THE PROBLEM WITH PLATINUM

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Ovarian cancer is difficult to treat, largely because tumours are often found late and develop resistance to initial treatment: platinum-based therapy. New approaches promise to break through the platinum barrier. By **David Holmes**; *illustration by* **Lucy Reading-Ikkanda.**

BIG PROBLEM, LITTLE PROGRESS

BAD TIMING

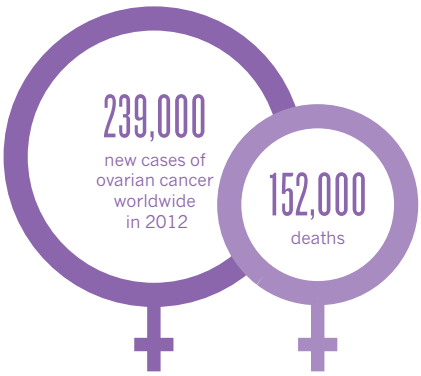
The earlier that ovarian cancer is identified, the better the odds are that treatment will be successful. Women are not screened because current methods are not reliable enough to predict whether or not women have the disease. Early symptoms of ovarian cancer are often confused with irritable bowel or premenstrual syndrome, so most people are diagnosed with late-stage disease.

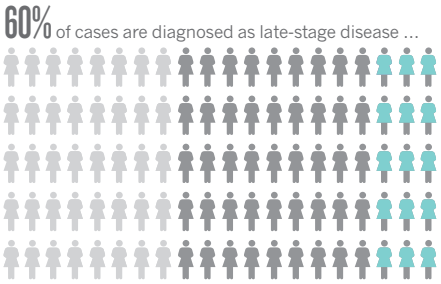
THE TOLL OF RESISTANCE

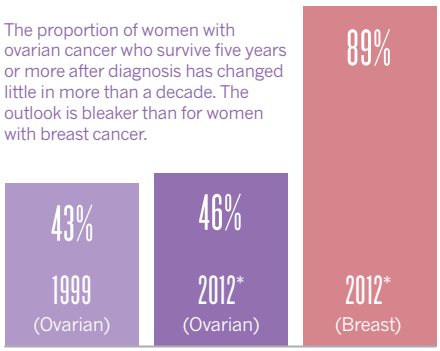
Of US women diagnosed with ovarian cancer, 60% have late-stage disease. Most of these initially respond well to treatment with a combination of paclitaxel (a drug that interferes with cell division) and carboplatin (a platinum-based drug that damages cancer-cell DNA). However, more than half will relapse within 18 months of diagnosis.

SLOW PROGRESS

The late stage at which most ovarian cancers are diagnosed, the fact that such a high proportion become resistant to platinum-based chemotherapy, and the small number of approved alternatives to platinum therapy, mean that ovarian cancer has a relatively low five-year survival rate. In the United States, for example, it is just 45.6%.

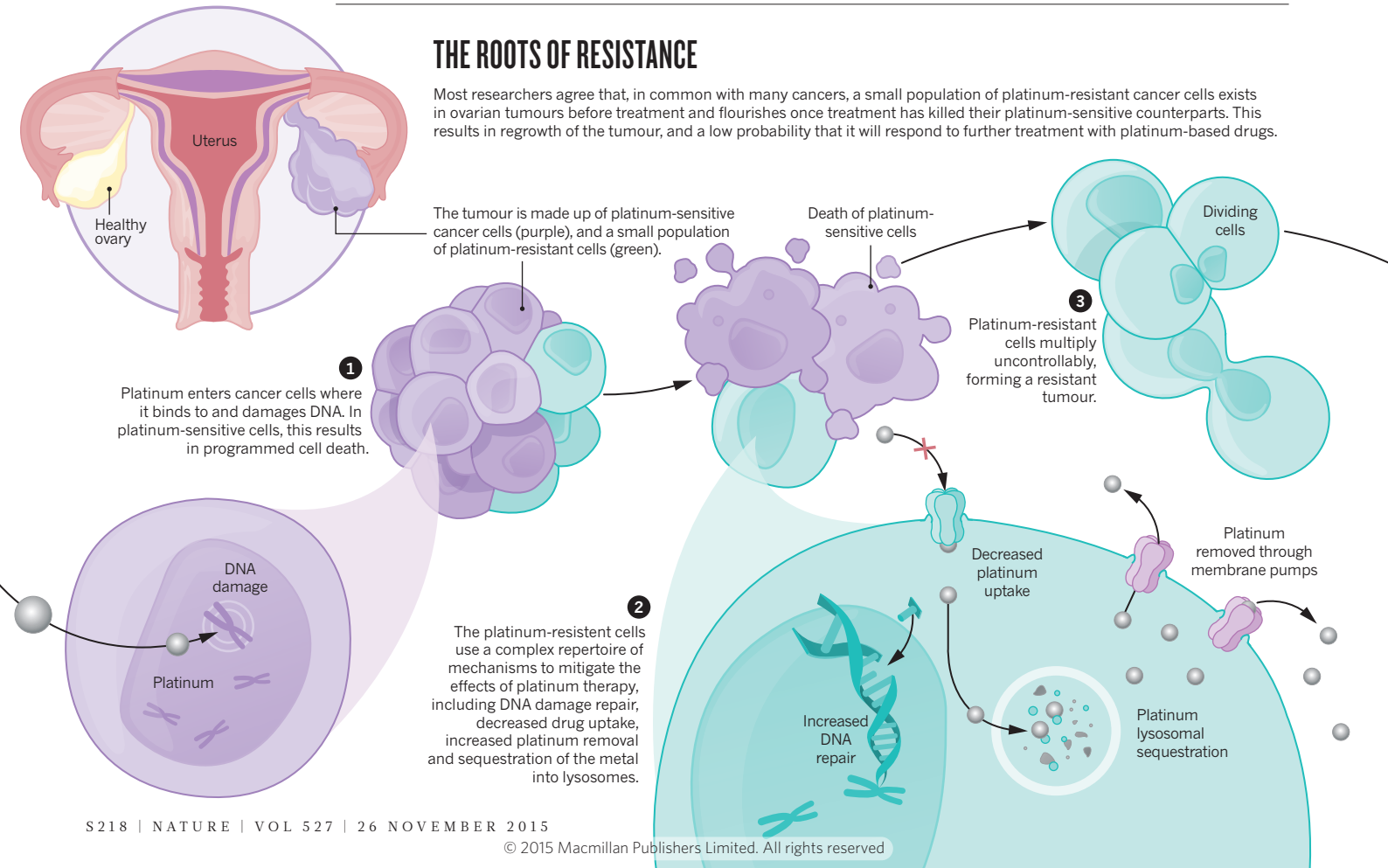






THE ROOTS OF RESISTANCE

Most researchers agree that, in common with many cancers, a small population of platinum-resistant cancer cells exists in ovarian tumours before treatment and flourishes once treatment has killed their platinum-sensitive counterparts. This results in regrowth of the tumour, and a low probability that it will respond to further treatment with platinum-based drugs.



THE NEW WAVE OF THERAPY

From priming the immune system to fight ovarian tumours to cutting off the cancer's blood supply, researchers are testing a variety of ways to overcome resistance to platinum-based chemotherapy.

SCRAMBLING THE CODE

Ramping up DNA-repair pathways is one of the ways that cancer cells resist the DNA-damaging effects of platinum. If those DNA-repair pathways could be dampened down it might be possible to resensitize cancer cells to platinum. There are several drugs in development that aim to do just that. PARP inhibitors disrupt the mechanism by which damaged parts of DNA are removed, and the drug trabectedin binds directly to and damages the DNA. Both have shown early promise. The drug topotecan blocks the action of the enzyme TOP1, which helps to repair DNA damage, and is already licensed for the treatment of recurrent ovarian cancer. However, its effect on overall survival is limited.

DNA damage and disruption of DNA-repair mechanisms leads to cell death.

IMMUNE BOOSTERS

Priming the immune system to recognize and attack cancer cells might be an effective way of stunting the growth of tumours in people with recurrent ovarian cancer. A UK trial called TRIOC is testing whether the TroVax vaccine, which has this priming effect, can boost an individual's anticancer immune response enough to slow the growth of recurrent ovarian tumours and delay the need for a second line of chemotherapy. In the trial, the vaccine is given to people who have high levels of a marker called CA125 in their blood, which indicates that a cancer may have returned.

The vaccine-primed immune system releases antibodies and T cells to bind to antigens on the cell surface.

HORMONE THERAPY

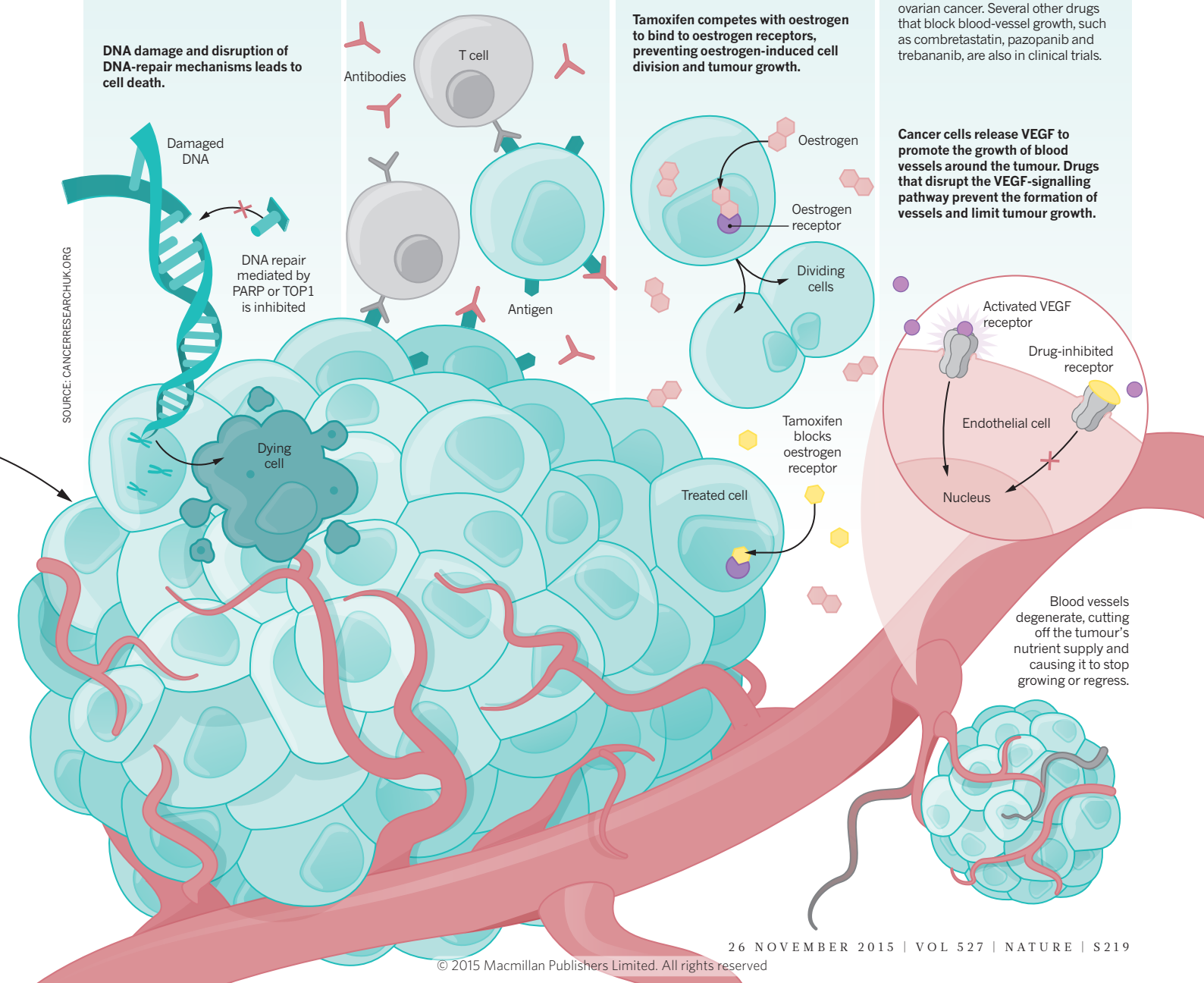
Similar to many breast cancers, some ovarian cancer cells have oestrogen receptors on their surface and may require the hormone to grow and spread. This has led researchers to test the hormone treatment tamoxifen, which is often used to treat oestrogen-receptor-positive breast cancers, in women with advanced ovarian cancer. Tamoxifen blocks oestrogen from reaching the cells and has been shown to work for a small proportion of women with recurrent cancer that does not respond to chemotherapy. Several other hormone treatments, such as letrozole and anastrozole, are also in clinical trials.

Tamoxifen competes with oestrogen to bind to oestrogen receptors, preventing oestrogen-induced cell division and tumour growth.

STARVING THE TUMOUR

Several treatments are in clinical trials to assess whether blocking the blood supply to tumours can slow down their recurrence. The antibody bevacizumab prevents the formation of new blood cells by inhibiting activity of the signalling protein VEGF, which is involved in the growth of blood vessels. The drug has already been approved by the US Food and Drug Administration and the European Medicines Agency for use in combination with chemotherapy for platinum-resistant relapsed ovarian cancer. Another drug — cediranib — disrupts the formation of blood vessels around the tumour by inhibiting a type of signalling protein called tyrosine kinase. In a trial called ICON6, the drug increased survival by three months compared with standard treatment for recurrent ovarian cancer. Several other drugs that block blood-vessel growth, such as combretastatin, pazopanib and trebananib, are also in clinical trials.

Cancer cells release VEGF to promote the growth of blood vessels around the tumour. Drugs that disrupt the VEGF-signalling pathway prevent the formation of vessels and limit tumour growth.



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