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Cancer therapy that engineers patient white blood cells to recognize and destroy tumors in their body posts impressive phase II result: 47% of patients experienced a complete remission, 5x better than current standard of care.

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April 17, 2023

Abstract

Kite Pharma is a biotech company that manufactures CAR-T cells. Essentially, CAR-T cells are T-cells taken from a patient, engineered to recognize and destroy the patient's tumor, and then put back in the body to kill the cancer cells. The CAR-T concept has been exciting researchers for several years now, but clinical studies were typically small and mostly focused on testing the safety of the technology. Last night, KITE Pharma released new data from their ongoing pivotal (meaning intended to be used to apply for FDA approval) phase II study using CAR-T cells in Non-Hodgkin Lymphoma. The results were very impressive. KTE-C19 (the CAR-T drug) met the primary endpoint of objective response rate (ORR), $p < 0.0001$, with an ORR of 76 percent, including 47 percent complete remissions (CR). Historically, standard of care has an 8% CR rate for these patients. While very exciting, there are still several concerns with the technology: namely safety, and duration of remission. A number of patients experienced adverse events related to the drug, and two died as a result of treatment. Additionally, while 47% of patients experienced a complete remission, some had relapsed three months later. This is part of the Science Discussion Series, so I will try to check in intermittently during the day to help discuss this clinical trial, CAR-T cells and other cool technologies in the immunotherapy space.

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REDDIT

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SIRT6 R/SCIENCE

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These kinds of treatments are very promising. It will take some time to figure out why some patients' immune responses are so severe and others tolerate the engineered cells so well. Also, it will be interesting to compare tumor cells before treatment and after the cancer returns to see if the return is due to some newly acquired mutations/epigenetic markers.

High_Point_Genetics

Also, it will be interesting to compare tumor cells before treatment and after the cancer returns to see if the return is due to some newly acquired mutations/epigenetic markers.

I think there is an excellent chance many of the relapsed tumors will be CD19 negative. It is becoming pretty widely understood that CD19 (the protein that the CAR-T cells recognize) is an imperfect target. It is widely expressed across almost the entire B-cell lineage (enhancing toxicity because the CAR-T cells will kill non-cancerous B-cells). It is also not essential for tumor survival, so there is strong evolutionary pressure on the tumor to find ways to lose CD19 expression. These are all problems that can be addressed in next generation immuno oncology medicines though.

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How long will it take to establish the safety and duration of remission statistics? What kinds of thresholds would be necessary to validate this as a viable treatment?

shiruken

The trial endpoints calls for 12 month post treatment follow-up. We will have a better idea of what long term remission rates look like then.

The company has reported that patients who are in a stable remission at three months tend to remain in remission for longer durations, suggesting that relapse in this setting is a more acute event.

Since the prognosis is so dismal for relapsed/refractory patients, I expect this to become an approved treatment. Most analysts have suggested that CR rates in excess of 30% would guarantee approval (the study reported CR rate of 47%).

Duration of remission is also not a critical issue, in my opinion. Obviously, a durable remission is preferable, but even a temporary complete remission opens up many more options for clinicians. For instance, at a CR the patient is a much better candidate for potentially curative autologous stem cell transplantation.

Would this be for all tumours, including brain tumours? My daughter has a brain tumour that might be recurring so stuff like this really interests me. I get confused by the blood brain barrier to know if some of this research applies to cancer in all areas of the body.

china-owns-pandas

In theory the technology is only limited by the ability of researchers to find a surface antigen that sufficiently differentiates the cancer cells from the non-cancerous cells.

In practice, though, this can be quite challenging. Even in this study, the surface antigen the researchers chose marks most B-cells in addition to the cancer cells. It just so happens that it is possible to live with massive B-cell depletion.

Additionally, there are safety concerns. Having several million T-cells suddenly put into body and set loose on tumor cells (and non-tumor cells) can create a bit of a mess. Inflammation, and something called cytokine storm are serious safety concerns. And brains, in particular, are very sensitive to inflammation and swelling.

All that said, early stage clinical trials have begun to investigate CAR-Ts for the most dangerous types of brain tumors.

If there seems to be recurring relapses, why not just extend the treatment duration?

avogando

Here is the dosing regimen for the study (taken from clinicaltrials.gov):

A conditioning chemotherapy regimen of fludarabine and cyclophosphamide will be administered followed by a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg

So the patients were infused with the CAR-Ts. Some pre-clinical/early clinical work using CAR-Ts in general has shown that CAR-Ts *can* persist in patients for several years. So it is unclear why the patients relapsed. And it is certainly a point that should be investigated. My guess would be that the

tumors lost the marker that the CAR-T cells used to identify and destroy the cancer cells. There are other possibilities though. For instance, maybe the tumor was able to create an immunosuppressive microenvironment, diminishing the ability of the CAR-T cells to initiate tumor killing.

Is there some kind of adjuvant to go along with the engineered cells? Maybe there's a dosage/titration assessment that would foster killing the cancer but not so high as to over-stimulate the immune system, leading to death.

Kolabunyi

This is a subject of active research. One idea that is popular is to put a gene in the CAR-Ts that makes them 'turn-off'/die on demand.

Other ideas have envisioned a two-point receptor system, where you can better control where the CAR-T gets 'turned on'.

It is important to distinguish between remission and cure. My wife's cancer, multiple myelonma, is considered incurable. Remissions tend to last 2-3 years. Can be just a few months.

BillTowne

It is an important distinction. But it is also worth noting that a complete remission gives clinicians so much more flexibility. For example, patients in CR are much better candidates for potentially curative autologous stem cell transplants.

I have read articles about immunotherapy for a number of years. Are any of them approved by the FDA? Are we still a long way away before this be omes approved? Has there been any research about treatment paths that combine immunotherapy and more traditional therapies?

Also there are many types of cancer. If we look at the number of patients who get cancer what percentage of them have cancers where there have been strong results with immunotherapy?

Youtoo2

Keytruda and Opdivo are immuno therapies currently approved by the FDA.

Dozens more are in the queue for approval.

CAR-Ts seem very likely to gain approval within the next year or so.

My mother was a researcher at KITE when it was just a few people. I can take questions if anyone's interested.

ayyKITE

Is she still there?

Is this what TotalBiscuit's doing?

hoseja

I don't think so. I wasn't familiar with this person, but upon Googling it, it seems he is battling a different type of cancer (metastatic colon cancer?).

This actually leads to an interesting distinction for the types of cancers that CAR-Ts work best on right now. Most CAR-Ts have had their success in liquid tumors (blood cancers). Solid tumors (essentially non-blood cancer) have been a struggle for CAR-Ts.

Eli5: in the big picture of curing cancer, does this make a significant difference?

whitewill0wbark

Yes. I think some for of this therapy (getting the body's immune system to attack the tumor cells) will be a mainstay of cancer treatment for decades to come. Whether it is CAR-Ts, adoptive T-cells, bispecific antibodies, checkpoint inhibitors or some combination of immuno-oncology drugs remains to be seen.

Is this treatment based on crispr?

westerschwelle

Not in the current iteration. Some groups are testing it, though. I think the two most important pieces of tech here are 1) the antibody that is fashioned into the chimeric receptor and 2) the pipeline for efficiently expanding and transducing patient derived T-cells with the CAR-T construct.

Wow. So cool when I see a front page article about the applicational model for the research my lab is doing.

jyuunbug

What lab are you in?

Does't it still have to go through Phase III before it can gain FDA approval.

fizzyboymonkeyface

Normally, yes. But this drug has FDA breakthrough designation. This means that they are allowed to submit a pivotal Phase II study as the basis of their application for approval.

Stock was up 9% today.

stan93

Funnily enough, JUNO was up more - ~12%.

This will be the last we hear about it. So many good things waste away in scientific studies, never to be applied in the real world. Sad.

ded2me

This was a clinical trial, conducted in the "real world" on "real-life" patients.