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Working Group 3

Clinical, Regulatory, Implementation and Scalability Challenges of Adoptive Cellular Therapy

Clinical Questions

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With two approved anti-CD19 CAR T cell therapies in the setting of r/rLCL, what are the ethical considerations around institutions continuing to enroll/treat patients with local “home brewed” CAR-T therapies, other non-FDA approved therapies (bispecific T cell engagers, ADC etc) in the same setting without having all treatment options exhausted and exposing oncology patients to potentially lower efficacious therapies?

- Existing CART drugs have response rate 60-80%
- Ethical consideration evaluated by local IRBs
- How do you target same patient populations for new trials?
  - Retreat patients who relapse
  - Lymphodepletion after first CART therapy makes subsequent manufacturing very challenging. Have to go back to first apheresis (cryopreserved)
  - Target antigen loss a concern (up to 30% of patients)
  - It could be easier if you are giving with a new therapy (non-CD19 CAR)
    - Quick relapse gives small window of opportunity for subsequent therapy
- Institutional reimbursement and accreditation processes are limiting number of patients that can be treated with approved therapies
- Toxicity of approved drugs are discouraging patients and delay adoption
  - New therapies may be less toxic or provide more benefit

What ‘bar’ will new therapies need to achieve in order to be approved?

- Are “me too” performance characteristics sufficient?
- Reduced cost/easier access
- Better performance characteristics
  - More potent
  - Less toxic
- Easier manufacturing process
  - Allogeneic products
  - Other cell types

- Do new drugs need to show non-inferiority/superiority to approved agents in randomized trial?
  - No head to head trial of the 2 approved drugs
  - This isn’t happening for any IO agents (e.g. checkpoint agents)

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Are single arm studies vs. comparator randomized studies or vs. historical controls still reasonable, considering that there's are now various "real world data" evidence and more available treatment options in heme malignancies.

- Yescarta – SCHOLAR 1 – retrospective analysis of real world patient outcomes
  - Performance of patients on approved SOC therapies vs response seen in ZUMA1
    - 6 months vs 9 months
    - Effect size was convincing of benefit, when effect size is smaller, it's harder to use historical controls
    - Challenge with current populations is crossover to CART after failed SOC
    - Crossovers make it hard to interpret OS, agency is now accepting PFS + trend in OS
  - In solid tumors, single arm studies will continue to be used

- Ask – a dataset that can allow performance of approved drugs to be compared in retrospective analyses would be idea
- Translational research is still unfunded, coming from academic, and a big unmet meet

Given the nature of “living drugs” such as CAR T, should (3+3) dose escalation be reassessed? Should the field find better safety guards in the dose finding or “run in” safety portions of phase 1/2 trials? Should evolution of primary endpoints take into consideration the high response rates achieved, with ORR being deemphasized as a reliable end point? Instead shift focus to look more into other predictive factors associated with prolong benefits including negative PET-CT rate or MRD? Further, immune reconstitution (and return to normal life) should be considered an important secondary endpoint (current PROs are not designed to capture this benefit).

- 3+3 design based on rapid toxicities seen with conventional chemotherapies. Is that appropriate for cell therapies?
  - CRS tends to happen quickly
  - Neurological toxicity has 2 types – 1 with CRS, 1 afebrile at 5-10 days (corticosteroids)
  - Neutropenia occurs at late onset - outside of 28 day window. Not well captured with conventional DLT assessment criteria

- Option for single patient dose escalation with enough supportive evidence of safety
- Lack of appropriate animal models to replicate human biology
- FDA has been concerned about starting dose
  - Especially in solid tumors, low level target expression on healthy tissues presents toxicity risk
  - Need to identify more private/tumor specific epitopes for targeting
- Expansion of CART after infusion makes “dosing” a nebulous concept and unique for each patient
  - Need to validate new endpoints for the CART studies – CT scans? MRD?
  - Pharmas now collecting PK/PD data at early timepoints. Also, the relationship between PK/PD and efficacy is unclear

With academic thought leaders and treatment centers getting more familiar with cellular therapy and continuous improvement in toxicity management of CRS and NE leading to improved safety profiles, what are the next steps in expanding the access of patients to these therapies, beyond current accredited centers?

- First, safety profile of product must be improved
  - CRS is mostly manageable
  - NE remains a problem
    - Kite sees that early treatment with steroids limits severity of AE
    - Lack of animal models is severely hampering research on NE
    - GBM trials are not seeing higher incidences of NE, but also don't see as much CAR expansion or CRS.
      - STM publication – at high dose of intracranial CAR + IL12 did induce CRS
    - NK therapies not seeing CRS/NE – tox will likely be product specific

Improving Access, Part II

- Cost is also inhibiting patient access
  - Centers are losing money treating patients with autologous product
  - Allogenic products may reduce overall costs due to more efficient manufacturing
- Supportive care is a major cost driver as well
  - 30% patients end up in ICU
- Continuous evolution of ACT landscape will change treatment options for patients
- Bringing ACT to community hospitals will be possible once toxicity issue is addressed
  - 8 states do not have ACT treatment centers
  - Patients are very sick and are not able to travel
  - Goal – treat in outpatient setting

Although the general impression could be that all CAR-T are similar in efficacy or safety profiles, the academic community are aware of key differences. What can HCPs or industry do better to appropriately inform patients of key differences between treatment options in terms of safety or efficacy (overall survival, complete response rate etc) to ensure an informed treatment related decision.

- Need for Patient Advocacy Groups to drive adoption and provide information to candidate patients
  - Survivor Network
  - Also provide patient experience with treatment and long term consequences
  - Kite Connect – 24h phone service with Q&A
- Provider education will be key to driving patient education
- Need for unbiased resources to provide information to doctors and patient
  - From pharmas, MSL teams provide information
  - Need for 3rd party groups to provide education
    - Cooperative oncology groups
    - Insurance companies? Nonprofit research orgs (FDA/NIH)?

Regulatory Questions

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In January 2019, FDA officials commented that CBER anticipates a "near future" with 200 Investigational New Drug (IND) Applications a year by 2020, leading to approvals of between 10 and 20 cell / gene therapies each year starting in 2025. How is CBER preparing for this and can we expect changes in terms of CBER's review practices for cell therapy INDs and BLAs including interactions with sponsors? Additionally, is there insight on any new cell /gene therapy guidelines that CBER is planning to issue in the near future?

- How can we speed up or improve the review process to reflect a changing field where more data is available and preserve patient safety?
- Should retreatment be a part of the approval process?

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With respect to cell therapy INDs and BLAs reviews, sponsors generally interface directly with the CBER Review Team via the CBER Regulatory Project Managers. How will the CBER Review Teams and the FDA Oncology Center of Excellence (OCE) plan to work together with consideration of the anticipated increase in cell therapy IND and BLA filings?

- Corporate interactions with FDA – type B meeting
  - Bring a series of questions for FDA involving approval of filing
    - IND – likely written or telecon feedback
    - BLA – in person
- FDA guidelines vary in terms of detail
  - CMC guidelines quite detailed – safety and purity
  - Cell therapies lack a potency assay that correlates with efficacy
- Need retrospective analysis of products that fail
  - Characterization of complex products (e.g. gene edited CART, iPSC derived products)

During a recent AAADV Workshop Case Study Sessions relating to CAR-T therapy in May 2019, comments from a CBER Reviewer at this session indicated that sponsors can re-negotiate the 15-year safety follow-up requirement over time with additional data. Is CBER considering modifying the FDA Guideline associated with long term follow-up after administration of human gene therapy products in this regard?

- For 15 years, collect blood yearly and bank
  - True for any gene modified cell product
  - Biologic/small molecules are followed for 5 years, but blood collection not required
  - Concern is about RCR (replication compotent retrovirus) and viral integration into genome with oncogenic potential
    - Now in Switzerland, they have to biopsy all secondary malignancies and study retroviral integration
    - In ROW, only biopsy heme malignancy
  - How do you handle patients who decline to participate in follow on monitoring?
    - Not reported to FDA, patient can still receive Yescarta; unclear what happens in Switzerland
- This represents a large cost
- Strain on patient and physician. Drives up cost of therapy.
  - Must be paid for by company
- Can the commitment be reduced?
  - FDA considering reducing RCR guidelines. 3 blood collections in 1st year, then biobanking for next 14 years
  - Most CARTs are cleared in 1-2 years

Implementation and Scalability Challenges

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A private, wholly owned subsidiary of the Peter Mac Cancer Center in Australia recently received a GMP license for the production of CAR-T therapies. This is the first instance of an academic center affiliate getting approval for commercial GMP production. Is this going to be an alternative model for scaling out CAR-T manufacturing? What are the implications for companies like Kite, Novartis, BMS, and Allogene that are investing heavily in a more traditional centralized manufacturing model of production?

- Would this be for the approved products (Yescarta) or for "home brew" CART? This would be in open-ended clinical trial
- Would the companies share their manufacturing IP to ensure consistence and best practices?
- How would the centers move this into a commercialized products?
  - What does the financial model look like?
- Are centralized or decentralized models more attractive for the pharmas?
  - Decentralized manufacturing represents a disruption of the current system
- How would the regulatory oversight change if a decentralized model is adopted?
  - If yescarta is made at MSKCC, who is responsible for the product?
  - What would be the source of the lentiviral vector?

Decentralization, Part II

- Tech Transfer
  - Hard to show product equivalency
- Building satellite GMP facilities are a major investment
  - GMP storage facility, trained personnel, product characterization processes
- What if the satellite facilities operate as a CMO?
  - Allows smaller companies to be more nimble because they don't have to build their own facilities
  - But, these require a high level of oversight
  - How does this change with the emergence of allogeneic products?
    - Shifts economics back to centralized manufacturing

A major issue/bottleneck with respect to scale out of CAR-T manufacturing is the lag time associated with QC release testing. Are there things that can be implemented, from a QC perspective, that'll increase the speed of turning therapies around to patients? Are there any strategies from the stem cell transplant world that can be implemented for CAR-T therapy QC testing and release?

- Takes Kite 1 week to release product
  - Patients are really sick – need to speed up process
- What are implications if you give a product to the patient before QC release is available
- Relax on RCR testing b/c have never seen RCR event?
- 7/9 species of mycoplasma, fungal and bacterial contamination – qPCR and culture
- Coculture with target cell line and product - IFNg ELIZA
  - Can this be automated or improved?
- Who does these assay in the company? At Kite, Tech Ops
- E.g CD19-His flow assay to assess transduction efficiency
  - Risk from commercially sources antibody
  - Challenge – show equivalency and reproducibility of new assays. Solution – better conversations with FDA that make it easier to make changes in QC processes
- Can we learn from processes in transplant or dialysis communities?

For solid tumor indications where patient populations are considerably larger than leukemic/lymphoma populations currently being addressed, is there a place for autologous treatment? Can we conceive of manufacturing in the auto setting or is an allogeneic approach a better path for near-term investment?

- E.g. Prostate Cancer 30-60,000 patients would could be addressed with effective cell product
- Currently, Kite can manufacture 4,000 lots
- Decentralized manufacturing can provide additional capacity
- Companies can partner with academic centers
- Allogeneic cell products allow more efficient manufacturing
- If you can achieve clinical efficacy, the market will find a way to make the economics work
  - Could be TILs, ADCs, next gen engineered CARs, autologous therapies, alternative cell types
  - Biomarkers – improve patient selection – right drug to the right patient