

Don't put the CAR-T before the Horse: Proper Planning for Novel Gene Therapies in an Uncertain Regulatory Environment

Andrew Ruskin

Partner

Morgan, Lewis & Bockius LLP

1111 Pennsylvania Ave. NW

Washington, D.C. 20004

(202) 739-5960

andrew.ruskin@morganlewis.com

Valerie Rinkle

President

Valorize Consulting LLC

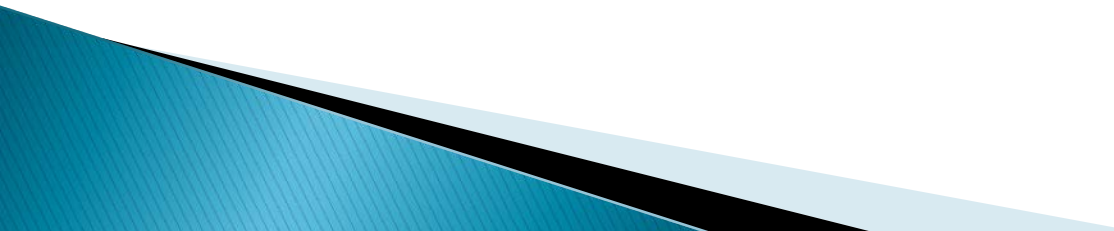
30 South Barneburg Road

Medford, OR 97504

(541) 840-8280

Valerie.rinkle@valorizeconsulting.com

Agenda

- ▶ History of Cell & Gene Therapy
 - ▶ Clinical Trial Reimbursement & Implications
 - ▶ Commercial Product Reimbursement & Implications
 - Medicare
 - Medicaid
 - Commercial
 - ▶ Wrap-up & Questions
- 

History of Cell and Gene Therapy

- ▶ 1970s. *In vitro* insertion of DNA.
- ▶ 1980s. Clinical trial testing using viruses to affect changes to DNA begins on humans.
- ▶ 1990s. Gene therapy used to cure “bubble boy” syndrome. Jesse Gelsinger dies in treatment for a different genetic disorder.

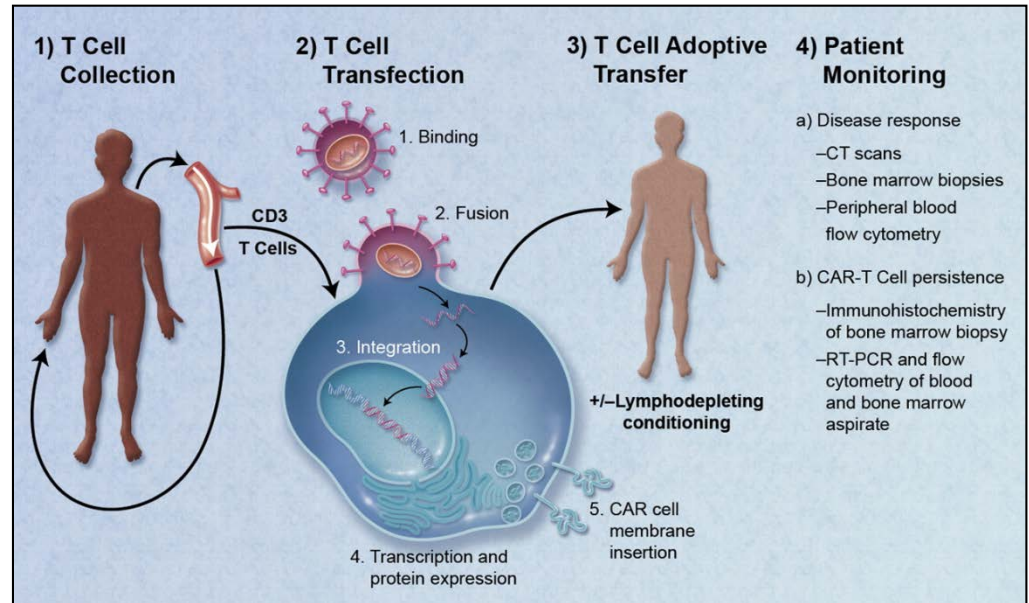
History of Cell and Gene Therapy

- ▶ 2003. China approves gene therapy for head and neck squamous cell carcinoma.
- ▶ 2010. Provenge approved.
- ▶ 2012. EU approves gene therapy for genetic disorder for pancreatitis, at a cost of \$1.6 million per treatment
- ▶ 2017. Kymriah first gene therapy approved in US. Yescarta approved. Luxturna also approved.
- ▶ 2018. Kymriah gets second indication. CMS begins to grapple with payment questions.

What is Chimeric Antigen Receptor T Cell Therapy?

- ▶ CAR-T uses the patient's immune system T-cells, genetically engineers the cells to produce receptors called Chimeric Antigen Receptors (or CARs) on the cell surface. These modified cells are reinfused back into the patient, and the CARs allow the cells to seek out a certain protein (or antigen) on the tumor cells, and then kill the cancer cells

Image source: WikiMedia Commons



FDA approved for Relapsed/Refractory (R/R) Acute Myeloid Leukemia and R/R Large B-Cell Lymphoma. Patients get a reaction called a Cytokine Release Syndrome which may “storm” to the point of requiring inpatient admission and/or significant additional drugs/services

- DIFFERENT DISEASE TARGETS
- FIRST/SECOND LINE TREATMENTS
- SOLID TUMORS VS BLOOD BASED CANCERS
- GENETIC/HEREDITARY CONDITIONS
- ALLOGENEIC/DONOR-BASED
- HOME BREW OR 'BEDSIDE' CAPABILITIES
- DOZENS OF COMPANIES AND ACADEMIC CENTERS INVOLVED

First FDA Approved Products

CAR-T Kymriah™ (Novartis)

- ▶ Approved August 30, 2017 for pediatric R/r or refractory acute leukemia with price of \$475,000
- ▶ Approved May 1, 2018 for = Adult r/r Large B-cell lymphoma subtypes with price of \$373,000
- ▶ Hospital inpatient & outpatient
- ▶ Requires facility certification & approx. 69 currently certified
- ▶ Also requires FACT accreditation
- ▶ Initial Public announcement of outcomes-based payment model with CMS for Medicaid

www.us.Kymriah.com

CAR-T Yescarta™ (Kite/Gilead)

- ▶ Approved October 18, 2017 for Adult r/r Large B-cell lymphoma subtypes with price of \$373,000
- ▶ Hospital inpatient & outpatient
- ▶ No offer or contract with hospital for cell collection and lab processing
- ▶ Requires facility certification & approx. 63 currently certified
- ▶ Also requires FACT accreditation
- ▶ No outcomes based pricing model

www.Yescarta.com

Luxturna (Spark Therapeutics)

- First gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene
- Indication for confirmed biallelic RPE65 mutation-associated retinal dystrophy that leads to vision loss and may cause complete blindness in certain patients
- \$475,000 per eye & may need more than one treatment per eye

Clinical Trial Reimbursement & Implications

- ▶ CMS considers all unapproved products to be “experimental” and therefore generally excluded from coverage
- ▶ CMS requires the CT include evaluation of an item or service that falls within a Medicare benefit category & that it must have a “therapeutic intent”
- ▶ The CT item or service is excluded, but otherwise “routine services” are covered

Clinical Trial Reimbursement & Implications

- ▶ CMS' CTP Defines Covered “Routine Costs” as:
 - Items and services typically provided absent a clinical trial
 - Items and services, such as administration of product, required solely for the investigation of the item, including appropriate monitoring of effects and prevention of complications
 - Treatment of complications
- ▶ Colloquially known as “Standard of Care”

Clinical Trial Reimbursement & Implications

- ▶ CMS' CTP Defines Excluded Costs as
 - The investigational item itself
 - Data collection not directly related to clinical management
 - Items and services “customarily” provided by research sponsors free of charge to any enrollee in the trial

Applying the CTP to CAR-T

There is no SOC for CAR-T services – therefore, routine costs are hard to define:

- ▶ Cell collection can be hospital inpatient or outpatient & first manufacturer provided fair market value (FMV) payment for cell collection & lab processing similar to Provenge
- ▶ Infusion often inpatient, but may be outpatient, particularly for pediatric patients
 - So is a full inpatient admission, the SOC for administration of CAR-T?
- ▶ Drugs to condition patient for cell collection & mild myeloablation are being used for FDA labeled indications, but for CAR-T
- ▶ Drugs for post-infusion complications such as Tocilizumab are FDA approved and are being used per label

Clinical Trial Compliance Implications

- ▶ CMS CTP FAQs (Sept. 2008)
 - Paying for clinical trial costs when a commercial payer denies payment vitiates ability to have Medicare pay for SOC in the clinical trial
 - FAQs revised in 2009 to remove this Q&A, but CMS officials have stated that this is still their policy
- ▶ Implication for gene therapy trials – what other sites charge the study budget could remove coverage for your site

Clinical Trial Compliance Implications

- ▶ **OIG Pharmaceutical Manufacturer Compliance Program Guidance**
 - Holding providers harmless for non-payment by payers removes “ordinary financial risk” and raises AKS concerns
- ▶ **Implication for gene therapy trials – seeking payment from clinical trial sponsors for non-payment from payers could raise program integrity concerns**

Clinical Trial Compliance Implications

- ▶ **OIG Beneficiary Inducement Special Bulletin**
 - Considered creating a safe harbor for furnishing items of value to clinical trial subjects in a government-sponsored trials.
 - Never moved forward with the safe harbor.
- ▶ **Implication for gene therapy trials – removing coinsurance for care rendered during clinical trial, including for drugs used in the therapy, raises potential concerns.**

Commercial Product Reimbursement & Implications

Before billing & payment, coverage must be in place:

- ▶ National Coverage Decision expected May 2019
 - But in the meantime, all “medically accepted indications” are covered, *i.e.*, labeled indication, and indications supported by nationally recognized cancer compendia
 - Question as to whether CMS has the statutory authority to limit coverage further for these products
- ▶ Medicaid: State-by-state
- ▶ Commercial: Blues Distinction Centers for Cellular Immunotherapy – policies guide Blue Cross/Blue Shield plans and may be adopted by other national payers

Commercial Product Reimbursement & Implications

- ▶ Once FDA approved, particularly for cancer treatment, the drug usually is covered by CMS whether by Part A or Part B
- ▶ Part A Payment is a bundled, per-discharge payment called an “MS-DRG” or a “DRG” for short
 - Typically no separate payment for drugs
 - Data used to set weights are generally 2–3 years old
 - CMS almost never establishes new DRGs (exception in 2003 for drug eluting stents)
 - To compensate for stale data, CMS uses New Technology Add-On Payment (NTAP) to pay for breakthrough technologies
 - There are also “outlier” payments that defray a portion of extremely high costs

Commercial Product Reimbursement & Implications

- ▶ CAR-T = “Perfect storm”
 - Extremely high cost not recognized in DRG payment
 - Limited number of hospitals that have to bear the brunt of the limited payment
 - Poor payment is likely to limit access; but CMS says they never actually “see” this happen

Commercial Product Reimbursement & Implications

- ▶ What are the ripple effects of the high cost of CAR-T?
 - CMS concerned with creating a separate DRG for CAR-T because of budget neutrality
 - If it has its own DRG, it could be paid much, much better, but would drain away money from all other services hospitals provide
 - Would essentially be a “wealth transfer” from community hospitals to AMCs
 - But . . . AMCs still qualify for outlier payments, which, however, is also set from a fixed pool of funds
 - Over time, technologies like CAR-T can dry up the outlier pool and make it impossible for other less-costly outlier cases to get any payment
 - An exception: NTAPs do *not* have to be budget neutral
 - However, to qualify for NTAP status, a product must be a unique breakthrough technology – **Future CAR-Ts might not qualify**

Public Comments to CMS on CAR-T

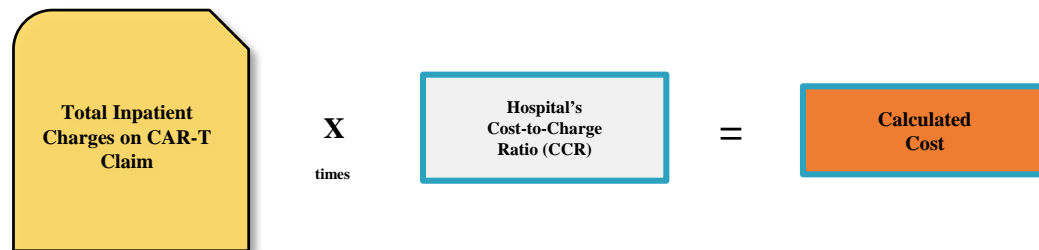
CMS held out hope in the IPPS proposed rule for different/unique solutions & solicited comments....

- ▶ AAMC – consider a “carve-out” and pay separately
- ▶ AHA– “carve-out” and pay separately & increase NTAP percentage & protect outliers & other MS-DRGs
- ▶ Since initial products fight blood cancers, other major comments were submitted by:
 - American Society of Blood & Marrow Transplantation (ASBMT)
 - MS-DRG + ASP for product; CCR of 1.0 for NTAP; raise NTAP
 - American Society of Hematology (ASH) – similar to ASBMT
 - National Donor Marrow Program (NMDP) – similar to ASBMT

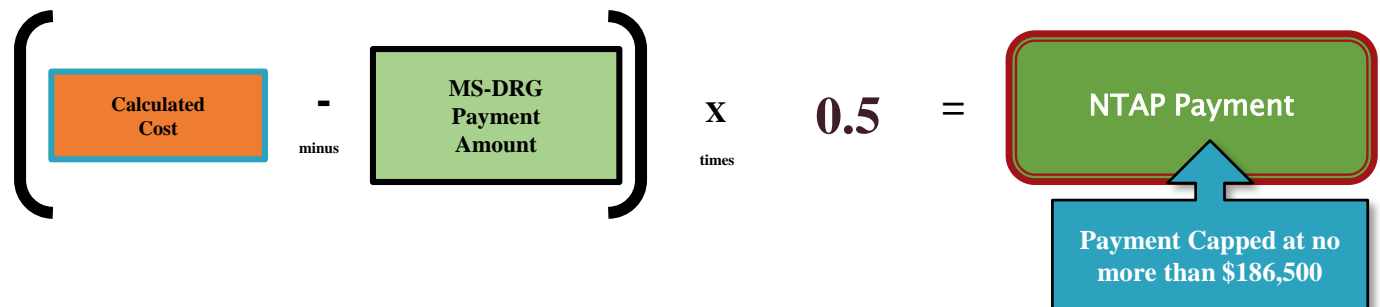
IPPS Hospital NTAP Formula

- ▶ NTAP = separate additional payment for 2-3 years of no more than 50% of the cost of the new technology which is pre-determined by CMS (for CAR-T this means a maximum possible payment of \$186,500 for the product)
- CMS computes **“calculated cost”** by taking total inpatient billed charges multiplied by the hospital’s CCR from the most recently filed cost report and if this exceeds the MS-DRG payment, then an NTAP (the lesser of 50% of the excess cost or the maximum NTAP)

Step 1: Get “Calculated Cost”



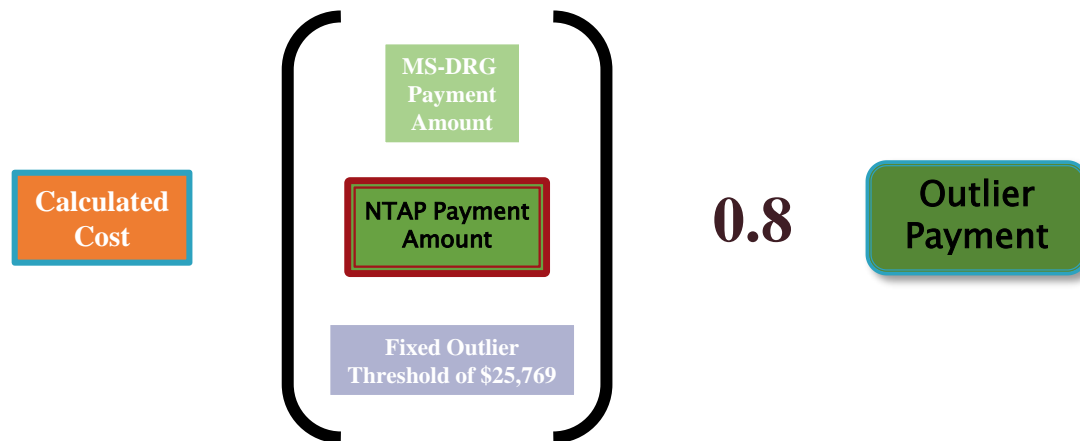
Step 2: Use Calculated Cost to Get NTAP Payment Amount



Final NTAP amount paid in addition to DRG Payment

FY 2019 IPPS Hospital Outlier Formula

CMS computes a **calculated cost** for the case and compares this to the sum of the DRG payment + NTAP + the fixed loss outlier and **if** there is “excess cost” CMS makes an outlier payment equal to 80% of the excess cost



Example Medicare CAR-T Payment



Example Calculation (USING ROUND NUMBERS)

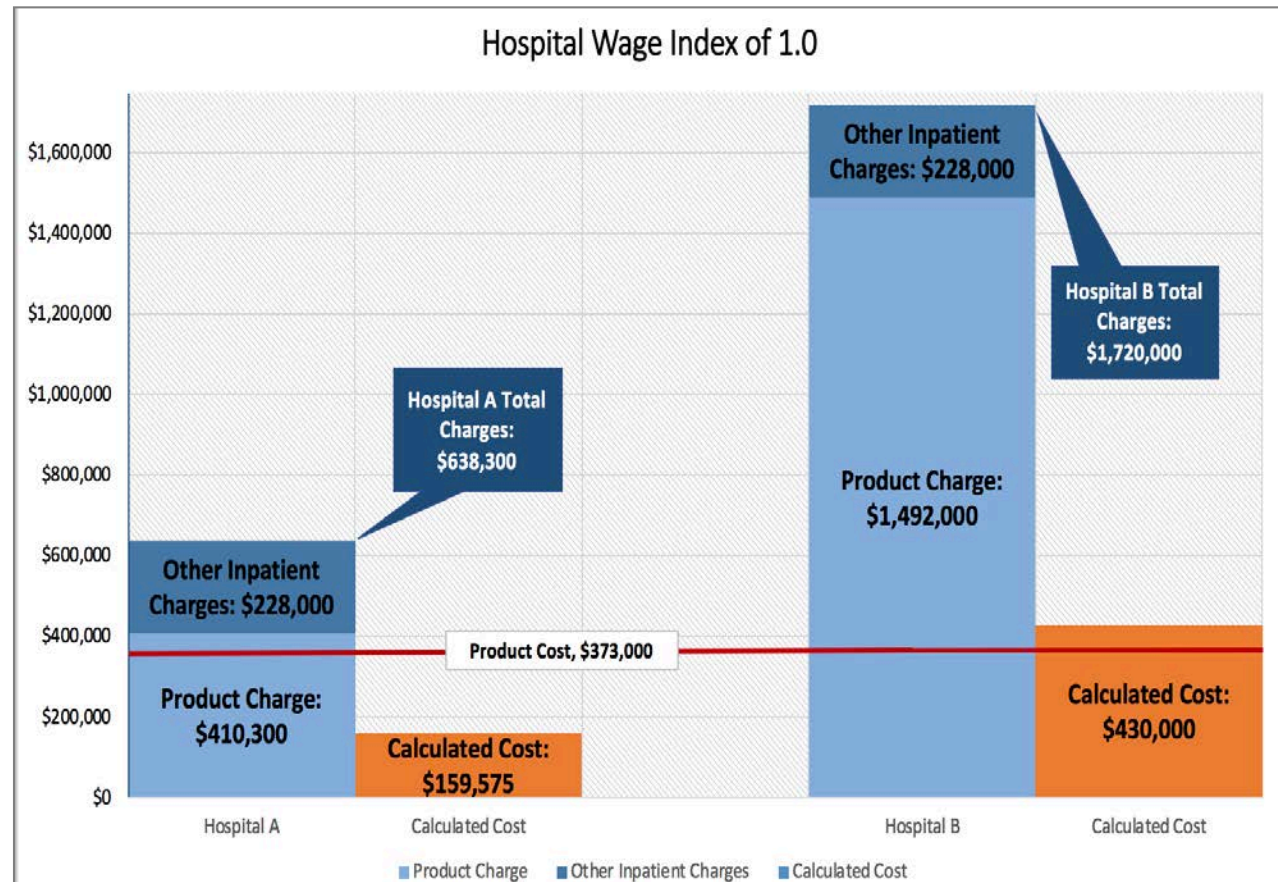
1. \$600,000 in Total Covered Billed Charges (including charges for CAR-T that costs approximate **\$500,000**) \times 0.25 CCR = Calculated Costs of \$150,000
2. Calculated Cost of \$150,000 less MS-DRG Payment of \$40,000 = \$110,000
3. \$110,000 \times 0.50 = \$55,000 for NTAP Payment, then
4. Take Calculated Costs of \$150,000 & subtract (sum of of MS-DRG Payment of \$40,000 plus NTAP Payment of \$55,000 plus Fixed Outlier Threshold of \$25,000 or \$120,000) = \$30,000
5. \$30,000 \times 0.80 = \$24,000 for Outlier Payment
6. Total Case Payment = MS-DRG \$40,000 plus NTAP of \$55,000 plus Outlier of \$24,000 equals a total of \$119,000 **compared to approximate CAR-T cost of \$500,000**

A huge loss on a per case basis!

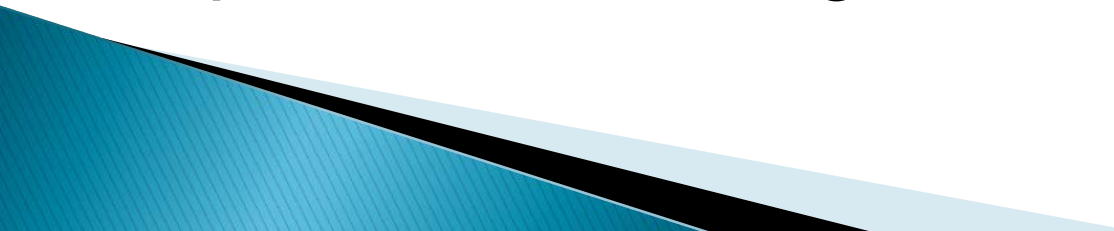
By Design – Charges Matter

Compare Two Hospitals

- Hospital A and B have the same patient care costs of \$228,000, but each hospital set very different charges amounts for the CAR-T product. Hospital A marks-up 110% & Hospital B by 400% or using its CCR of 0.25
- CMS takes the total billed charges and reduces them to a “calculated cost” using the hospital’s overall CCR which happens to be .25 for both Hospital A and B
- Given the difference in total charges, CMS “calculated costs” are different and this information is used in determining the final inpatient payment amounts via the NTAP & Outlier formulas



By Design – Charges Matter

- Getting charges correct is the difference between losing a little money or ***a lot*** of money.
 - CMS' citations and also compliant with law, appropriate “formula” for pricing is to take actual invoice expense or cost and divide by the hospital's CCR to establish the “gross” or list price in the chargemaster
- 

Understanding Outpatient Reimbursement


- ▶ Outpatient services are paid at a bundled, per-service rate called an “APC”
 - For certain types of drugs, payment is separately available
 - Where available, payment is based on the average sales price, or “ASP” of the drug, plus 6%
 - Manufacturers submit to CMS quarterly data of their pricing to all non-governmental and non-340B customers, net of discounts, and CMS calculates an ASP value to which it adds 6%
 - Separate drug payment, plus the 6% markup, means that delivery in the HOPD is always more favorable
 - *If purchasing under the 340B program, HOPD service delivery becomes even more advantageous*

Assuming Court decision prevails and CMS' 340B payment policy is stopped!!

Understanding Outpatient Reimbursement

- ▶ Outpatient reimbursement, however, isn't perfect
 - First the HCPCS Committee decided that hospital cell collection & lab processing services should be part of the drug description
 - Then CMS decided that these services would not qualify for separate payment under the outpatient department fee schedule
 - If a hospital is going to get paid, it will need to get paid as a supplier of services to the manufacturer, and not as a Medicare provider
 - Essentially, CAR-T is a hybrid drug and hybrid “process”

Hospital Billing of CAR-T

- Additional advocacy led to the creation of other HIPAA transaction code sets specific to cell and gene therapy services that hospitals must use on claims as of April 1, 2019, including cell collection and lab processing services
 - Payers are required to accept these new codes
 - CMS acknowledged they will accept the codes which seems to contradict their reimbursement policies described on the prior slide!
- 

Physician Payment

- ▶ Physicians will only sometimes get paid
 - Physicians have to use a procedure code that is considered an “experimental” code
 - Medicare will pay physician for CAR-T infusion service, but it will be Medicare carrier priced, meaning lots of paperwork
 - Commercial payers will only sometimes pay for the services
 - Like hospital outpatient departments, the collection of the T-Cells is not separately payable

Commercial Product Reimbursement and Implications – Medicaid

- ▶ Novartis & CMS made a “big splash” of outcomes-based payment when FDA approved the pediatric indications product. Outcomes were defined as “complete response” within 30 days of infusion
- ▶ However, Politico reported in July that CMS officials quietly cancelled the plan after it drew internal and external scrutiny & criticism
- ▶ Pediatric indication impacts approximately 700 patients a year, most of which are covered by commercial insurance
- ▶ Medicaid programs are unprepared for extreme high cost so payment ranges from cost-based “carve out” for product (NY) to no separate product payment (Managed Medicaid in KS) to no coverage for product at all (IL)
- ▶ Medicaid programs typically do not have NTAP and usually a less generous outlier formula, if at all

Commercial Product Reimbursement and Implications – Commercial Payers

- ▶ Sophistication of managed care division is key:
 - Single case agreements (SCA) are critical to commercial payor coverage and payment
 - Most attempt to ensure CAR-T product carve-out plus other stop-loss for high patient care services if complications
 - Additional services for CAR-T patients such as baseline MRI for neurological status & carve-out for other high cost drugs like tocilizumab
 - Peer-to-peer prior authorization is common, so spell out the details to shorten length of time
 - Education/advocacy with payor medical directors or medical policy coordinators to add/clarify/expand coverage may also be needed

Commercial Product Reimbursement – Compliance Implications

- ▶ Depending upon how it is structured, the arrangement with the manufacturer can raise AKS concerns
 - AKS attaches criminal and civil monetary penalty liability to knowingly and willfully receiving or giving something of value in exchange for Federal healthcare program business

Commercial Product Reimbursement – Compliance Implications

- ▶ For instance, can the hospital charge the manufacturer for cell collection services?
- ▶ Although value would be going to the hospital and the hospital would be referring patients to the manufacturer, that doesn't necessarily mean that the AKS has been violated
- ▶ Even if the personal services safe harbor cannot be strictly complied with, risk can be reduced through FMV payments

Commercial Product Reimbursement – Compliance Implications

- ▶ What about seeking payment for payment denials?
 - OIG Pharma Compliance Program Guidance calls into question whether hospitals can be held harmless for payment denials

Commercial Product Reimbursement – Compliance Implications

- ▶ What about seeking payment for payer shortfalls?
 - OIG Advisory Opinion 18–14 (Nov. 16, 2018) states that OIG considered it problematic to furnish drugs for free to hospital inpatients where the manufacturer would still make money on use of the product after discharge
 - Implication is that, if manufacturer defrays its costs for hospitals based on their payments, but the manufacturer still makes a profit, and the government gets no benefit, there could be AKS risk

Commercial Product Reimbursement – Compliance Implications

- ▶ Why do manufacturers charge so much?
 - Pricing tends to be set at the cost of whatever therapy is being replaced, or the price of the most recently launched product most similar to the new product
- ▶ Why don't manufacturers discount more?
 - Discounting starts to occur when there is substantial competition, but less so for products reimbursed under ASP.
- ▶ Is 340B pricing available?
 - Only once the product is used in the HOPD.

Commercial Product Reimbursement – Compliance Implications

- ▶ Can manufacturers defray the patient's coinsurance?
 - OIG in numerous instances has made it clear that assistance with patient coinsurance for Medicare and Medicaid beneficiaries raises AKS concerns
 - Assistance with coinsurance for commercially insured patients also has *some* degree of risk due to concerns with pull-through

Commercial Product Reimbursement – Compliance Implications

- ▶ What provisions can a manufacturer agreement include to reduce the hospital's risk?
 - Indemnification – needed to protect hospital in case it gets sued as the “supplier of cell collection services” to the manufacturer
 - Reduction in payment because of: (a) nonperformance of the product; or (b) unusual toxicity or other side effects
 - Provisions that provide for installment payments, instead of a lump sum payment, tied to the patient reaching certain treatment milestones

Commercial Product Reimbursement – Compliance Implications

- ▶ What provisions can a manufacturer agreement include to reduce the hospital's risk? (*cont*)
 - Price protection clause against price increases
 - Early termination right for changes in the regulatory environment
 - Protections against patent infringement
 - Allowances for any accreditations needed to become an approved site
 - Provisions for free or substantially discounted drug for self-pay patients

Questions?

