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Introduction

Presenters

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Agenda

- Investment landscape for immunotherapy, including CAR-T
- Key IP issues relating to immunotherapy and CAR-T
- FDA regulatory pathways impacting success of CAR-T and immunotherapy
- Reimbursement/pricing strategies that will impact the market

Overview of Immunotherapy Landscape

- Monoclonal antibodies as Immune Checkpoint Inhibitors (e.g., anti-PD1 Abs – Nivolumab & Pembrolizumab)
- Antibody Drug Conjugates (ADCs) (e.g., Kadcyla – trastuzumab MAb conjugated to emtansine)
- Bispecific Antibodies (e.g., blinatumomab targeting CD19 and CD3 to bring immune cells closer to cancer cells)
- T-cell therapy, including CAR-T (e.g., Kymriah & Yescarta – modified T cells directed to CD19)

Overview of Immunotherapy Landscape

- Individualized CAR-T treatments are administered a single time and customized for a single patient
- Traditional immunotherapies based on antibodies are for larger patient populations and require multiple treatments
- Some traditional antibody-based immunotherapies are now facing or will soon face biosimilar competition (e.g., Herceptin)

Overview of Immunotherapy Landscape

KYMRIAH™ (tisagenlecleucel) suspension for intravenous infusion
Initial U.S. Approval: 2017

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. (2.2, 2.3, 5.1)**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed. (5.2)**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. (5.3)**

----------INDICATIONS AND USAGE----------
KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. (1)

Kymriah price: $475,000 (only one treatment needed)

Adcetris price: $100,000 (over course of treatment)

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use
Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See full prescribing information for complete boxed warning.
JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.1).

RECENT MAJOR CHANGES

Indications and Usage, primary cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides (1)	11/2017
Dosage and Administration, Dosage (2.1)	11/2017
Warnings and Precautions, Gastrointestinal Complications (5.12)	11/2017

INDICATIONS AND USAGE
ADCETRIS is a CD30-directed antibody-drug conjugate indicated for treatment of adult patients with:

- Classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation (1.1).
- Classical Hodgkin lymphoma after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates (1.2).
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen (1.3).

  Accelerated approval was granted for the sALCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy (1.4).

DOSAGE AND ADMINISTRATION

- Administer only as an intravenous infusion over 30 minutes every 3 weeks (2.1).
- The recommended dose is 1.8 mg/kg up to a maximum of 180 mg (2.1).
- Reduce dose in patients with mild hepatic impairment (2.2).

Overview of Immunotherapy Landscape

- Emerging CAR-T carries higher price but only requires one treatment and works in patients for whom all other options failed
- Will cost of production decline with improved technology, lowering the price over time?
- Will safety profiles improve?
- Will new pricing approaches be adopted such as those based on patient outcomes?
- How will improving antibody and antibody drug conjugate therapy impact market and biosimilars to them?

Conflict Statement

- Involved with ADC Therapeutics (Switzerland)
  - PBD-based ADCs
  - Responsible for IP strategy
  - Personally invested
  - Invested via the two private equity funds with which I work
- Previously involved with Spirogen, which was sold in October 2013 to AstraZeneca/Medimmune
- Will present on a Business Perspective of relevant facts for consideration in investments
  - ADC companies such as ADCT, Stemcentrx/AbbVie, AZ/MedImmune, Seattle Genetics, Genentech and others
  - CAR-T companies such as Kite/Gilead, Juno, Novartis and others

Investment Opportunities and Value for CAR-T and ADC

- Some recent relevant facts:
  - Stemcentrx acquired for around $10B by AbbVie in 2016
    - RovaT is PBD based ADC targeting DLL3 showing efficacy in SCLC – median survival less than one year
    - 68 percent stabilization of disease, 18 percent reduction in tumor size
      - If overexpress DLL3, see 89 percent and 39 percent, respectively
      - As third line treatment, saw 92 percent stabilized with two living longer than 18 months
    - Adverse events include rash, fluid accumulation and low platelet count
    - BLA expected in next few months

Investment Opportunities and Value for CAR-T and ADC (cont'd.)

- Some recent relevant facts:
  - Novartis CAR-T
    - Approval for Kymriah this year for patients up to 25 years old with B cell precursor acute lymphoblastic leukemia – cost $475K
    - 83 percent remission compared to a 10 percent 5-year survival rate
    - Network of centers to train for use of therapy and appropriate care
    - One time treatment – adverse reactions in 49 percent of patients at grade 3 or 4 including cytokine release syndrome
    - REMS – risk evaluation and mitigation strategy
  - Juno
    - Permanently halted CAR-T program after two patient deaths this year

Relevant Facts (cont'd.)

- Kite
  - Acquired by Gilead for about $12B this year – for CAR and TCR
    - Engineers cells to empower the immune system to recognize and kill tumors
    - BLA submitted for Yescarta for treatment of relapsed and refractory large B cell lymphoma in patients who failed at least two traditional treatments and not eligible for transplants
    - Priority review granted and approved six weeks early
    - EU – submitted at MAA to EMA for similar indication and others
    - Based on data showing positive results in patients with chemorefractory aggressive non Hodgkin lymphoma
    - 72 percent response with 51 percent complete remission – median follow up of eight months
    - Four fatalities with three related to CAR-T
    - REMS boxed warning
    - Cost $375K

Relevant Facts (cont'd.)

- ADCs are biologics with relatively straightforward CMC
  - Multiple dosing likely vs. one dose for CAR-T
  - Not specific for patients
- CAR-Ts are biologics with complex CMC
  - 17 days to re-engineer cells specific for patient
  - Said to be for patients who have run out of options
  - Side effect profile includes death and cytokine release syndrome
  - Potentially vulnerable to infections and may require other therapies to deal with adverse effects

What Factors to Consider to Assess Long-Term Prospects of Investments?

- Will the FDA approve the therapy?
- Is this a platform technology for the company or a one "drug" deal?
- CMC – can this be performed effectively and reproducibly?
- Value of IP
  - Biologic protection of 12 years in the U.S.
    - Will this apply for personalized technology?
    - NCE gets five years in the U.S. and 10 in EP/JP
  - Can you protect a product that is sold or used by a doctor?
  - How to police in countries with a patent – and can you avoid in other countries?
  - Any trade secrets that prevent competition – e.g., to reduce chance of adverse effects or death?

What Factors to Consider to Assess Long-Term Prospects of Investments? (cont'd.)

- Cost of treatment and reimbursement likelihood
- Is this a first line or later line treatment – what is the chance to make it an earlier treatment?
- What is the opportunity for off-label use?
- Will you sell a kit, or use a central lab?

How Do You Value Companies When the Price for Treatment is $375K vs. Lower Prices for Alternate Treatments?

- Orphan drugs are priced at these high levels, so it is not without precedent – some as high as $840K a year, 29 are $336K a year – there is no choice but to pay in those instances.
- What if the payment is made only if the patient survives?
- What if reimbursement is made only if the patient has the correct antigen?
- Is the treatment a cure vs. an increased chance to survive longer?
- What is the adverse effect profile in comparison?
  - What is the quality of life with and without treatment?
- What other options exist?
- Does the market show that ADCs and CAR-T companies have similar values vis a vis Stemcentrx and Kite?

Will New Gene Editing Techniques Help to Lower the Costs of Single Patient Immunotherapy?

- Not clear how this will be approved as genetic changes are not fully reproducible although advances are being made
- CMC still an issue and perhaps even more of a challenge given the complexity of the CRISPR system
- Not clear it would bring costs down and certainly may add a layer of royalty payments

How Will Reimbursement Models Accommodate Prices for Therapies Over $375K?

- Okay for some orphan diseases for other technology?
- Possibly an issue in EP where efficacy and value are considered closely
- Depends on the benefit expected and the cost for that benefit
- If becomes a first line therapy, will that cost be less relevant as saves on other costs?
- What if that cost is just the start and other costs are incurred for treatment of adverse effects?
- What if the T cells are collected early in case the therapy is needed, so that it can be applied immediately upon failure of others – how is that to be reimbursed?

USPTO Initiative

- Cancer Immunotherapy Pilot Program
  - Applications relating to immunotherapy can be advanced out of turn (accorded special status).
    - Application contains at least one claim encompassing a method of ameliorating, treating, or preventing a malignancy in a human subject wherein the steps of the method assist or boost the immune system in eradicating cancerous cells
    - File a petition to make special and the objective of the Pilot Program is to complete the examination of the application within twelve months of special status granted

USPTO Initiative (cont'd)

- Application will be advanced out of turn for examination without meeting other accelerated examination requirements under other programs
  - *e.g.,* the requirement for an examination support document or the Prioritized Examination (Track I) program
- Pilot program has been extended to December 2018 – originally set to expire in June 2017
  - Petitions must be filed on or before December 31, 2017
- USPTO can extend or terminate, depending on the effectiveness of the program

IP Strategies

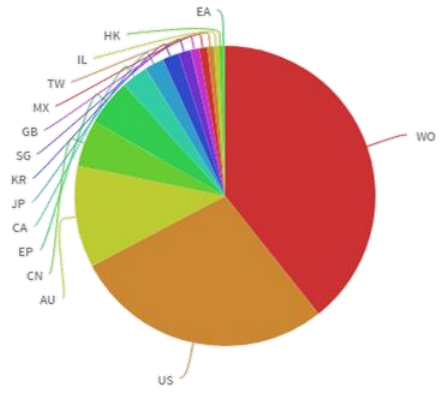
- Patent filing vs. trade secret
  - Competitive edge
    - Preparing an enabling disclosure, but withholding certain information to maintain competitive advantage
    - Decision to not file application
  - Identifiable infringer? Single infringer?
    - Difficult to show infringement activity?
    - Activities be tied to a single infringer?
  - Competitor design around opportunities
    - Strategic considerations for filing outside U.S.

IP Strategies (cont'd)

- Patent claiming
  - Manufacturing method
    - Preparation of cells just removed from body
    - Manufacturing CAR-T cells
    - Improved methods (e.g., using TALEN, CRISPR or other gene editing technology for CAR-T cells)
  - Compositions
    - CAR-T cells themselves (new constructs, new targets, on/off switches, modifications for optimization, etc.)
    - Expanded CAR-T cells
  - Treatment method
  - Mechanism of action

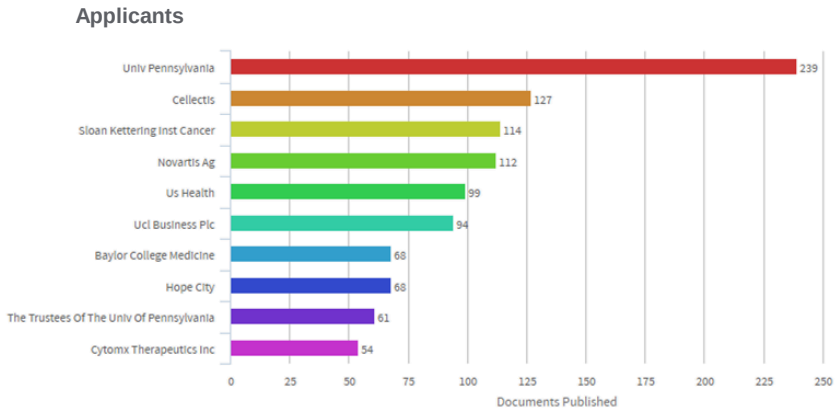
Where Are Patents Being Filed?

Jurisdictions



https://www.lens.org/lens/search?p=0&q=%22chimeric+antigen+receptors%22&v=analysis#f/

By Whom?



https://www.lens.org/lens/search?p=0&q=%22chimeric+antigen+receptors%22&v=analysis#f/

Overview

- Regulatory issues
  - Two recent CAR-T products BLA approvals
    - Kymriah (tisagenlecleucel) – Novartis
    - Yescarta (axicabtagene ciloleucel) – Gilead/Kite
  - Accelerated development and approval process
  - Great rewards, but also significant patient risks
  - REMS and postmarketing studies

Indications for Use

- Kymriah – B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse (in patients aged 2-25)
- Yescarta – Treatment of adult patients with relapsed or refractory large B-cell non-Hodgkin lymphoma in patients for whom at least two other types of treatments for their blood cancer failed
  - Submittal Date / Approval Date
    - Kymriah: Feb. 2, 2017 / Aug. 30, 2017 (6 months, 28 days)
    - Yescarta: March 31, 2017 / October 18, 2017 (6 months, 18 days)

Development Process

- Kymriah development timeline

Date	Milestone
4/22/2013	PreIND Meeting
3/03/2014	PreIND Meeting
3/04/2014	Special Protocol Assessment (SPA)
9/23/2014	IND 16130 submission
9/23/2014	Rare Disease Designation
1/31/2014	Orphan Designation: Acute Lymphoblastic Leukemia
4/08/2015	First subject enrolled into Study CCTL019B2202
2/29/2016	Breakthrough Therapy Designation
11/21/2016	Pre-BLA Meeting
11/23/2016	Efficacy Assessment: Data Cut-off
12/16/2016	CCTL019B2202 Interim Analysis with 6 months follow-up
1/19/2017	Deaths and SAEs in ongoing studies cut-off
2/02/2017	BLA 125646 submission
3/15/2017	Rare Pediatric Disease Designation
3/28/2017	BLA 125646 filed
7/12/2017	Oncologic Drugs Advisory Committee Meeting
10/03/2017	PDUFA Action Due Date

Development Process

- Yescarta development timeline similar
  - IND submitted 12/14
  - Orphan designations for DLBCL (3/14), PMBCL (4/16), and FL (4/16)
  - Breakthrough designation on 12/15
  - Rolling submission – first module 12/2/16, final 3/31/17
  - PDUFA action date 11/29/17 (approval 10/18/17)

Rewards / (But) Risks

- Kymriah
  - The overall remission rate within three months of treatment was 83 percent.
- Yescarta
  - The complete remission rate after treatment with Yescarta was 51 percent.
- But: both contain black box warnings relating to cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms, and for neurological events, along with other serious side effects.

Rewards / (But) Risks

- REMS ("Risk evaluation and mitigation strategy")
  - REMS, includes elements to assure safe use (ETASU). The FDA is requiring that hospitals and their associated clinics that dispense be specially certified. As part of that certification, staff involved in the prescribing, dispensing or administering are required to be trained to recognize and manage CRS and nervous system toxicities.
  - Also, patients must be informed of the potential serious side effects and of the importance of promptly returning to the treatment site if side effects develop.
- Postmarketing studies also required
  - Both must conduct a multi-center study involving 1000/1500 patients enrolled within three months over a period of five years.
  - All subjects must be followed for 15 years from date of infusion.
  - Final study reports for both are due in December 2038.

Regulatory Items of Interest

- Both received:
  - 12-year biologics exclusivity
  - Orphan designations/exclusivity
    - PREA studies waived because of orphan designation
  - Priority Review and Breakthrough designations
- Kymriah also received:
  - Rare pediatric disease designation and voucher
    - Value has ranged from $67M to $350M
    - This is Novartis' second voucher

FDA Support of Technology

- FDA Commissioner Scott Gottlieb, M.D.
  - (survivor of Hodgkin's lymphoma)
- "Today marks another milestone in the development of a whole new scientific paradigm for the treatment of serious diseases. In just several decades, gene therapy has gone from being a promising concept to a practical solution to deadly and largely untreatable forms of cancer."
- "This approval demonstrates the continued momentum of this promising new area of medicine and we're committed to supporting and helping expedite the development of these products. We will soon release a comprehensive policy to address how we plan to support the development of cell-based regenerative medicine. That policy will also clarify how we will apply our expedited programs to breakthrough products that use CAR-T cells and other gene therapies. We remain committed to supporting the efficient development of safe and effective treatments that leverage these new scientific platforms."

Cost Considerations; Price Controls?

- Kymriah (Novartis) = $475,000; Yescarta (Gilead) = $373,000
  - Administered once; one chance to get paid!
- Kymriah pursuing a performance-based approach: patients will only pay if they have a response within 30 days of receiving the drug (Yescarta not yet on that model)
  - CMS (Medicare) apparently on board (per Novartis), but the details are unclear. Rep. Doggett letter dated September 13, 2017, asks 14 questions about CMS' agreement
- Express Scripts considering other alternatives: e.g., payment for treatment over time; establishing insurer risk pools, financing one-time payments. Consider how to handle when patient changes insurance.
- BlueCross BlueShield of North Carolina – CAR-T therapy covered when shown to be medically necessary because medical criteria and guidance are met (lots of requirements)

Kymriah Questions (Rep. Doggett)

- Estimates of numbers of patients?
- Source of 1-month period used to measure drug response? What if subsequent relapse?
- What is the agreed upon definition of success for 1-month outcome?
- CMS' plan to track savings?
- Metrics of success for program?
- How will patient data be collected by CMS?
- When will arrangement be ready – at market?
- What mechanism will be used to implement? Medicare or Medicaid?
- Novartis paid at the outset (and then refund) or after success?
- Consideration of Novartis profit margin and relation to price?
- Recognition of U.S. investment of $200M in pricing?
- Which political employees were involved in deciding approach?
- Will Novartis charge U.S. taxpayers [sic] the same as other companies, and did CMS consider Novartis' pricing plans?
- Is CMS willing to consider use of royalty free rights on CAR-T patents to enable more supply and lower prices?

NEHI Value-Based Contracting in Oncology (Oct. 2017 Whitepaper)

Recommendations:

- Stakeholders should expedite data collection efforts and develop patient-reported outcomes measures
- FDA should finalize guidance on exchange of information on new, not yet approved products. NEHI also supports off-label information exchange
- OIG should create new AKS safe harbors to support value-based contracting
- CMS needs to address "best price" to allow exemptions to avoid triggering other price cuts for manufacturers
- Congress should direct Nat. Acad. Of Medicine to investigate new long-term approaches to financing high cost therapies, as value-based contracting won't address all the challenges

The Challenges of Value-Based Pricing

- June 8, 2017, Article in STAT by Dana Goldman and Anupam Jena, *"Value-based drug pricing makes sense, but is difficult to pull off"*
  - Choosing the source of data (clinical trial vs. "real" patients)
  - Incorrect use of list prices – little relation to reimbursement
  - Falling drug prices – cost-effectiveness improves over time as prices fall. How to capture future expectations?
  - Changing evidence base – insurance coverage decisions may be based on outdated data
  - High-cost drugs can still be valuable – who should pay?
  - Need for transparency in price-modeling

Thank You

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