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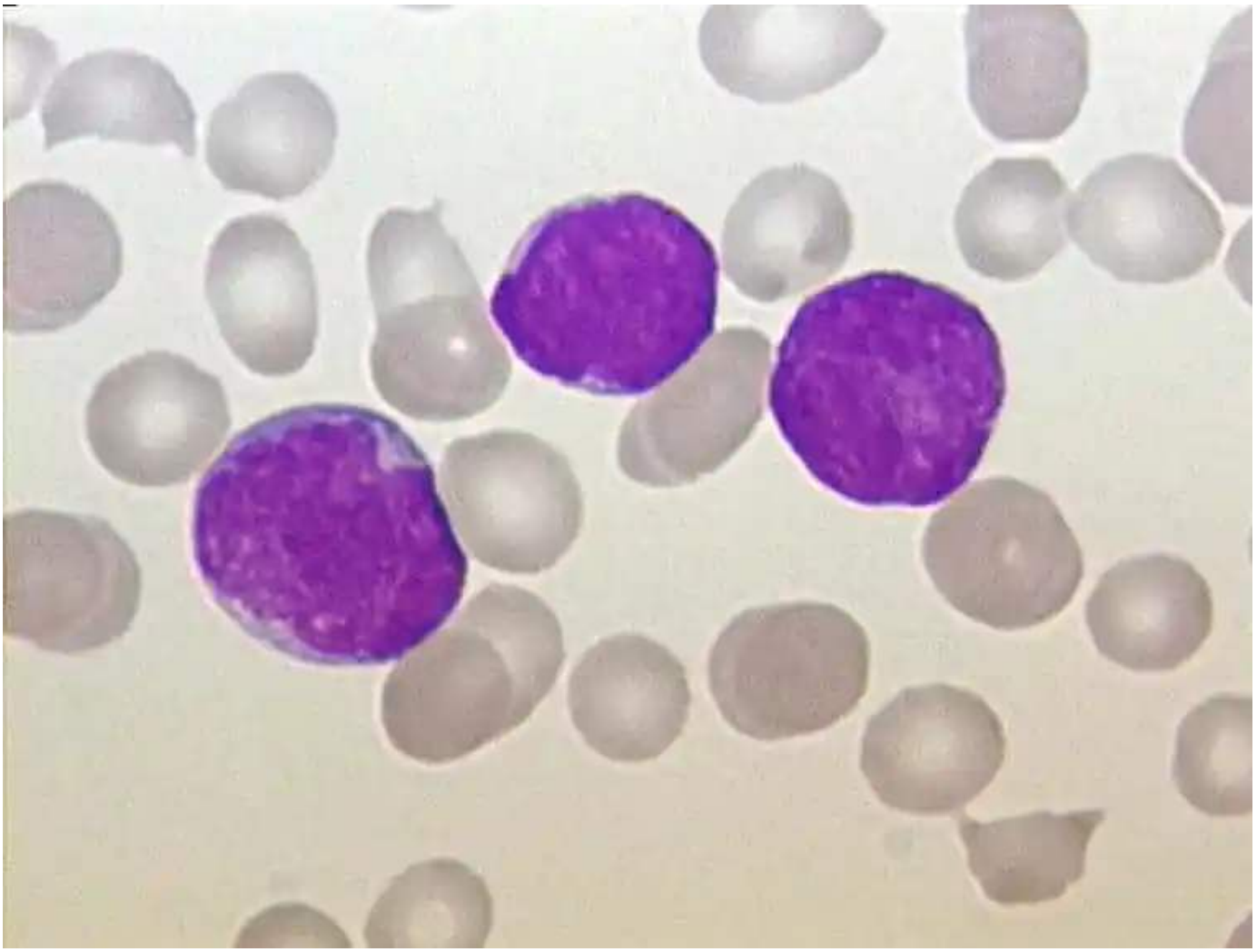
Onco-this-Week

January 5, 2019(https://sciwri.club/archives/date/2019/01/05)



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OTW in a Capsule

HIGHLIGHTS

1. ***BMS' Acquisition Of Celgene**: Touted As One Of The Biggest Acquisitions In Cancer Pharmacology, BMS' Purchase Of Celgene Adds A Solid Pipeline Of New Cancer Drugs Along With The Approved Ones. Six New Products Launches Are Anticipated To Boost The Near Term Annual Revenue – Do We See More Of Nivolumab's Combinations In Future To Combat Pembrolizumab's Success?*

2. ***Pembrolizumab's Multiple Approvals In Japan**: 2019 Could Not Have Started On A Better Note For Merck, Whose Blockbuster Drug Pembrolizumab Snapped Not One Or Two, But Five Approvals In Japan At A Go! With These Approvals, Pembrolizumab Is All Set To Be Prescribed For Japanese Patients As Monotherapy Or In Combination With Chemotherapy In 1L Non-Squamous NSCLC, 1L Squamous NSCLC, 1L PD-L1-Positive NSCLC, Adjuvant Melanoma And Previously-Treated MSI-H Solid Tumors.*

3. ***FDA Approval Of Dasatinib + Chemotherapy In 1L Ph+ Pediatric ALL Patients:** While Nowhere As Big A News As Acquisition Of Celgene, BMS Was Elated To Announce The Approval Of Dasatinib (In Combination With Chemotherapy) As The Only Second-Gen Tyrosine Kinase Inhibitor Approved For These Patients. Dasatinib Is Already Approved In Patients With Ph+ CML In Chronic Phase.*

(https://goo.gl/XM63s6)

DRUG APPROVALS

Japan PMDA approves Pembrolizumab as monotherapy or in combination with chemo in 1L non-sqNSCLC, 1L sqNSCLC, 1L PD-L1+ NSCLC, adjuvant melanoma and MSI-H solid tumors (https://investors.merck.com/news/press-release-details/2019/Mercks-KEYTRUDA-pembrolizumab-Receives-Five-New-Approvals-in-Japan-Including-in-Advanced-Non-Small-Cell-Lung-Cancer-NSCLC-as-Adjuvant-Therapy-for-Melanoma-and-in-Advanced-Microsatellite-Instabilit)

"These five simultaneous approvals of KEYTRUDA in Japan represent a significant achievement that involved extensive collaboration with the Japan Pharmaceuticals and Medical Devices Agency," said Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories. "We appreciate the Agency's efforts to expedite availability of this important medicine to more patients living with cancer in Japan."

> Merck's Keytruda(pembrolizumab) Receives 5 Approvals from PMDA, Japan across 3 indications @Merck (https://twitter.com/Merck?ref_src=twsrc%5Etfw) https://t.co/sodT33LFiY (https://t.co/sodT33LFiY) pic.twitter.com/BdXnt7RmYj (https://t.co/BdXnt7RmYj)
>
> — PharmaShots (@Pharmashot) January 4, 2019 (https://twitter.com/Pharmashot/status/1081179803829526528?ref_src=twsrc%5Etfw)

Dasatinib + chemotherapy approved by FDA in 1L Philadelphia chromosome-positive pediatric ALL patients (https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibbs-sprycel-dasatinib-tablets-now-approved-c)

"As treatments have advanced in recent years, we've seen improvements in outcomes for pediatric patients with Ph+ ALL overall, but there remains a need for additional options," said Stephen Hunger, MD, lead study author, chief of the division of oncology and director of the Center for Childhood Cancer Research at Children's Hospital of Philadelphia. "The Phase 2 CA180-372 trial was particularly informative because it was designed to limit the use of cranial irradiation and stem cell transplant. In the study, Sprycel plus chemotherapy demonstrated a three-year event-free survival benefit. These results show that Sprycel is an effective medication for physicians to consider for children and adolescents with Ph+ ALL."

Bristol-Myers Squibb Receives FDA's Approval for Sprycel (dasatinib) + CT in Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) @bmsnews (https://twitter.com/bmsnews?ref_src=twsrc%5Etfw) https://t.co/O1wphov8Qf (https://t.co/O1wphov8Qf) pic.twitter.com/rkJ11PhYVQ (https://t.co/rkJ11PhYVQ)

— PharmaShots (@Pharmashot) January 3, 2019 (https://twitter.com/Pharmashot/status/1080732261480390656?ref_src=twsrc%5Etfw)

REGULATORY NEWS

IND submitted for DHODH inhibitor ASLAN003 for evaluation as part of ongoing Ph II trial (http://aslanpharma.com/app/uploads/2019/01/190104_Press-Release_003-IND-EN.pdf)

Dr Carl Firth, CEO of ASLAN Pharmaceuticals, commented: "We're excited to begin enrolling U.S. patients in our ASLAN003 Phase 2 clinical trial. We have been encouraged to see half of our evaluable patients recruited to date in our lower dose cohorts show signs of clinical activity. We expect our clinical trial activity in the United States and Asia to be supportive of potential approval in major markets and to fulfil our desire for a submission of a robust, comprehensive and compelling data package."

'Orphan Drug' ASLAN003, potential Tx for acute myeloid leukemia (AML) -orally active, potent inhibitor of human dihydroorotate dehydrogenase (DHODH) – announces new positive data from ongoing phase 2a study #cancerresearch (https://twitter.com/hashtag/cancerresearch?src=hash&ref_src=twsrc%5Etfw) #AML (https://twitter.com/hashtag/AML?src=hash&ref_src=twsrc%5Etfw)@Aslanpharma (https://twitter.com/Aslanpharma?ref_src=twsrc%5Etfw) https://t.co/ypOdwUaqeo (https://t.co/ypOdwUaqeo) pic.twitter.com/03NkNa3rbj (https://t.co/03NkNa3rbj)

— Key Biologics, LLC (@keybio) December 16, 2018 (https://twitter.com/keybio/status/1074108365301825541?ref_src=twsrc%5Etfw)

SPA submitted for Ph III INSPIRE trial of Rigosertib + Azacitidine in 1L MDS patients (https://investor.onconova.com/news-releases/news-release-details/onconova-submits-special-protocol-assessment-spa-fda-phase-3)

Dr. Steve Fruchtman, President of Onconova, commented: "We remain focused in 2019 on the completion of the pivotal INSPIRE trial studying intravenous rigosertib in higher-risk MDS after patients fail to respond to or progress on hypomethylation therapy, the standard of care. The timely achievement of this regulatory milestone of this SPA submission is an important step in advancing the development of rigosertib for patients with earlier stage higher-risk MDS. We believe that the promising data in hand, including the data from the Phase 2 expansion trial of oral rigosertib and azacitidine presented at this year's 2018 ASH Annual Meeting, provides a strong scientific rationale for the proposed Phase 3 program. As the INSPIRE trial continues to mature, we look forward to a constructive engagement with the FDA on future studies. We also aim to help fund these additional studies through expanding our partnerships."

Oral Rigosertib With Standard Dose Azacitidine https://t.co/PjdjfqSVRM (https://t.co/PjdjfqSVRM) @MountSinai (https://twitter.com/MountSinai?ref_src=twsrc%5Etfw) @ASH_hematology (https://twitter.com/ASH_hematology?ref_src=twsrc%5Etfw) pic.twitter.com/cQwvFA005t (https://t.co/cQwvFA005t)

— Oncology Tube (@oncologytube) January 1, 2019 (https://twitter.com/oncologytube/status/1080178190373568513?ref_src=twsrc%5Etfw)

TRIAL RESULTS

Positive preliminary 12-month data from registration Ph III VISTA trial of Vicinium for NMIBC patients (https://www.businesswire.com/news/home/20190103005202/en/Sesen-Bio-Announces-Positive-Preliminary-12-Month-Data)

"Non-muscle invasive bladder cancer is a very prevalent cancer that can progress to become incurable. The usual treatment for patients who relapse or become refractory to BCG, today's standard-of-care, is complete bladder removal or radical cystectomy," said Michael A.S. Jewett, M.D., Professor of Surgery, Division of Urology, University of Toronto. "Removing the bladder is a potentially morbid and complex surgery with potential for side effects that can drastically reduce a patient's quality of life. In fact, many patients choose not to undergo bladder removal. I am very encouraged by the data generated to-date with intravesical Vicinium as an alternative after BCG failure. Based on the strength of the clinical activity observed, and the consistently favorable safety and tolerability, I believe that Vicinium has the potential to change the treatment outcome for patients."

Sesen Bio Announces Positive Preliminary 12-Month Data from Registration Phase 3 VISTA Trial of Vicinium for Non-Muscle Invasive Bladder Cancer – Business Wire https://t.co/fnfjQycBaL (https://t.co/fnfjQycBaL) pic.twitter.com/WMe4G5JiYr (https://t.co/WMe4G5JiYr)

— Swallow This – The War On Cancer! (@miracle_cures) January 4, 2019 (https://twitter.com/miracle_cures/status/1081178955946778625?ref_src=twsrc%5Etfw)

SPECIAL STATUSES

Orphan Drug Designation granted to Wnt inhibitor SM08502 in pancreatic cancer (https://www.samumed.com/medium/image/samumed-granted-orphan-drug-designation-for-sm08502-for-the-treatment-of-pancreatic-cancer_513/view.aspx)

"The FDA ODD designation for SM08502 is an important regulatory milestone and highlights the importance of finding treatments for a significant unmet need in pancreatic cancer," said Dr. Yusuf Yazici, Chief Medical Officer of Samumed.

FDA grants Orphan status to @Samumed_LLC (https://twitter.com/Samumed_LLC?ref_src=twsrc%5Etfw)'s SM08502 vs pancreatic #cancer (https://twitter.com/hashtag/cancer?src=hash&ref_src=twsrc%5Etfw) currently in Ph1 #clinicaltrials (https://twitter.com/hashtag/clinicaltrials?src=hash&ref_src=twsrc%5Etfw)

Hope Wnt pathway inhibitor attenuates gene expression controlling #tumor (https://twitter.com/hashtag/tumor?src=hash&ref_src=twsrc%5Etfw) differentiation & proliferationhttps://t.co/VoGqTuWhoF (https://t.co/VoGqTuWhoF)#oncology (https://twitter.com/hashtag/oncology?src=hash&ref_src=twsrc%5Etfw) @LifeSciAdvisors (https://twitter.com/LifeSciAdvisors?ref_src=twsrc%5Etfw) @LifeSciPR (https://twitter.com/LifeSciPR?ref_src=twsrc%5Etfw) pic.twitter.com/qC8SnLrOql (https://t.co/qC8SnLrOql)

— DDNews Online (@DDNewsOnline) January 3, 2019 (https://twitter.com/DDNewsOnline/status/1080948417084440576?ref_src=twsrc%5Etfw)

PROGRAM/TRIAL STATUSES

Unum Therapeutics announces 2019 goals and expected milestones from ATTCK-34-01, ATTCK-20-03 and ATTCK-17-01 trials (https://investors.unumrx.com/news-releases/news-release-details/unum-therapeutics-announces-2019-goals-and-expected-milestones/)

"Unum made substantial progress in 2018 as we reported early data from our programs in non-Hodgkin lymphoma and multiple myeloma, while simultaneously expanding applications of our ACTR platform into solid tumors and introducing a second novel technology platform, BOXR, designed to improve the functionality of engineered T cells," said Chuck Wilson, CEO of Unum. "We expect 2019 also to be a year of significant momentum, with data expected from all four of our ongoing clinical programs, including readouts from the ATTCK-20-03 and ATTCK-17-01 trials, as well as an initial data readout from our first study in solid tumors. Additionally, we continue to innovate in the field of cell therapy and have recently nominated our first development candidate from our BOXR technology platform to advance toward clinical development."

Unum Therapeutics announces 2019 goals and expected milestones https://t.co/BYa2vwoqR6 (https://t.co/BYa2vwoqR6) INVESTINGcom

— FinanzLinksMarkets (@FinanzLinksUS) January 3, 2019 (https://twitter.com/FinanzLinksUS/status/1080842996566810624?ref_src=twsrc%5Etfw)

Enrollment completed in Ph II ZENITH20 trial of Poziotinib EGFR cohort for previously treated NSCLC patients with Ex20 insertion mutations (http://investor.sppirx.com/news-releases/news-release-details/spectrum-pharmaceuticals-announces-full-enrollment-poziotinib)

"The rapid rate at which we enrolled our Phase 2 previously treated EGFR exon 20 insertion mutations cohort speaks to the critical unmet medical need and demonstrates that the poziotinib program is aggressively advancing," said Joe Turgeon, President and Chief Executive Officer of Spectrum Pharmaceuticals. "We are pleased with the results seen in smaller poziotinib trials and look forward to data from this larger, multi-center trial in the second half of the year."

Spectrum Pharma Fully Enrolls 1St Cohort in Poziotinib Study https://t.co/p8IxSGOEvo (https://t.co/p8IxSGOEvo) pic.twitter.com/GB6m9rV3Pn (https://t.co/GB6m9rV3Pn)

— ASOII (@ASOIideas) January 3, 2019 (https://twitter.com/ASOIideas/status/1080858734975315968?ref_src=twsrc%5Etfw)

100 mg cohort in Ph Ib/II trial of BTKi Vecabrutinib opened in R/R CLL and other B-cell malignancies patients (http://ir.sunesis.com/news-releases/news-release-details/sunesis-pharmaceuticals-announces-advancement-100mg-cohort-phase)

> $SNSS (https://twitter.com/search?q=%24SNSS&src=ctag&ref_src=twsrc%5Etfw) – Sunesis Pharmaceuticals initiates 100mg cohort of Phase 1b/2 trial of Vecabrutinib in patients with CLL https://t.co/iH2IjYuO8E (https://t.co/iH2IjYuO8E)
>
> — Breaking News (@MarketCurrents) January 2, 2019 (https://twitter.com/MarketCurrents/status/1080459365230960640?ref_src=twsrc%5Etfw)

"We are excited to study the 100 mg dose level as we continue the dose escalation portion of this study," said Dayton Misfeldt, Sunesis interim Chief Executive Officer. "Thus far, we have seen an encouraging safety profile, evidence of pharmacodynamic activity in CLL and other B cell cancer patients both with and without BTK C481 mutations, and some improvements in clinical symptoms. We anticipate that the target dose level for vecabrutinib will likely be between 100 mg and 300 mg BID and look forward to providing a clinical update on potentially active dose levels at a major medical meeting in the second quarter of 2019."

Enrolment completed for Ph II/III TreeTopp trial of pan-HER inhibitor Varlitinib in 2L BTC patients (http://aslanpharma.com/app/uploads/2019/01/190102-Press-Release-ASLAN-TreeTopp-Completes-Enrolment_EN.pdf)

Dr Mark McHale, Chief Operating Officer of ASLAN Pharmaceuticals, said: "TreeTopp has generated strong levels of interest from the international oncology community, which enabled us to recruit patients into the study ahead of our timeline and demonstrates the clear need for a new therapy to treat BTC, a cancer that is often diagnosed at an advanced stage with limited treatment options and poor survival rates."

> $ASLN (https://twitter.com/search?q=%24ASLN&src=ctag&ref_src=twsrc%5Etfw) Completes Enrolment for Global Pivotal TreeTopp Study investigating varlitinib in secondline biliary tract cancer. Topline data expected in 2H 2019: $ASLN (https://twitter.com/search?q=%24ASLN&src=ctag&ref_src=twsrc%5Etfw) Completes Enrolment for... https://t.co/l4YYLWVlDI (https://t.co/l4YYLWVlDI) #breastcancer (https://twitter.com/hashtag/breastcancer?src=hash&ref_src=twsrc%5Etfw) #braincancer (https://twitter.com/hashtag/braincancer?src=hash&ref_src=twsrc%5Etfw) #oncology (https://twitter.com/hashtag/oncology?src=hash&ref_src=twsrc%5Etfw) #prostatecancer (https://twitter.com/hashtag/prostatecancer?src=hash&ref_src=twsrc%5Etfw) #cancertreatment (https://twitter.com/hashtag/cancertreatment?src=hash&ref_src=twsrc%5Etfw)
>
> — Cancer News (@Cancer_bio) January 2, 2019 (https://twitter.com/Cancer_bio/status/1080416188990074881?ref_src=twsrc%5Etfw)

First patient randomized in Ph III trial of Rituximab biosimilar JHL1101 in DLBCL (https://www.prnewswire.com/news-releases/jhl-biotech-announces-first-patient-randomized-in-the-phase-iii-study-of-jhl1101-to-treat-diffuse-large-b-cell-lymphoma-300771029.html)

"Rituximab is an important biologic for the treatment of lymphoma and rheumatoid arthritis. Unfortunately, it is very expensive for patients and healthcare payers. JHL1101 would provide an affordable treatment for these patients," said Mr. Racho Jordanov, CEO, JHL Biotech. "This is a significant milestone for JHL, and a step forward

in our goal to become a global leader in developing, manufacturing, and commercializing biologics."

> Update on PRIMA Study Progression Free Survival from patients with Rituximab Maintenance https://t.co/MGns5iHAc9 (https://t.co/MGns5iHAc9) pic.twitter.com/GlEA8Or88e (https://t.co/GlEA8Or88e)
>
> — Oncology Tube (@oncologytube) January 5, 2019 (https://twitter.com/oncologytube/status/1081656949156962304?ref_src=twsrc%5Etfw)

First patient dosed in Ph III ORIENT-15 trial of PD-1 inhibitor Sintilimab in 1L Esophageal Cancer pts (http://innoventbio.com/en/#/news/124)

"The incidence of esophageal squamous cell carcinoma in Asian countries is much higher than in western countries. Today, patients have no treatment options other than chemotherapy and radiation therapy. Immune checkpoint inhibitors have brought new hope to patients with this life-threatening disease. Based on the efficacy signals and the safety profile from previous trials, we hope to validate the therapeutic potential of Tyvyt® (sintilimab injection) in combination with chemotherapy in ORIENT-15, a phase III trial," said Professor Lin Shen from the Beijing Cancer Hospital.

> China's Innovent Biologics Emerges As Immuno-Oncology Competitor With Sintilimab Approval https://t.co/SxhUSvcxAG (https://t.co/SxhUSvcxAG)
>
> — Ian Haydock (@ScripIanHaydock) January 4, 2019 (https://twitter.com/ScripIanHaydock/status/1080985029889581057?ref_src=twsrc%5Etfw)

COLLABORATIONS, ACQUISITIONS & LICENSING DEALS

BMS to acquire Celgene for $74 billion (https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-acquire-celgene-create-premier-innovative)

"Together with Celgene, we are creating an innovative biopharma leader, with leading franchises and a deep and broad pipeline that will drive sustainable growth and deliver new options for patients across a range of serious diseases," said Giovanni Caforio, M.D., Chairman and Chief Executive Officer of Bristol-Myers Squibb. "As a combined entity, we will enhance our leadership positions across our portfolio, including in cancer and immunology and inflammation. We will also benefit from an expanded early- and late-stage pipeline that includes six expected near-term product launches. Together, our pipeline holds significant promise for patients, allowing us to accelerate new options through a broader range of cutting-edge technologies and discovery platforms."

> BMS acquisition of Celgene the 3rd largest deal in Pharma history. #Pharmaceutical (https://twitter.com/hashtag/Pharmaceutical?src=hash&ref_src=twsrc%5Etfw) #businessdevelopment (https://twitter.com/hashtag/businessdevelopment?src=hash&ref_src=twsrc%5Etfw) pic.twitter.com/sv9UKpxSSp (https://t.co/sv9UKpxSSp)
>
> — Kieron Lewis (@lewiskd100) January 5, 2019 (https://twitter.com/lewiskd100/status/1081512553161912320?ref_src=twsrc%5Etfw)

AbbVie and Tizona Therapeutics to develop CD39-targeted therapeutics, including TTX-030 (https://

news.abbvie.com/news/press-releases/abbvie-and-tizona-therapeutics-announce-strategic-collaboration-to-develop-first-in-class-immunotherapy-for-cancer-targeting-cd39.htm)

"Immuno-oncology is one of AbbVie's key focus areas in our mission to discover and develop medicines that drive transformational improvements in cancer treatment," said Mo Trikha, Ph.D., Vice President, Head of Oncology Early Development, AbbVie. "Exploring the tumor microenvironment as a source of targets that can be modulated to inhibit cancer growth holds tremendous promise. The Tizona team has generated compelling preclinical data for their TTX-030 program, and we look forward to a productive collaboration focused on rapidly advancing this novel first-in-class antibody."

> Portfolio News: Tizona Therapeutics @tizonatx (https://twitter.com/tizonatx?ref_src=twsrc%5Etfw) and AbbVie @abbvie (https://twitter.com/abbvie?ref_src=twsrc%5Etfw) form a collaboration to develop first-in-class immunotherapy for cancer targeting CD39 https://t.co/uUhrEuJklX (https://t.co/uUhrEuJklX) pic.twitter.com/AmiKiNTcOW (https://t.co/AmiKiNTcOW)
>
> — Abingworth (@Abingworthbio) January 3, 2019 (https://twitter.com/Abingworthbio/status/1080841644679880704?ref_src=twsrc%5Etfw)

Takeda announces multiple cell therapy collaborations to advance its immuno-oncology portfolio (https://www.takeda.com/newsroom/newsreleases/2019/takeda-announces-multiple-cell-therapy-collaborations-to-advance-the-companys-novel-immuno-oncology-portfolio2/)

"We are excited by the recent momentum in oncology R&D, especially around the curative potential of cell-based therapies through our growing partnership network," said Phil Rowlands, Ph.D., Head, Oncology Therapeutic Area Unit, Takeda. "We look forward to continuing to collaborate with some of the leading pioneers in the field to fuel research and discovery with the aim of targeting novel mechanisms of action in the cancer-immunity cycle to help us fulfill our aspiration to cure cancer."

> Takeda builds arsenal for immuno-oncology research, creates cell therapy group: Takeda's presence in cancer — fortified by its $5.2 billion Ariad buyout — is growing, as it announced a range of agreements in immuno-oncology and the creation of a cell... https://t.co/Fp7440eEHT (https://t.co/Fp7440eEHT)
>
> — cafepharma (@cafepharma) January 4, 2019 (https://twitter.com/cafepharma/status/1081168252565315585?ref_src=twsrc%5Etfw)

Atara Biotherapeutics exclusively licenses Mesothelin-targeted CAR T for mesothelin-associated solid tumors (http://investors.atarabio.com/news-releases/news-release-details/atara-biotherapeutics-exclusively-licenses-mesothelin-targeted)

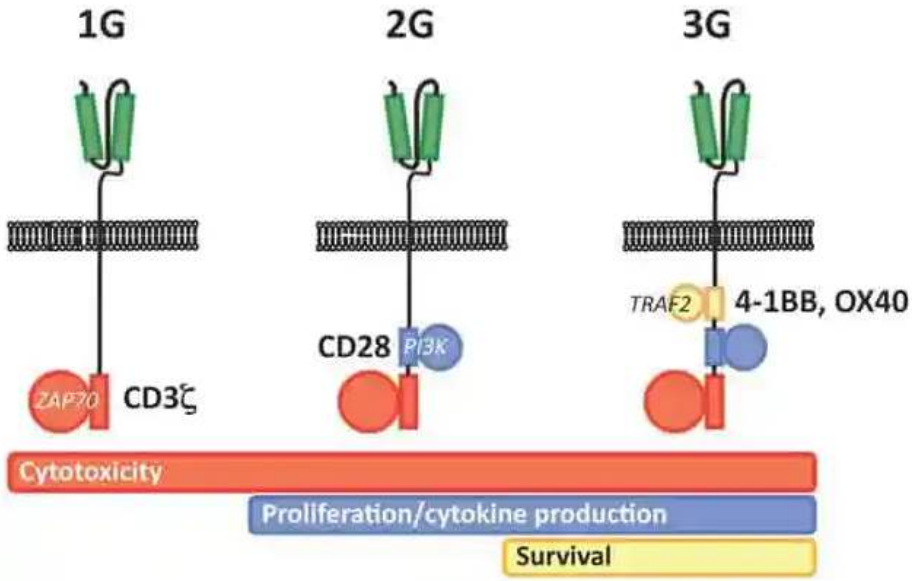
> Atara Biotherapeutics Exclusively Licenses Mesothelin-Targeted CAR T Immunotherapy for Solid ... https://t.co/4FQq9Fdocq (https://t.co/4FQq9Fdocq)
>
> — Follement-bijoux (@Follementbijoux) January 3, 2019 (https://twitter.com/Follementbijoux/status/1080893580179324928?ref_src=twsrc%5Etfw)

"We look forward to collaborating with Atara to develop a next-generation mesothelin-targeted CAR T immunotherapy," said Michel Sadelain, M.D., Ph.D., Director, Center for Cell Engineering, and Head, Gene

Expression and Gene Transfer Laboratory at MSK. “Our novel mesothelin 1XX CAR is designed to extend functional CAR T cell persistence by sustaining T cell effector functions without precipitating exhaustion provides a complementary technology to tackle challenging tumor microenvironments.”

OTW Trivia

Generations of Chimeric Antigen Receptor T-Cells (CAR-Ts)



*(**Source**: https://commons.wikimedia.org/wiki/File:Depiction_of_3_generations_of_CARs.jpg (https://commons.wikimedia.org/wiki/File:Depiction_of_3_generations_of_CARs.jpg))*

CAR-Ts (chimeric antigen or artificial receptor T cell receptor) are engineered to design a T cell with an arbitrary specificity by attaching it to a monoclonal antibody. There are three generations of CAR-Ts:

1. **First generation CAR-Ts:** The original, first-generation CAR-Ts have CD3 ζ transmembrane or intracellular domain which transmit the signals from endogenous TCRs. However, these first gen CAR-Ts could not produce enough IL-2, so in order to kill tumor cells IL-2 was administered.
2. **Second generation CAR-Ts:** Second gen CAR-Ts added various intracellular signaling domains from co-stimulatory protein receptors (such as CD28 or CD137/4-1BB) to the cytoplasmic tail of the CAR-Ts. These extra domains improved the cytotoxicity, proliferative responses, and sustained effector functions of CAR-Ts and extended the life of CAR-Ts *in vivo.*
3. **Third generation CAR-Ts**: The third-generation CARs were engineered by combining multiple signaling

domains (e.g., CD3ζ-CD28-OX40 or CD3ζ-CD28-41BB) to further augment activation signals with stronger cytokine production and killing ability. Enhanced cytotoxicity, however, was accompanied by substantial toxicity issues.

4. **Fourth generation CAR-Ts:** The fourth gen CAR-Ts use second gen constructs as a base and have added IL-12 component to boost T-cell activation and attract innate immune cells.

*(**Source**: https://www.creative-biolabs.com/car-t/car-design-construction.htm (https://www.creative-biolabs.com/car-t/car-design-construction.htm))*

About the Author:


(https://i0.wp.com/www.sciwri.club/wp-content/uploads/2018/03/RT.jpg)

Richa (https://www.linkedin.com/in/richatewari/) earned her PhD at the National Brain Research Centre, India. For her thesis, she worked on the dreaded Glioblastoma multiforme. That was her first in-depth exposure to academic research in cancer biology. After her PhD, she expanded her research experience by working in the field of immunology at UCLA, USA. After her return to India, Richa switched to a corporate setting but continued her engagement with the cancer field. She is currently loving her work, which affords her the opportunity to continue developing her knowledge in the biomedical field of cancer. Outside of work, she enjoys watching, identifying and photographing birds.

Editor and Blog Design:

Abhi Dey (https://www.linkedin.com/in/abhinavdey/)

Abhi graduated from the Molecular Biophysics Unit of IISc (Bangalore, India) in 2011. As a Biomedical Scientist, he has worked with all three life-forms in his 13-year research career, viz., particulate, unicellular and multicellular. He is currently an Assistant Scientist at Emory University (Atlanta, GA) studying mechanisms of tumor recurrence in kids with brain tumors. As a postdoctoral fellow, he was the recipient of two Young Investigator Awards from Alex Lemonade Stand Foundation (Philadelphia, PA) and Rockland Immunochemicals. His current research has been funded by Northwestern Mutual Foundation (Milwaukee, WI), CURE Childhood Cancer Foundation (Atlanta, GA) and American Association for Cancer Research (AACR). When he is not on the bench you will find him spending time with his family or exploring the world through traveling and blogging.

Image Sources: Wikipedia and Twitter

Cover image: Acute lymphoblastic leukemia (ALL), peripheral blood of a child, Pappenheim stain, magnification x100 Source (https://commons.wikimedia.org/wiki/File:ALL_-_Peripherial_Blood_-_Diagnosis_-_01.jpg)

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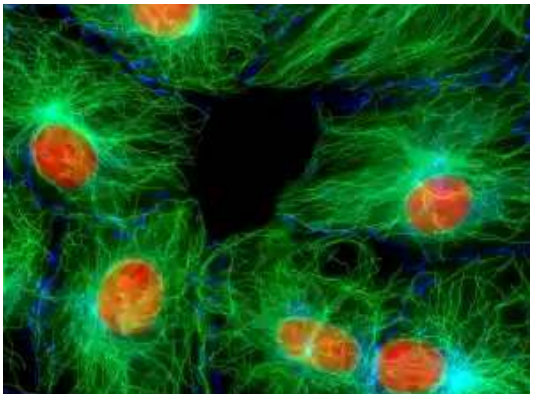

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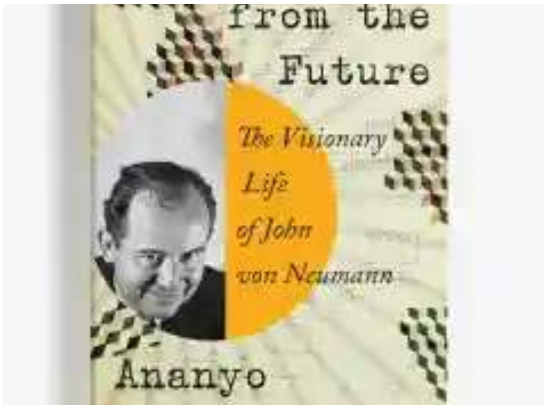

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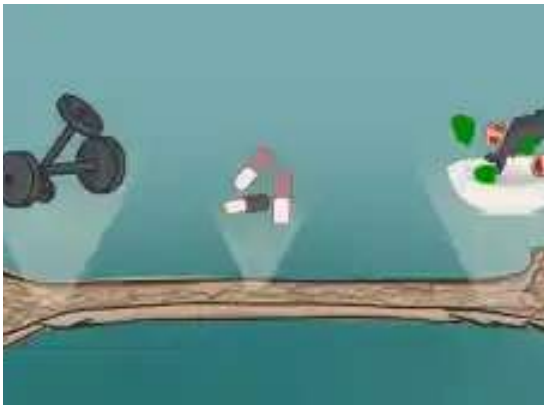

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