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ONCOLOGY

T Cell-Based Therapies in Oncology: Landscape Evolution After a Turbulent 1H2020

White Paper

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Six months ago, we published an in-depth review of the cell-based immunotherapy landscape, including forward-facing declarations of 2020 data releases, filings, etc. that would address key outstanding questions, namely:

Autologous CD-19 CAR-T	*How will the autologous CD-19 CAR-T space evolve, with the **potential entry of BMS / Celgene's liso-cel** and ongoing expansions of **Gilead's YESCARTA** and **Novartis' KYMRIAH**?*
Autologous BCMA CAR-T	***When** will BCMA CAR-T enter the market, and how will the **BMS / Celgene's ide-cel** and **Janssen's JNJ-4528 competition** shake out, as well as vs **out-of-class BCMA targeted therapies**?*
Other CAR-T Targets	*What **other CAR-T targets** will be successful in **liquid tumors**?*
Allogeneic CAR-T	*How will **allogeneic** ("off the shelf") CAR-T **compare to the autologous CAR-Ts**?*
Solid Tumor CAR-T	*Will **CAR-T** be able to demonstrate **success in solid tumors**?*
TCR-T	*Will **TCR-T** be able to demonstrate **unambiguous clinical efficacy**?*
Other T Cell Therapy	*Outside of CAR-T and TCR, will **other T Cell-based therapies succeed** (e.g., TILs)?*

GLOSSARY	
Autologous	Refers to cell therapies generated from the patient's own cells ("personalized", "bespoke")
Allogeneic	Refers to cell therapies generated from donor cells ("off the shelf")
Antigen	Fragment of a protein that is recognized by a T Cell Receptor; either expressed on a cell surface or presented at the cell surface via the MHC for the immune system to scan and classify as either "self" or "non-self"
CAR-T Cell	Chimeric Antigen Receptor; T Cell modified with a genetically-engineered CAR that recognizes a tumor-specific cell surface protein; does not require MHC presentation or HLA matching, but can only target antigens expressed on the cell surface
GvHD	Graft vs Host Disease; occurs when a donor immune cell classifies the recipient's cells as foreign and attacks them, initiating a potentially fatal immune response; has been an anticipated concern for allogeneic cell therapies
MHC	Major Histocompatibility Complex; Set of cell surface proteins that captures antigens and presents them at the cell surface for scanning by TCRs; MHC are mutated in some tumors as a form of immune resistance
T Cell	In this paper refers to CD8+ Cytotoxic T Cells; Recognizes "non-self" antigens and kills cells expressing those antigens
TCR-T Cell	T Cell Receptor; T Cell modified with a genetically-engineered TCR that recognizes an MHC-presented antigen (protein expressed anywhere in the cell, not just on the cell surface as required by CAR-T); requires donor:host immune matching (histocompatibility)
TILs	Tumor Infiltrating Lymphocytes; tumor-targeting T Cells removed from the patient, then expanded and reinfused

Six months later, despite the unprecedented and unanticipated impact of COVID-19 on corporate operations, clinical trial functions, and regulatory body decision-making, there have been multiple key decisions and updates that both inform these questions and impact the trajectory of specific therapies. Most notably, BMS / Celgene suffered dual setbacks from the FDA, who rejected their BCMA CAR-T ide-cel and delayed a decision on their CD-19 CAR-T liso-cel. Both decisions put milestone payouts at risk.

On the other hand, Janssen announced promising data for their BCMA CAR-T JNJ-4528, putting them in a competitive position relative to the now-delayed ide-cel. Beyond the autologous (patient-derived) CAR-T therapies, Allogene's and Celyad's allogeneic ("off the shelf") CAR-Ts, Adaptimmune's TCR-T, and Iovance's TILs also had a good ASCO with promising data releases.

Here, we review in more detail the revised status of several key milestones declared at the end of year (EOY) 2019.

Autologous CD-19 CAR-T

There have been several delays to EOY 2019 declared timelines, most notably with BMS / Celgene's liso-cel. At the beginning of the year, liso-cel was well-positioned in DLBCL, with a potentially superior efficacy / safety profile that could disrupt the established positions of YESCARTA and KYMRIAH. Indeed, they achieved FDA priority review in February, putting them on track for a mid-year approval. However, in May the FDA pushed back the decision to November, citing the need to review additional data. This new timeline puts Celgene's Dec 31 approval milestone payout deadline at risk.

Gilead / Kite met their declared Q1 filing milestone for KTE-X19 CAR-T (a next generation version of their already-approved YESCARTA, with improved manufacturing), and are on track for approval with priority review from both the FDA and EMA. If successful, this would be the first CAR-T approval in MCL.

Will the marketed / late stage **autologous CD-19 CAR-Ts expand** into other tumor types / earlier lines?
Where will they **directly compete**? Will **combinations** unlock further efficacy?

Key Milestone & Implication	*EOY 2019 Declared Timing (*estimated)*	*1H2020 Status*	*Details*
BMS / Celgene's liso-cel FDA approval decision (DLBCL) - Safety / tolerability profile appears superior; could disrupt YESCARTA and KYMRIAH in DLBCL	**1Q20**	**DELAYED**	Achieved priority review in Feb, but in May, **FDA extended review an additional 3 months** after receiving additional requested info, pushing **decision date to Nov** (putting Dec 31 milestone payout deadline at risk)
Gilead / Kite's KTE-X19 FDA and EMA filing (MCL) - First approval in MCL specifically; potential to expand into other NHL subtypes and compete there	**1Q20**	**DONE**	Filed for FDA approval Dec19; **PDUFA Aug**; EMA marketing application accepted Jan, **priority granted by both FDA and EMA**; ASCO data shows comparable efficacy; also presented encouraging ALL data at ASCO (Ph1/2 only; Ph2 still ongoing)
Gilead's YESCARTA Ph2 **data / filing** (indolent NHL) - YESCARTA would have a broader indication (more subtypes of NHL) than competitors	*2020	**ON TRACK**	Gilead CAR-T med Yescarta delivers 93% response rate in slow-growing indolent NHL; plans to file "later this year"
Gilead's YESCARTA + atezolizumab Ph2 **data** (DLBCL)	*2019	**NO UPDATE**	These combination regimen datasets will indicate whether addition of a checkpoint inhibitor or standard of care can boost CAR-T efficacy
Novartis' KYMRIAH + pembrolizumab Ph1 **data** (DLBCL)	*2020		
Gilead's YESCARTA + rituximab or **lenolidomide** Ph2 **data** (DLBCL)	*2020		

Autologous BCMA CAR-T (and other targets)

At the beginning of the year, BMS/Celgene enjoyed a clear advantage with their BMCA CAR-T ide-cel on track for a first approval in multiple myeloma, ahead of Janssen's competitor CAR-T JNJ-4528 as well as out-of-class ADC (Antibody Drug Conjugate) competition. However, in May the FDA unexpectedly rejected ide-cel's application, citing gaps in manufacturing information. Given their March 2021 approval milestone payout deadline, they must resubmit by end of July or risk missing this deadline.

Milestone payouts aside, this delay also opens the door for both in-class competitors (Janssen's JNJ-4528, which made a splash at ASCO with "early, deep, durable" responses) as well as out-of-class BCMA competitors, namely GSK's ADC, belantamab mafodotin, which received FDA priority review in January. If successful, it will now be the first BCMA-targeted approval.

Beyond CD-19 and BCMA, at least one additional target, Precision Biosciences' CD20 CAR-T PBCAR20A, has entered the clinic on schedule. This sets the stage to see evidence of new target efficacy soon.

Will **BCMA CAR-T** launch? Which product(s) will **succeed in the market**? Other autologous CAR-T targets?			
Key Milestone & Implication	*EOY 2019 Declared Timing (*estimated)*	*1H2020 Status*	*Details*
BMS / Celgene's **BCMA** CAR-T **ide-cel** final **data release / filing** (MM) - Would be first non-CD-19 CAR-T approval; would hint at success of other earlier stage BCMA CAR-T	**1H20**	**DELAYED**	**FDA rejected the application** in May (requesting more manufacturing info); they must now resubmit by end of July or risk missing the March 2021 approval milestone payment
Janssen's **BCMA** CAR-T **JNJ-4528** pivotal **data release / filing** (MM) - Would compete with ide-cel	**2H20**	**ON TRACK**	ASCO **Ph1b data indicated "early, deep, durable responses"** with 86% complete response at a median follow-up of 11.5 months and 86% progression free at 9 months
Out-of-class BCMA competition in MM – both ADCs and bispecifics could compete with CAR-T; **GSK's ADC belantamab mafodotin** is on track to be **first BCMA approval**	*n/a*	**ON TRACK** *(competitive threat)*	**GSK's BCMA-ADC was granted priority FDA review** in Jan 2020; presented additional data at ASCO showing a durable 32% response rate
Precision Biosciences' **CD20** CAR-T **PBCAR20A** Ph1 **trial start** (MCL, CLL, SLL) - Could demonstrate efficacy for allogeneic new target CD20 and underserved liquid tumors (CLL, SLL)	**1Q20**	**DONE**	Study started March 24, 2020 (per clinicaltrials.gov); first patient dosed in April

Allogeneic CAR-T

Given the significant cost and manufacturing burden of preparing the personalized "bespoke" autologous CAR-T therapies, manufacturers are attempting to prove at least equivalent (if not superior) efficacy of the cheaper and more scalable allogeneic "off the shelf" CAR-T therapies. They also must demonstrate that donor-derived allogeneic CAR-T do not trigger dangerous immune reactions between donor and host immune cells, e.g., Graft vs. Host Disease (GvHD).

While we do not yet have a mature dataset for comparing the newly-developed allogeneic CAR-T to the established autologous CD-19 CAR-T, Allogene did announce additional responses seen with their allogeneic CD-19 CAR-T ALLO-501. This is an encouraging sign. Another Q1 anticipated data release, from Precision Bioscience's CD-19 CAR-T PBCAR0191, is not yet announced, but is still "expected in 2020".

Aside from CD-19 CAR-T, Celyad announced additional positive safety data for their allogeneic NKG2D CAR-T CYAD-101, with no signs of GvHD or other donor:host immune reactions.

Cellectis' allogeneic CAR-T portfolio continues to be plagued with safety issues however. Their CS1-targeted UCARTCS1 was placed on clinical hold as of July 6 due to a patient death from cardiac arrest. This is their second clinical hold, after UCART123 was placed on hold in 2017 after the first patient treated died. While it is unclear whether the recent death is due to the UCARTCS1, both deaths occurred at high doses, raising the question of whether doses can safely go high enough to ensure efficacy.

How will **allogeneic** ("off the shelf") **CAR-T compare** to the **autologous** CAR-Ts?			
Key Milestone & Implication	*EOY 2019 Declared Timing (*estimated)*	*1H2020 Status*	*Details*
Precision Biosciences' **CD-19** CAR-T **PBCAR0191** Ph1 **data release** (ALL) - Will enable early comparison to KYMRIAH in ALL	**1Q20**	**DELAYED**	Company website now states "Ph1 data expected 2020"
Celyad's **NKG2D** CAR-T Ph1 **data releases** (mCRC): allogeneic **CYAD-101** vs autologous **CYAD-01 -** Will enable allogeneic vs autologous **solid tumor comparison**	*2020	**ON TRACK**	ASCO: released additional safety data (positive, no GvHD) for CYAD-101; announced expansion cohort for FOLFIRI refractive patients
Allogene's **CD-19** CAR-T **ALLO-501 Ph1 data releases (NHL)** - will enable comparison to autologous CAR-T	*2020	**ON TRACK**	ASCO: additional blood cancer responses seen with Allogene's off-the-shelf CAR-T cells (ALLO-501)
Allogene's **CD-19** CAR-T **UCART19 registrational trial start -** Associated Ph1 data release will enable comparison to KYMRIAH in ALL; reg. trial start will suggest launch timing	**2H20**	**NO UPDATE**	

Solid Tumor CAR-T

Celyad's NKG2D CAR-T CYAD-101 is also noteworthy as the leading solid tumor CAR-T in clinic. While they did not release additional efficacy data at ASCO, they did announce an expansion cohort in CRC (for FOLFIRI refractive patients). Another solid tumor CAR-T, Bellicum's HER-2 CAR-T BPX-603 is still on track to enter the clinic later this year, after achieving FDA IND clearance on June 15.

Will **CAR-T** succeed in **solid tumors**?			
Key Milestone & Implication	*EOY 2019 Declared Timing (*estimated)*	*1H2020 Status*	*Details*
Celyad's **NKG2D** CAR-T Ph1 **data** (colorectal / CRC): allogeneic **CYAD-101** vs autologous **CYAD-01 -** Could confirm prelim data (Jul) showing disease control in solid tumor (mCRC) for both autologous and allogeneic	*2020	**ON TRACK**	ASCO: released additional safety data (positive, no GvHD) for CYAD-101; announced expansion cohort for FOLFIRI refractive patients
Bellicum's **HER-2 + activation + safety switch** CAR-T **BPX-603** Ph1 **trial start -** Could demonstrate efficacy for dual efficacy / safety switch	**2020**	**ON TRACK**	received FDA IND clearance on June 15, will initiate Ph1/2 trial "later this year"
City of Hope's **IL13Ra2 CAR-T** Ph1 **data** (Glioblastoma) - Could confirm prelim data (1 CR in multifocal Glioblastoma)	*2020	**NO UPDATE**	

TCR-T

The TCR-T cell therapies differ from CAR-T in that they do not require surface expression of their target proteins but do require functioning immune presentation as well as histocompatibility between donor and host immune systems. They have been under clinical development for quite some time with mixed efficacy and safety data. TC2's mesothelin TCR TC-210 had previously declared a 1Q20 data release, but in March they announced COVID-related delays would be pushing this out to "mid 2020".

Adaptimmune's MAGE A4 SPEAR T Cell (their proprietary TCR platform) ADP-A2M4 did deliver promising durability and efficacy, shown at ASCO. This keeps them on track for their 2022 filing in synovial sarcoma.

Will **TCR** T Cell Therapies achieve **early stage clinical success?**			
Key Milestone & Implication	*EOY 2019 Declared Timing (*estimated)*	*1H2020 Status*	*Details*
TC2's **mesothelin** TCR **TC-210 Ph1 data release** (ovarian, NSCLC, MPM, cholangiocarcinoma) - Would be first evidence of efficacy for mesothelin next-gen TCRs	**1Q20**	**DELAYED**	In March, company acknowledged COVID impact on clinical trial and says interim results will be released "mid 2020"
Adaptimmune's **MAGE A4** SPEAR T Cell **ADP-A2M4** Ph2 **data** (soft tissue sarcoma) - would be first evidence of efficacy for MAGE-A4 next-gen TCRs	*2022	**ON TRACK**	Durability and efficacy data presented at ASCO support potential for SPEARHEAD-1 as a registrational trial for sarcoma - commercial launch planned in the US in 2022
Medigene's **PRAME** TCR **MDG1011 Ph1/2 data release** (AML, MDS, MM) - Would demonstrate TCR efficacy in liquid cancers	*2020	**NO UPDATE**	ASCO: additional blood cancer responses seen with Allogene's off-the-shelf CAR-T cells (ALLO-501)

Other T Cell Therapy

Aside from CAR-T and TCR-T, there is a notable lack of update on Bellicum's safety switch modified T Cell rivo-cel, which reached its pivotal endpoint one year ago (in July 2019) but still has not made any updates on filing. Iovance did announce efficacy data for their Tumor Infiltrating Lymphocyte (TIL; an expanded population of each patient's existing activated T Cells) lifileucel in melanoma, showing a durable response of at least 18.7 months. If approved, this would be the first approval for TILs, which have been under clinical development for quite some time.

Will **non-CAR-T, non-TCR** T Cell Therapies (TILs, etc) achieve **registrational success?**			
Key Milestone & Implication	*EOY 2019 Declared Timing (*estimated)*	*1H2020 Status*	*Details*
Bellicum's safety switch modified T Cell therapy **rivo-cel filing** (post-HSCT in pediatric liquid cancers) - Would be first safety switch modified T Cell therapy approval	*2020	**NO UPDATE** *(DELAYED?)*	Pivotal endpoint was reached in July 2019, but Bellicum has not yet declared estimated date for filing
Tessa Therapeutics' **Epstein Barr Virus-Specific T Cell TT10** Ph3 **data** (nasopharyngeal carcinoma) - would be first approval for VST (T Cells primed by viral antigens to treat virus-induced cancers)	*2020	**NO UPDATE**	
TC Biopharm's **expanded Gamma Delta T Cell** therapy **TCB002** Ph1 **data** (AML) - not registrational, but would be first proof of efficacy for Gamma Delta T Cell therapy	*2020	**NO UPDATE**	
Iovance's TILs **lifileucel** pivotal Ph2 **data** (melanoma) – would be first approval for TILs	*2020	**ON TRACK**	ASCO: long-term interim data shows 36.4% ORR, with median duration of response not reached at 18.7 months

Upcoming 2H2020 Milestones

Over the next 6 months we anticipate significant activity with expected filings and FDA decisions, particularly within the autologous CD-19 and BCMA CAR-T spaces. We also look forward to additional data releases on the allogeneic CD-19 CAR-Ts, which will clarify to what extent the allogeneic approaches can supplant the established autologous therapies. Aside from these specific clinical attributes and competitive positioning questions within the T Cell therapy space, we also expect additional clarity on the scope and magnitude of the COVID-19 pandemic impact, particularly on earlier stage clinical trials.

	Key 2H2020 Milestone & Implication	*Declared Timing*
Autologous CD-19 CAR-T	**BMS / Celgene's liso-cel FDA approval decision** (DLBCL) - Safety / tolerability profile appears superior; could disrupt YESCARTA and KYMRIAH in DLBCL	**Nov 2020**
	Gilead / Kite's KTE-X19 FDA and EMA approval decision (MCL) - First approval in MCL specifically; potential to expand into other NHL subtypes and compete there	**FDA: Aug 2020 EMA: unknown**
	Gilead's YESCARTA filing (indolent NHL) - YESCARTA would have a broader indication (more subtypes of NHL) than competitors	**EOY 2020**
BCMA CAR-T	BMS / Celgene's **BCMA** CAR-T **ide-cel** updated **filing** (MM) - Would be first non-CD-19 CAR-T approval; would hint at success of other earlier stage BCMA CAR-T	**July 2020**
	Janssen's **BCMA** CAR-T **JNJ-4528** pivotal **data release / filing** (MM) - Would compete with ide-cel	**2H20**
	BCMA competition: GSK's ADC **belantamab mafodotin FDA approval**	**2H20**
Allogeneic CD-19 CAR-T	Precision Biosciences' **CD-19** CAR-T **PBCAR0191** Ph1 **data release** (ALL) - Will enable early comparison to KYMRIAH in ALL	**2H20**
	Allogene's **CD-19** CAR-T **UCART19 registrational trial start -** Associated Ph1 data release will enable comparison to KYMRIAH in ALL; reg. trial start will suggest launch timing	**2H20**
Solid Tumor CAR-T	Bellicum's **HER-2 + activation + safety switch** CAR-T **BPX-603** Ph1 **trial start -** Could demonstrate efficacy for dual efficacy / safety switch in solid tumors	**2H20**
TCR-T	TC2's **mesothelin** TCR **TC-210 Ph1 data release** (ovarian, NSCLC, MPM, cholangiocarcinoma) - Would be first evidence of efficacy for mesothelin next-gen TCRs	**3Q20**

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