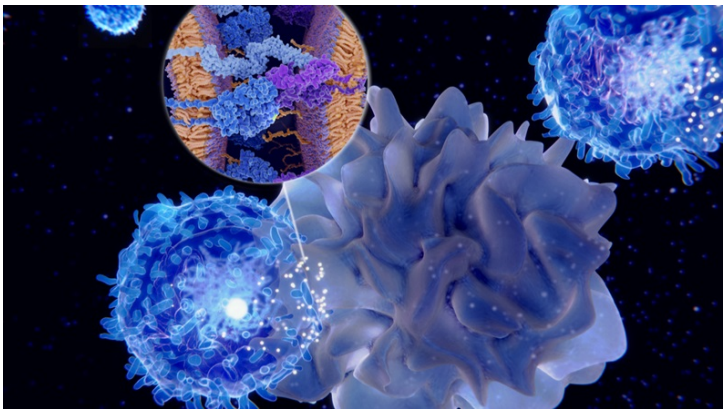
Opening The Door For Cell Therapy In Solid Tumors

10 Sep 2019 | **ANALYSIS**

by Daniel Chancellor | Daniel.Chancellor@informa.com

Executive Summary

The next frontier for cell therapy is solid tumors – and of the many attempts to move from liquid to solid tumors, tumor infiltrating lymphocytes and other CAR-T constructs are some of the most promising.



SEVERAL GROUPS SHARED RESEARCH AT ASCO FOR NEW CAR-T DESIGNS IN WELL-DEFINED SUBGROUPS OF PATIENTS WITH SOLID TUMORS THAT HAVE FAILED PREVIOUS CONVENTIONAL THERAPIES.

Source: Shutterstock

The first wave of chimeric antigen receptor T-cell (CAR-T) therapies – the CD19-targeted Kymriah from Novartis and Yescarta from Gilead – are now being established in the blood cancers acute lymphoblastic leukemia and diffuse large B-cell lymphoma, respectively, and attention has turned towards different CAR-T constructs and other cell therapy approaches that may show promise in the much larger solid tumor setting.

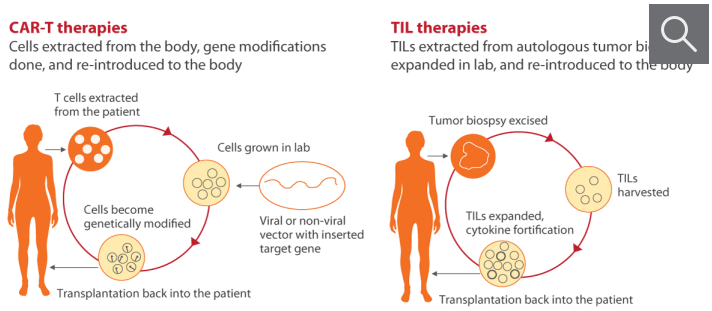
Over 90% of cancers arise from solid organs, but so far the development of effective cell therapies for these tumors has eluded developers. Solving this problem will be essential for cell therapy to move away from its current niche to become a mainstream treatment modality. At this year's American Society of Clinical Oncology (ASCO) annual meeting, experts reviewed some of the latest approaches aimed at tackling solid tumors via cell therapies, with promising advances for tumor-infiltrating lymphocytes (TILs) and novel CAR-T antigens.

TILs Show The Greatest Promise For A Range Of Solid Tumors

Speaking at the end of ASCO, Christopher Klebanoff of Memorial Sloan Kettering Cancer Center talked through the latest in oncology cell therapy research to emerge at the meeting. Overall, it appears that while individual CAR-T therapies are starting to show proof of concept in solid tumors in defined patient populations, the best evidence of efficacy in solid tumors continues to come from adoptive cell therapy using TILs, based on the research of the US National Cancer Institute and Iovance Biotherapeutics Inc.

TILs are part of the body's natural anti-cancer machinery. They are able to recognize many different neoantigens expressed by tumor cells, and migrate throughout the body, even crossing the blood-brain barrier. This exquisite efficacy of these cells is boosted using TIL therapy, an individualized process that has been refined over a period of three decades. It entails harvesting TILs from a tumor biopsy, determining which particular TILS have the most potent anti-tumor efficacy, then expanding them *ex vivo* in the presence of cytokines, before reinfusing millions of these highly specific lymphocytes into the patient in the hopes of overwhelming the cancer. Unlike CAR-T manufacture, no genetic engineering of the cell therapy is required. (*See graphic*.)

Tumor-infiltrating lymphocyte therapy process



Since the clinical and regulatory work for these products has been conducted in tandem by academia and industry, it looks likely that TIL therapy will become the latest immuno-oncology approach to reach the market. New proof-of-concept trials are under way across a range of treatment settings, meaning that TILs may also have large-scale application.

Achieving this scale may be important if TIL is to be a commercially viable proposition, avoiding some of the pitfalls that Dendreon faced with its personalized cancer vaccine Provenge (sipuleucel-T) – including manufacturing, distribution and reimbursement. (Also see "No Happy Endings For Dendreon As It Closes Another Chapter" - Pink Sheet, 10 Nov, 2014.) The total cost of TIL will also need to be carefully considered, taking into account the high incidence of solid tumors. Kymriah and Yescarta bear high costs that reflect their complex nature, but they are used in smaller populations. In addition, TILs are being studied in combination trials with expensive checkpoint inhibitors, so the costs will be additive.

To date, adoptive cell transfer of TILs has been mainly tried out in metastatic melanoma patients, and early results look highly promising. The first

evidence for the approach was published by Stephanie Goff of the NCI in 2011 and looked at 194 such patients who had exhausted all prior therapies. Response was seen in 107 patients (56%), including 46 complete responses (24%). For those patients that achieve a complete response, TIL appears capable of eliminating the last cancer cell. Only two of these patients have died with up to 12 years of follow-up, pointing towards TIL as a remarkable curative treatment option in this setting. TILs have also been shown to mediate complete regression among metastatic breast cancer patients, with partial responses also noted in gastrointestinal cancers.

With such strong proof of concept, Iovance Biotherapeutics quickly took up the baton and is now one of the leading companies pioneering the commercialization of this approach, and has partnered with the NCI for the technology. Iovance's proprietary manufacturing approach enables the production and infusion of 10^9–10^{11} TILs within 22 days of biopsy, and the company has invested in a 136,000 sq ft facility to enable GMP production on the scale required to treat a number of different solid tumors by 2022. With the infrastructure to deliver cell therapies on this scale in place, Iovance now needs to generate enough clinical data to support its planned first regulatory filings, potentially in 2020.

Iovance, therefore, attracted a lot of attention at ASCO for its presentations on its candidates, Contego (lifileucel; LN-144) in melanoma and LN-145 in cervical carcinoma.

For melanoma, Iovance released data for 66 patients in cohort 2 of its innovaTIL-01 trial, showing a 38% objective response rate, 80% disease control rate and median duration of response not reached with an 8.8-month follow-up.

In cervical carcinoma, LN-145 similarly achieved a 44% objective response rate and 85% disease control rate after 7.4 months of patient follow-up in the innovaTIL-04 study. While the data are not as remarkable as previously reported by the NCI, they are very promising for Iovance's prospects of reaching the market in such heavily pre-treated patients. Both programs have been awarded fast-track status and breakthrough therapy designation at the US Food and Drug Administration, and Iovance hopes to file Contego for approval in the second half of 2020 upon the completion of cohort 4 of innovaTIL-01.

Iovance's Tumor-Infiltrating Lymphocyte Clinical Data At ASCO

	Contego in melanoma	LN-145 in cervical carcinoma
Number of evaluable patients	66	27
Objective response rate	38%	44%
Disease control rate	80%	85%
Complete responses	2 patients	3 patients
Partial response	23 patients	9 patients
Median duration of response	n/a	n/a
Median follow-up	8.8 months	7.4 months

Source: Biomedtracker

Mesothelin-Directed CAR-T Cells Show Potential In Pleural Cancers And Beyond

While TILs stole the cell therapy show at ASCO, several other groups were sharing research for new CAR-T designs in well-defined subgroups of patients with solid tumors that have failed previous conventional therapies. The challenge is selecting an appropriate antigen that is essential for tumor growth, with universal expression on the surface of tumor cells and limited expression in normal tissues, to limit toxicity.

Among the new CAR-Ts discussed at the meeting were programs against Claudin 18.2 and B7-H3, while CEA, HER2, and GD2 are also widely studied, but perhaps the target with the broadest therapeutic potential in solid tumors is mesothelin.

Mesothelin is a cell-surface antigen expressed in the majority of solid tumors, including 85%-90% of mesotheliomas, with an estimated annual incidence and prevalence of 340,000 and 2 million patients, respectively, in the US alone. To date, no drugs against mesothelin – small-molecule, biologic, or otherwise – have progressed as far as Phase III, although the CAR-T modality is now showing clinical promise.

Atara Biotherapeutics Inc. and collaborators at Memorial Sloan Kettering Cancer Center announced results from a trial of 27 patients with advanced pleural cancers, evaluating an anti-mesothelin CAR-T construct using a novel 1XX signaling domain and PD-1 dominant negative receptor. As shown in the table below, the results for 16 evaluable patients with mesothelioma are highly encouraging, with a 63% response rate including three complete responses. Furthermore, there was little association with cytokine release syndrome or neurotoxicity, which are limiting side effects noted with currently approved CD19-targeted CAR-T therapies.

Phase I Study Of Anti-Mesothelin CAR-T In Advanced Mesothelioma

Measure	Result
Number of patients	27
Number of evaluable mesothelioma patients	16
12-month overall survival	80%
Best overall response rate	63%
Investigator-assessed complete responses	3 patients
Partial responses	7 patients

Source: Biomedtracker

The trial also confirmed the benefits of combining the CAR-T and anti-PD-1 approaches in mesothelin-expressing cancers: the effectiveness of the CAR-T therapy alone was potentiated by an increase in PD-L1 expression on tumor cells as a result of treatment. Thus, the administration of the mesothelin-targeted CAR-T treatment seemed to prime the tumor to be treated more effectively by anti-PD-1 therapy, while the administration of a PD-1 inhibitor also seemed to prolong the effect of the previously administered CAR-T cells.

Atara is expected to begin subsequent development of this CAR-T candidate in mesothelioma, with the possibility that the company could move directly into a registration-enabling study that would allow for

accelerated approval.

Considering the expression of mesothelin across various tumor types, a broader development program would also have large commercial appeal. Atara is likely to face competition from other companies seeking to develop mesothelin-targeting drugs, however. There are 13 separate clinical programs featuring a number of drug and tumor types. (*See table.*)

Clinical-Stage Pipeline For Mesothelin-Targeting Drugs In Oncology

Drug	Company	Mechanism	Indications
amatuximab	Eisai	Mesothelin MAb	Mesothelioma
anetumab ravtansine	Bayer	Mesothelin ADC	Unspecified solid tumors
BMS-986148	Bristol-Myers Squibb	Mesothelin ADC	Unspecified solid tumors
HPN-536	Harpoon Therapeutics	Trivalent polypeptide binding mesothelin, HSA, and CD3	Ovarian, pancreatic, and solid cancers
n/a	Shenzhen BinDeBio	Mesothelin CAR-T	Pancreatic cancer
TC-210	TCR2 Therapeutics	Mesothelin TCR	Mesothelioma, biliary, ovarian, and non-small cell lung cancer
ABBV-428	AbbVie	CD40/mesothelin bispecific antibody	Unspecified solid tumors
ATA2271	Atara Biotherapeutics	Mesothelin CAR-T	Unspecified solid tumors
BAY-2287411	Bayer	Mesothelin ADC	Mesothelioma, ovarian cancer
MCY-M11	MaxCyte	Mesothelin CAR-T	Mesothelioma, ovarian cancer
n/a	Hebei Senlang Biotechnology	Mesothelin CAR-T	Mesothelioma, pancreatic, and ovarian cancer
n/a	Novartis	Mesothelin CAR-T	Mesothelioma, pancreatic, and ovarian cancer
n/a	Shanghai Unicar-Therapy Biomed	Mesothelin CAR-T	Pancreatic cancer

ADC = antibody-drug conjugate; CAR-T = chimeric antigen receptor T-cells; HSA = human serum albumin; MAb = monoclonal antibody; TCR = T-cell receptor. Source: Pharmaprojects