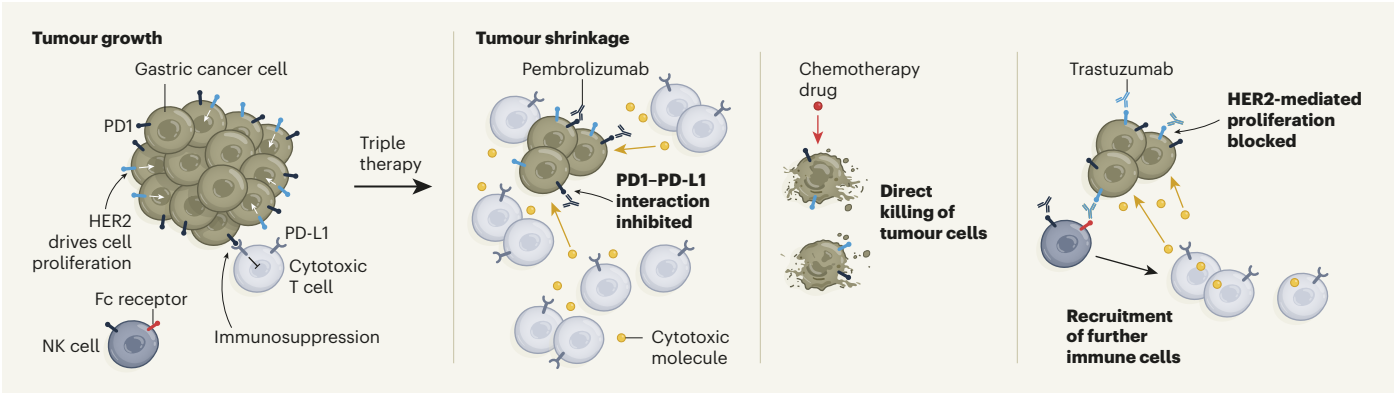

Figure 1 | A three-pronged approach to treating stomach cancer. A range of factors contribute to the aggressive growth of gastric tumours. Some of these cancers express the protein HER2, which drives cell proliferation. Moreover, anticancer responses by immune cells such as natural killer (NK) cells or cytotoxic T cells can be suppressed. One mechanism of such immunosuppression is an interaction between the proteins PD1 and PD-L1. Janjigian *et al.*[1] present results of a phase III clinical trial that tested the effect of combining three treatments (the antibody pembrolizumab, chemotherapy and the antibody trastuzumab). Pembrolizumab binds to PD1 and prevents it from binding to PD-L1 to inhibit immune cells. This prevents immunosuppression of cytotoxic T cells, allowing these cells to release cytotoxic molecules that kill cancer cells. Chemotherapy directly kills cancer cells. Trastuzumab binds both the HER2 receptor and the Fc receptor on NK cells. This treatment prevents HER2 from boosting cell division, and also activates NK cells, which results in the recruitment of cytotoxic T cells.

The authors present efficacy data from the planned interim analysis for the first 264 enrolled individuals. Of these, 133 were allocated to the pembrolizumab arm of the study and 131 to the placebo arm.

The authors report that, by combining pembrolizumab with chemotherapy and trastuzumab, a substantial decrease in tumour size (measured through an assessment of tumour shrinkage that is called the objective response) was observed in 74% of the individuals, compared with 52% of the people who received placebo plus chemotherapy and trastuzumab. Not only did more people respond to the pembrolizumab-containing treatment, but the tumour shrank further in the people who received pembrolizumab than in those who didn't. For instance, a complete response (the disappearance of all tumour locations on scans) was more frequent with pembrolizumab treatment than with the placebo (11% compared with 3% of individuals).

In the past decade, immunotherapy has revolutionized the treatment of cancer. One of the most crucial features of immunotherapy is the duration of the response. In contrast to most anticancer treatments, the effect of immunotherapy in a subset of patients is maintained long after the treatment has been stopped. This is referred to as the plateau, and corresponds to the flattening of survival-time curves as time passes.

Although Janjigian and colleagues' results are impressive in terms of the tumour responses, the findings also demand careful interpretation. The authors observe only a small difference in the median duration of the response between the two treatment arms (1.1 months longer in the arm with pembrolizumab). Data on progression-free survival (time until tumour growth resumes) and overall survival (survival duration) will be essential to fully understand the long-term effects of the proposed treatment. It is expected, and much hoped for, that the observed improvement in tumour responses will also lead to an improved survival time. Those data are expected to become available in the next few years.

Side effects of immunotherapy are distinct from those of conventional anticancer treatments and are directly linked to the activation of the immune system. By blocking PD-1, the guard against autoimmunity is let down, and this might lead to unwanted immune reactions in other tissues and organs. However, the toxicity profile after the inclusion of pembrolizumab was manageable in this study, indicating that this is a feasible and safe treatment.

> **"In the past decade, immunotherapy has revolutionized the treatment of cancer."**

Given that PD-1 blockade seems to complement trastuzumab and chemotherapy for the treatment of HER2-positive gastric cancers, Janjigian and colleagues' study has moved the field forwards, and their findings could be the next, long-awaited development in the treatment of these cancers. Although the US Food and Drug Administration has given its approval (through an accelerated process for drugs that fill an unmet medical need), the European Medicines Agency has not, and this treatment is expected to become available in Europe only if survival data show that the addition of pembrolizumab provides a clear benefit. Considering that this is a costly therapy, there is a need to find predictive biomarkers that can be used to identify people who are most likely to respond to this proposed treatment regimen.

In the meantime, the field is evolving quickly: advances include the development of promising new treatments for HER2-positive gastric (and other) cancers that use trastuzumab deruxtecan, an antibody–drug conjugate that combines chemotherapy with trastuzumab in a single drug[7]. Another big step forward will be the ability to provide treatment at an earlier stage of the disease, before the tumour has spread to distant locations. The immune systems of people with early-stage cancer are less suppressed than are those of people with cancer at a later stage. Therefore, individuals who have early-stage cancer might be more amenable to stimulation by immunotherapy combinations, which might help to achieve the ultimate goal — a cure for more people.

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1. Janjigian, Y. Y. *et al. Nature* **600** 727–730 (2021).
2. Janjigian, Y. Y. *et al. Lancet* **398**, 27–40 (2021).
3. Baselga, J. *et al. J. Clin. Oncol.* **14**, 737–744 (1996).
4. Slamon, D. J. *et al. N. Engl. J. Med.* **344**, 783–792 (2001).
5. Bang, Y.-J. *et al. Lancet* **376**, 687–697 (2010).
6. Gall, V. A. *et al. Cancer Res.* **77**, 5374–5383 (2017).
7. Shitara, K. *et al. N. Engl. J. Med.* **382**, 2419–2430 (2020).

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