Control Strategies for Antibody-based Immuno-oncology Products: It Starts with Product Design!

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Disclaimer

- The views presented today do not represent official FDA policy, but rather represent my opinion based on my experience as a reviewer of monoclonal antibody and related products at the FDA.
What are Immunotherapy Products?

• Immune Checkpoint Modulators
  – Immune checkpoint proteins normally keep immune responses in check by preventing overly intense responses that might damage normal cells as well as abnormal cells.

• Therapeutic Antibodies
  – Unmodified mAbs
  – Antibody-Drug Conjugates (ADCs) and other immunoconjugates
  – Bispecific antibodies (BsAbs)

• Immune System Modulators
  – Interleukins
  – Interferons

https://www.cancer.gov/research/areas/treatment/immunotherapy-using-immune-system#1
What are Immunotherapy Products?

- Immune Cell Therapy
  - CAR T cells
  - Adoptive Cell Transfer (TILs)

- Cancer Treatment Vaccines
  - Autologous tumor cells
  - Cancer associated antigens
Recent mAb Approvals

2017 > 9 approvals?

Immuno-oncology approvals

- ipilimumab
- pembrolizumab
- nivolumab
- blinatumomab
- elotuzumab
- atezolizumab

What is a Control Strategy?

• A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.
Control Strategy for Immuno-Oncology Products

• The approach to developing a control strategy for immuno-oncology products (checkpoint inhibitors/modulators and BsAbs) is no different than for conventional mAbs and conjugated-mAbs.

• Each product has unique properties that should be understood in order to establish appropriate in-process controls, controls of input materials, specifications for drug substance and drug product.

• As you design new products, consider how immuno-oncology products are being developed today. This will also help develop your eventual control strategy.
Product Class Combinations -
All combinations are possible

SOC +

4-1BB,

TRAF2
Five approved for oncology, promote T cell/NK cell activity:
- Ipilimumab: IgG1 anti-CTLA4
- Pembrolizumab: IgG4 anti-PD1
- Nivolumab: IgG4 anti-PD1
- Atezolizumab: IgG1 anti-PD-L1
- Elotuzumab: IgG1 anti-SLAMF7

Two approved for non-oncology, inhibit T cell activity:
- Abatacept: CTLA4-Ig
- Belatacept: CTLA4-Ig
Clinical experience with checkpoint inhibitors

- In general, ORR is ~10 - <50%
  - Developing checkpoint inhibitor combinations and other combinations to improve ORR
- Immune mediated adverse events ~70-90%
  - All grades
- Can this improve with changes in dosing regimens?

Michot et al. 2016 Eur J Cancer 54:139
Some Development Challenges for Checkpoint Inhibitor and Immunostimulatory mAbs

- CMC development challenges not different from intact mAbs

- Can a rational design be applied?
  - Can the mAbs be engineered so they will work well in a greater number of patients?
  - Can the mAbs be engineered in some way to reduce safety concerns?

- Lack of effector function for checkpoint inhibitors
  - IgG4
  - Engineering IgG1

- Engineering immunostimulatory mAbs for enhanced activity
  - (IgG2 hinge - White et al. Cancer Cell 2015. 27:138)

- Engineering Ig-FcRn interactions or V regions to modulate half-life
  - Improved tumor penetration?
Bispecific Antibodies

• Altogether there are currently >60 BsAb formats
  – Most are still in preclinical development

• Ig Structure

• Bispecific Fragments
  • Appended Ig Structure
  • Bispecific Fusion Proteins
  • Bispecific Conjugates

• BsAbs that engage T cells or NK cells come in different formats
BsAb: Ig Structure - monovalent for each ag

- Quadroma – catumaxomab approved in EU for malignant ascites in EpCam^+ tumors

New platforms solved problems of incorrect H and L chain pairing
- Knobs-into-hole (KIH) – unfavorable pairing for C_H homodimers, favors heterodimers
- Cross mAb – KIH with C_L/ C_H1 domain swap to ensure correct H/L chain pairing

Speiss et al. Molecular Immunology 2015
BsAb: Fragments

- BiTE (bispecific T cell engager) is a single polypeptide chain that links two sFv.
  - Blinatumomab anti-CD3 x CD19 approved for preB-cell ALL in 2014
- DART (dual affinity retargeting) uses two polypeptides stabilized by a disulfide bridge
- TandAb (tandem antibody structure) is bivalent and bispecific

Speiss et al. Molecular Immunology 2015
Some Development Challenges for Bispecifics/Multispecifics

- Manufacturability
- Stability
  - Depending on platform, the design of construct is empirical
- Half-life (if no Fc)
  - Fusion to Fc, albumin or PEG conjugation, V region engineering (lower pI)
- Antigen specificity, affinity, density
  - Compatible on/off rates?
- Potency assay
  - Simultaneous binding to both ags
- If designed to engage effector cells
  - Is there cytokine release or activation in the absence of binding to target cells
  - anti-CD3 homodimers?
- Target mediated disposition
  - Is soluble antigen present?
- Small constructs
  - Balance short half life with more rapid distribution and tissue penetration
- Continuous dosing
  - Sterility assurance
Considerations for different bispecific platforms – trade offs

- Bispecific mAb fragments
  - Short half life
  - More rapid tissue distribution and better penetration
  - Continuous infusion (microbial concerns)
  - Less complex structure (no glycan)
  - Easier to manufacture and characterize

- Bispecific intact mAbs
  - Longer half life
  - Less tumor penetration
  - More complex structure
  - More characterization needed
  - Control strategy more complex
FDA experience with some bispecifics in oncology indications

• Most are designed to engage effector cell (T cell or FcγR expressing cells) and tumor target

• Factors associated with toxicity
  – Total body tumor burden is a risk factor for a poor response
  – Specific patterns of toxicity are associated with specific targets
  – Prior therapy or other features which reduce the numbers of resident effector cells in patients may reduce response
  – Higher tumor burden may increase the severity of CRS if T cells are not limiting
FDA experience with some bispecifics in oncology indications

- Factors limiting efficacy
  - Host specific factors: qualitative and quantitative defects in the T cells and accessory cells in older individuals or patients with certain tumor types,
  - Disease specific factors: heterogeneity of specific tumor types with respect to expression of tumor specific antigen or resistance phenotypes to T cells,
  - Resistance factors specific to the T cell (check points etc),
  - Problems intrinsic to the bispecifics
    - ADA seen more with some tumor targets
    - Poor penetration of solid tumors
Common Adverse Events Among Different Product Classes

• Cytokine Release Syndrome
  – mAbs, checkpoint inhibitors, bispecifics, CAR T cells and ADCs targeting cells of the immune system

• Immune-mediated adverse events
  – Major focus on checkpoint inhibitor labels, all classes can have immune-mediated AEs

• Tumor lysis syndrome
  – mAbs, checkpoint inhibitors, bispecifics, ADCs

• Infusion reactions
  – mAbs, checkpoint inhibitors, bispecifics, ADCs

• Neurotoxicity
  – Bispecifics, CAR T cells

• Peripheral neuropathy
  – ADCs
Cytokine Release Syndrome: Pre-Clinical Studies

- Monitor in vitro ability to induce cytokine release and proliferation of whole blood samples or PMBCs from multiple donors
- Dose titration of product in both soluble and plate bound form
- Measure IFNγ, TNFα, IL6 and other relevant cytokines
- Agonistic mAbs can exhibit a bell shaped dose response curve
  - Test levels that lead to low (e.g., 10-20%), medium and complete receptor saturation
- Include immobilized product, both wet and dry coated on the plate and a positive control antibody (OKT3)

Cytokine Release Syndrome
For bi-functional antibodies targeting T cells

- Cytokine release and proliferation with human PBMCs
  - Use product optimized stimulation conditions, 6-12 donors and relevant positive control
- Assess cytokine release and proliferation of PBMCs in the presence of targeted tumor antigen
- Assess/characterize the activity of both CD4+ and CD8+ T cells, cytokines, activation marker up-regulation, Granzyme B, etc
- Assess off-target T cell activation/ cell killing
- Characterize target cell killing and cytotoxicity pathway (e.g., caspase activation)
- Bi-functional binding/cellular potency assays.
The Goldilocks approach: Not too hot, not too cold, just right
Managing toxicity while improving efficacy

- Checkpoint inhibitors and immunostimulatory mAbs
  - Find a balance between activating the immune system and not inducing immune-mediated events

- Bispecifics and CAR T cells
  - Fine tuning affinities of each arm

- ADCs
  - Drug-linker chemistry, DAR to minimize toxicity and improve therapeutic index

- Combinations
  - Find the right combinations
Some final thoughts for control strategies...

• If specific amino acid in a CDR is engineered for optimal binding, may need to consider post-translational modifications

• Glycosylation and Fcγ Receptors
  – There is still more to learn!
  – Important to control glycoforms, even if effector function is not part of MOA
  – What effector cells are at site of tumor?
  – Is there a hierarchy of response through different FcγRs?
  – Role for IgG4 via FcγR binding?
    • TGN1412 (anti-CD28) interaction with FcγRIIB played a role in cytokine response (Bartholmaeus et al. JI, 2014 192:2091)

• BsAb considerations depend on the platform.
  – Should have a control strategy if anti-CD3 homodimers are possible.