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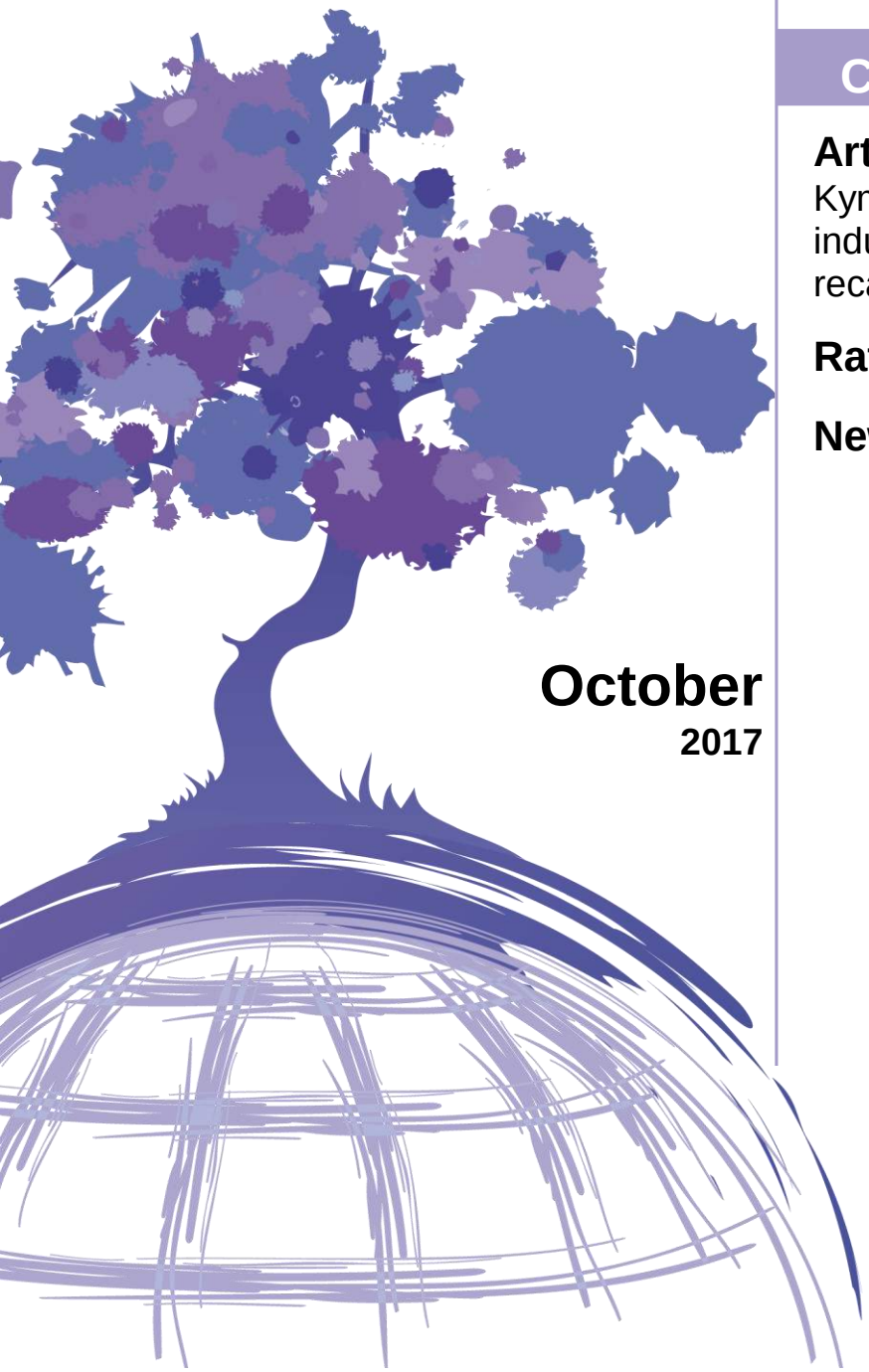

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Contents

Article

Kymriah®, a revolutionary drug to induce treatment remission in recalcitrant cancers

By **Dr. Malathi Lakshmikumaran**

In an unprecedented historic action, the US Food and Drug Administration (FDA) and Oncologic Drugs Advisory Committee (ODAC) unanimously approved CTL019 (tisagenlecleucel) or Kymriah®, an investigational chimeric antigen receptor T cell (CAR-T) therapy. Kymriah® has been approved for its use in the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia in paediatric and young adult patients, making it the first approval of a CAR-T therapy for humans. Novartis Inc. in partnership with University of Pennsylvania (UPenn) had filed a patent application (WO 2016109410 A2) for this technology on December 28, 2015. It has a priority date of December 29, 2014, in the United States and Canada. The patent application primarily recites a method of making immune effector cells including T cells that can be engineered to express chimeric antigen receptors (CARs) on their surface.

In layman's terms, it involves reprogramming an individual's immune cells to make them better at targeting diseased cells such as cancerous cells. This approval has made Novartis Inc. closer to potentially delivering the first-ever commercially approved CAR-T therapy, Kymriah®, to the patients in need.

Acute lymphoblastic leukaemia (ALL) is a type of cancer that occurs due to uncontrolled growth of white blood cells, particularly B cells, which overtake other types of cells in the bone marrow. The disease causes patients to become anaemic and prone to infections, and they bruise or bleed easily. ALL is the most common childhood cancer in the US. In India, it is the ninth most common cause of death among young children.

Chimeric Antigen Receptor (CAR) therapy is a kind of an adoptive cell therapy, which involves a combinatorial methodology that includes the aspects of cell therapy, gene therapy and immunotherapy methods. Cell therapy entails cellular material being injected into a patient that involve intact, living cells, for example, T cells capable of fighting cancer cells via cell-mediated immunity. Gene therapy is the delivery of nucleic acid polymers into a patient's cells as a drug to treat disease. Lastly, immunotherapy, also called biologic therapy, uses patient's own immune system to repair, stimulate, or boost their natural immune response.

Technically, the CAR-T therapy involves the extraction of T cells from the individual patient, which are then genetically modified and expanded under in vitro conditions. The chimeric T cells are then re-infused into the patient, ready to fight the tumour by specifically targeting the antigens on the cancer cell surface that leads to mounting of an immune response and consequently, the cell death of the targeted cancer cell as represented in **Figure 1.**

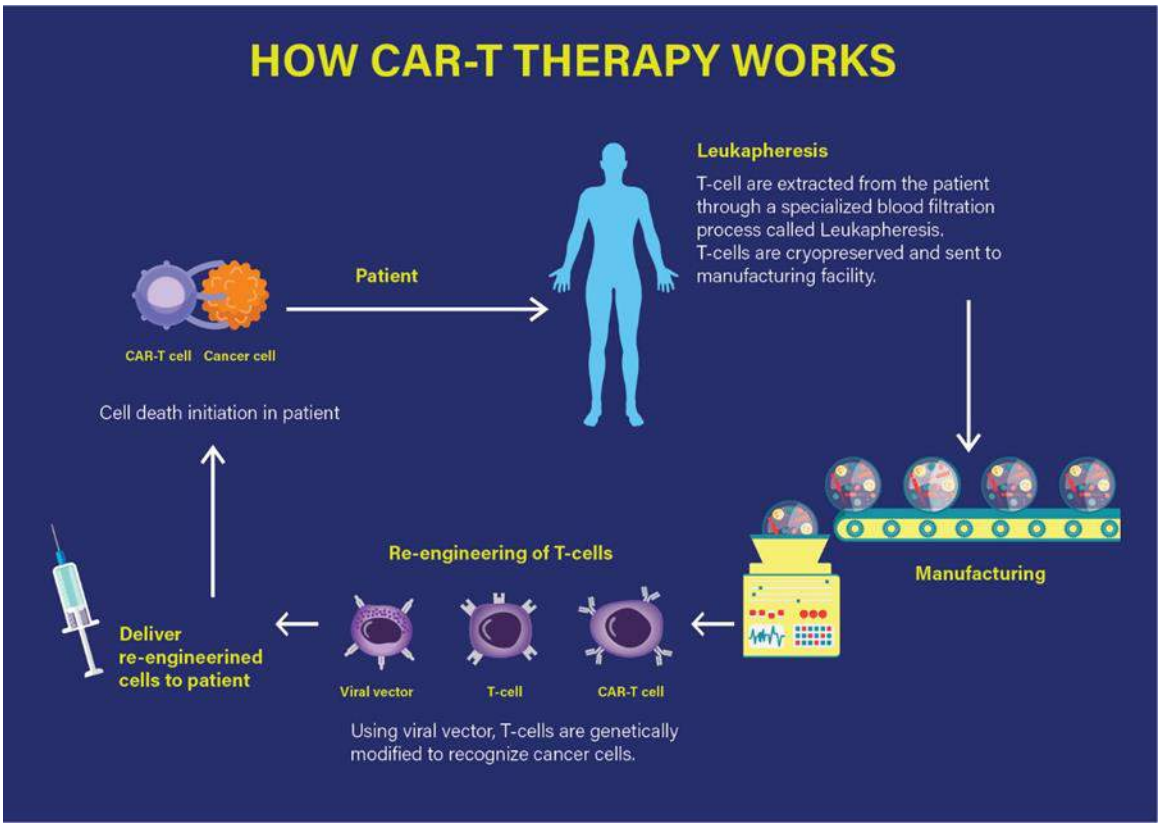

Figure 1: How CAR-T therapy works. (Adapted from https://labiotech.eu/car-t-approval-fda-novartis-kymriah/)

Specifically, a CAR-T therapy consists of the infusion of engineered T cells that express a chimeric antigenic receptor on their cell membrane. The CAR has an external (extracellular) target-binding domain, designed to recognize a specific tumour antigen; and an internal (cytosolic) activation domain responsible for activating the T cell. The CAR-T cell binds its target, such as cluster of differentiation (CD)-19. CD19 is one of the predetermined target antigens overexpressed on the surface of tumour cells such as B cells, in case of the patients with ALL. Coupling the T-cell receptor to a CD3ζ signalling domain paved the way for the first generation of CAR-T cells that were efficacious against CD19-expressing B-cell malignancies as investigated by the Novartis-UPenn partnership.

Novartis Inc. has a long history of being at the forefront of transformative cancer treatment. In 2012, Novartis Inc. partnered up with UPenn to propagate CAR-T therapies, including Kymriah®, the drug based on the CAR-T technology first developed by UPenn. Subsequently, other co-stimulatory domains have been included in the next generations of chimeric receptors to further enhance the immune response. The product approved and launched in partnership by Novartis Inc. is a one-time treatment for B-cell ALL. The remission rates have been reported as 83% after three months in clinical trials with patients, who did not respond to standard treatments.

Similar to cancer therapies, CAR-T clinical trials have reported severe side-effects in the treated patients, such as neurotoxicity, namely cerebral edema; and cytokine release syndrome (CRS). The Kymriah® trials also disclosed a strong cytokine release syndrome (CRS) in 49%

of the treated patients. Additionally, a small percentage of CAR-T therapy treated patients have shown relapses due to antigen loss such as CD19 from the surface of the tumorigenic B cells. However, most of these modalities are being dealt with in a combinatorial treatment regimen. For complications with CRS, conventional co-therapies, such as Actemra®, a rheumatoid arthritis drug, which is an anti-IL6 receptor antibody, has been successfully employed. Another approach has been the implementation of additional targets for the CAR-T cells, for example, CAR-T cell mixtures targeting CD19 and CD22 respectively are infused in a combination therapy into the individual cancer patients. In addition to the FDA's ODAC and subsequently, the FDA approval in August 2017, Kymriah® has also previously received PRIority MEdicines (PRIME) designation from the European Medicines Agency (EMA) in 2016.

Future looks bright and promising with this landmark approval that is going to change the treatment options in humans increasing survival in other recalcitrant diseases and decreasing morbidity. The advent of ground-breaking genetic engineering tools such as CRISPR/CAS9 system are adding to the capability and ease of transforming the individuals cells from patients, be it diseased or therapeutic cells. A paradigm shift is expected towards transformation to such adoptive cell therapies to supplement the reach of conventional surgical, chemo- and radio-therapeutic options along with the other advancements in medicine including the promising targeted therapies with small molecules and biologics.

[The author is Executive Director, IPR Practice in Lakshmikumaran & Sridharan, New Delhi]

Ratio decidendi

Trademark renewal – Effect of non-raising of defects and non-advertising of removal by Registry

A Single Judge of the Delhi High Court has dismissed a Writ Petition challenging an Order passed by the Registrar of Trademarks renewing the trademark for a period of 10 years in favour of Respondent. The petitioner asserted that the application for renewal was not filed before expiration and therefore in terms of Section 25(3) of Trademarks Act, the Registrar was required to remove the trademark from the Register. It was also argued that since the renewal application (filed after 17 days) was not accompanied by surcharge, in terms of Rule 11(5) of the Trademarks Rules, 2002 (Rule 10(5) of the 2017 Rules), the application was *non est* and hence could not have been scrutinised by the Registry.

The Court however dismissed the contentions, observing that the word used in Section 25(3) is 'may' and not 'shall', and that the proviso to Section 25(3) is couched in negative language which proscribes the Registrar from removing the mark, if an application is made in the prescribed form and surcharge is paid within a period of six months. It was noted that, in any event, the Registrar has to continue to retain the mark on the Register till expiry of six months from expiry of registration in order to provide a full play to proviso to Section 25(3). The Court in this regard also observed that since no deficiency was pointed out at the material time by the Registry,

respondent cannot be deprived of its valuable rights to cure defects within the prescribed period. It was noted that the Registrar further did not advertise removal of the trademark as required under section 25(4) read with Rule 66. The contention that the petitioner was required to be heard before granting renewal was also rejected by the Court observing that since the matter of renewal of trademark is strictly between Trademark Registry and the registered proprietor of the trademark, question of any third party right being considered at that stage does not arise. [*Epsilon Publishing House Pvt Ltd. v. Union of India* – Judgement dated 18-9-2017 in W.P. (C) 5568/2017 & CM No. 23379/2017, Delhi High Court].

Sale of grey market goods – UK SC upholds criminal penalty

Supreme Court of the United Kingdom has held that sale of grey market goods, i.e. goods which were authorized by the right holder to be manufactured by the third parties but were not allowed to be sold by them, would also attract criminal penalties under Section 92(1) of the Trade Marks Act 1994 of the United Kingdom. The contention that such goods are not true counterfeits and hence Section 92(1)(b) will not be applicable to these goods, was rejected by the Court. It was observed that the expression "such a sign" in (b) only means a sign such as is described in (a), and that the sign described in (a) is a sign which is "identical to, or likely to be mistaken for, a registered trade mark", and hence the grey market goods are caught by the expression.

The Court also noted that there was no point to suggest that the Parliament confined itself to criminalising fake goods but abjured criminalising of grey market goods. Reliance placed on wording of the predecessor of Section 92, Section 58A of the Trade Marks Act 1938, was also rejected by the Court in this regard. Similarly, dismissing the appeal, the Court rejected the argument of breach of rights of the appellant under Article 1, Protocol 1 to the European Convention on Human Rights noting that the Trademark Act does not deprive them of any property which they have and that the most it does was to regulate their use or the manner of their disposal. [*RvT*, Judgement dated 3-8-2017 in UK SC]

Use of trademark publicly and outwardly rather than large scale commercial use constitutes genuine use

The applicant, sold biscuits in distinctive packaging which was registered as a three-dimensional mark. The European Union Intellectual Property Office (EUIPO) cancelled the registration for lack of genuine use of the mark for a continuous period of five years. The applicant had changed the colour combination of the packaging and the EUIPO was of the view that the mark had not been used in the form it was registered. The CJEU however, held that on comparing the marks as registered and as used, the alterations like use of the word 'chocolate' along with the registered words 'mini O2', and stylisation of the word 'Gullon' were only an evolution of the mark and the essential elements had been retained. As regards 'genuine use' the Court, relying on precedents, held that production of accounting documents setting out sales figures or invoices is not necessary for the purposes of establishing genuine use of the mark and genuine use of a mark requires that that mark be used publicly and outwardly. It was also held that using a mark outwardly need not be aimed only at end consumers, and that the relevant public at which marks are aimed could include specialists, industrial customers and other professional users. In the case of the applicant, the documents produced- advertising material, press articles, screen shot of the website, etc. would lead to an inference that consumers had come

into contact with the goods directly or indirectly. Thus, the Court annulled the decision of the EUIPO. [*Galletas Gullón, SA v. European Union Intellectual Property Office*, Judgement of General Court, CJEU, dated 23-10-2017]

Passing off title of a non-existing film - HC refuses injunction

Madras High Court has dismissed an injunction application praying to restrain the respondent permanently from passing-off the title for a motion film, 'MERRASALAITAN' with 'MERSAL'. Court held that allegation of passing off, made in respect of a title to a non-existing film as on date, was based on the premise of probabilities and assumptions - assumed right to the title, assumed prejudice to reputation caused by non-existent use of the film title and assumed deception by the respondents.

The Court in this regard observed that there was no evidence on record to show that respondent had exploited the reputation of applicant in connection with the use of title in question, as the title has not been put to use even by applicant. It rejected the applicant's claim to have protected his right over the title by registering with Tamil Nadu Film Producers Council, and observed that such registration would not afford any statutory protection. [*A. Rajendran v. Thenandal Studios Ltd.* – Order dated 6-10-2017 in O.A. No. 942 of 2017 in C.S. No.747 of 2017, Madras High Court]

News Nuggets

Singapore High Court rules that it does not have power to revoke patent by way of counterclaim in infringement proceedings

In a recent decision *[Sun Electric Pte Ltd. v. Sunseap Group Pte Ltd.]* the Singapore High Court held that it does not possess original jurisdiction under the Patents Act to revoke a patent by way of a counterclaim in infringement proceedings. The High Court was of the view that on a literal and black-letter interpretation of Section 80(1) of the Singapore Patents Act, the provision only provides that the Registrar may revoke a patent and that Section 80(1) of the relevant Act is entirely silent as to whether the court may do so. It was observed that an order declaring the asserted claims invalid is not the same as an order for the revocation of the patent. The High Court held that the fact that it has jurisdiction to hear a claim concerning infringement of exclusive rights by patent or a claim against the proprietor of the patent, in circumstances where the validity of the patent is raised as a defence, does not necessarily mean that it has the jurisdiction or power to hear all proceedings, disputes and issues arising under the Patents Act including those which seek revocation of the patent.

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