Future Directions in Transplantation
One Future Direction in Transplantation: Accelerated Approvals of Immunosuppressants Using Surrogate Endpoints in Clinical Trials of Renal Transplant Recipients

FDA Workshop
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Can Early Surrogate Efficacy Endpoints for Renal Transplantation Immunosuppression Trials Reliably Predict Treatment Effects That Decrease Graft Failure?

Even the Romans Were Skeptical

“It seems to me that no soothsayer should be able to look at another soothsayer without laughing”

Cicero to Roman Senate
Disclosures

• Non-exclusive consulting in last 3 years for:
  - Novartis.
  - Astellas.
  - Genentech.
  - True North Therapeutics.

• Novartis stock and stock options.

• This presentation contains slides of record: \( N^{th} \) revision.
  - Slightly revised from the handouts.
I’m From the FDA, & I’m Here to Help

MOMMY, I’M SCARED OF THE GOVERNMENT
Don’t Be Scared: The FDA Initiated, Sponsored & Organized This Workshop

Thank you, FDA

• This “Work”shop has been a lot of work, mainly for the FDA.

• Monthly standing conference calls Feb through Aug, plus many more ad hoc conference calls

• Many, many drafts of the program agenda.
Also, Thank you:
Presenters, Moderators, Discussants & Audience
Organ Transplantation (Tx): A Work in Progress
The Future for Clinical Renal Tx: Decreased Immune-Mediated Graft Failure (1)

• To reach this goal, we need:
  ➢ “Immunosuppression” (IS) that is safer & more effective than standard of care (SOC) IS regimens.
    ✓ Safer & more effective immunosuppressive drugs/biologics (ISDs).
    ✓ Safer, more effective, feasible & convenient cell-based therapies..
  ➢ Better understanding of the pathophysiology of immune-mediated injuries in the graft.
  ➢ Improved adherence to prescribed ISDs.
ISDs Are Only Effective If They Are Taken as Prescribed

“You boys who have to take your medications with food, now’s the time.”
The Future for Clinical Renal Tx: Decreased Immune-Mediated Graft Failure (2)

• To reach this goal, we need:
  - **New trial designs:**
    - **New, more sensitive primary endpoints (EPs)** that offer the opportunity for new IS therapeutic approaches:
      - To prove efficacy &/or safety **superiority** vs. SOC ISDs.
      - For trials with acceptable durations, sample sizes & costs.
  - **Collaboration** among FDA, Tx community, industry, C-Path, NIH, CMS & others to evaluate new primary EPs proposed for FDA validation, qualification & acceptance.
Why Is It Important to Decrease Immune-Mediated Renal Tx Failure? (1)

• Tx is superior to dialysis for treatment of ESRD:

  ➢ Tx is *life-saving*:

      ▪ 987,009 life-yrs. saved by dialysis.
      ▪ 2,246,383 life-yrs. saved by Tx.

  ➢ Tx improves the way recipients *feel, function & survive.*

Rana A, et al. 2015. JAMA Surgery; 150: 252-259
Why Is It Important to Decrease Immune-Mediated Renal Tx Failure? (2)

• SRTR database.

➤ K-M estimates of $T_{1/2}$ for death-censored Tx failure:

✓ 1st Living donor = 16 yrs.

✓ 1st Standard criteria deceased donor = 13.1 yrs.

✓ 1st Expanded criteria donor = 9.2 yrs.

Why Is It Important to Decrease Immune-Mediated Non-Renal Tx Failure? (3)

- Actuarial (black solid line) and projected (gray dotted line) graft failure half-lives of liver, lung, heart and intestine.
Why Is It Important to Decrease Immune-Mediated Renal Tx Failure? (4)

- Death rates on dialysis after Tx failure in North America are unacceptable:
  - Overall annual adjusted death rates **3x higher** after failed Tx vs. functioning Tx (USRDS).
  - **78% greater death rate** vs. Tx candidates (US SRTR).
  - **Mortality HR = 2.07** when returned to dialysis 1 – 5 yrs. post Tx (Canadian Registry).

Australian Renal Tx Recipients’ Perspective: “Death is Preferable to Return to Dialysis.”

<table>
<thead>
<tr>
<th>Condition</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney rejection (failure)</td>
<td>High</td>
</tr>
<tr>
<td>Kidney function (failure)</td>
<td>Medium</td>
</tr>
<tr>
<td>Damage to other organs</td>
<td>Low</td>
</tr>
<tr>
<td>Death or survival</td>
<td>Medium</td>
</tr>
<tr>
<td>Cancer - other</td>
<td>Low</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Low</td>
</tr>
<tr>
<td>Cancer - skin</td>
<td>Low</td>
</tr>
<tr>
<td>CVD (cholesterol, blood pressure)</td>
<td>Low</td>
</tr>
<tr>
<td>Prone to infection</td>
<td>Low</td>
</tr>
<tr>
<td>Weight gain and excessive appetite</td>
<td>Low</td>
</tr>
<tr>
<td>Bone disease</td>
<td>Low</td>
</tr>
<tr>
<td>Impact on family</td>
<td>Low</td>
</tr>
<tr>
<td>Interaction with other drugs and food</td>
<td>Low</td>
</tr>
<tr>
<td>Depression</td>
<td>Low</td>
</tr>
<tr>
<td>Impact on work</td>
<td>Low</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>Low</td>
</tr>
<tr>
<td>Concentration and memory</td>
<td>Low</td>
</tr>
</tbody>
</table>
Multiple Causes of Renal Tx Failure
Schematic for Mechanisms of Immune-Mediated Tx Injuries


A. Acute rejection of organ allograft
   - Recipient T cell activation
     - CD8
     - CD4
   - Cytokine production
     - IFN-γ, TNF, IL-2, IL-17, IL-21, IL-23
     - Macrophage
     - Neutrophil
   - Direct allograft cell lysis
     - Destruction of organ parenchyma and blood vessels

B. Chronic rejection of organ allograft
   - Donor APC (allo MHC)
   - Host APC (self MHC, alloantigen)
   - Recipient T cell activation
     - CD4
   - DSA production
   - Recipient B cell activation
     - B cell
   - Complement deposition on antibody
   - Innate immune cell binding and activation
     - Macrophage
     - Neutrophil
     - NK cell
   - Direct allograft cell lysis
     - Destruction of organ parenchyma and blood vessels
Knowledge of Biologic Causes of Graft Injuries Defines Phenotypes of Sub-populations for Enriched Trial Enrollment
Some New ISD Targets & Approved & New ISDs:  
*But What Primary Efficacy EPs Will Enable New ISDs to Show Efficacy &/or Safety Superiority vs. SOC ISDs?*

1 yr. outcomes for current primary FDA EPs:

- **All-cause Tx failure** (return to dialysis, repeat Tx, or death with a functioning graft):
  - Cadaver donor (CD) = 7.7%.
  - Living donor (LD) = 3.3%.

- **Death**:
  - CD = 3.7%.
  - LD = 1.3%.

2014 USRDS Annual Report
Proving Efficacy Superiority of a New IS Therapy vs. SOC ISDs for Renal Tx Is Unlikely with Current 1 yr. Outcomes (2)

• **1 yr. outcomes** for current FDA primary FDA EPs:

  ➢ **Biopsy-proven acute rejection:**
    ✓ 1996 = 50 %
    ✓ **Now** = 7 – 9% for CD & LD.

• But we fail to detect & treat the innate & adaptive immune injuries that **begin at Tx, continue during the 1st yr.** & can be causes for many late Tx failures.

• Note: dnDSA & “Ab associated rejection” is a failure to suppress T-cell activation.
Ph 2 & 3 IS Trials Now Recruiting for Renal Tx Recipients

- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

- **Search terms:**
  - rejection | Open Studies | Exclude Unknown | Interventional Studies | kidney transplantation | immunosuppression | Child, Adult, Senior | Phase 2, 3

- **Only 9 trials listed.**
Perspectives on Barriers to Progress in Immunosuppression for Adult Renal Transplantation in the US

Randall E. Morris. MD, FRCP
Issues for NDA decisions from Ph 3 Tx IS trial data:

- **Subpart H (Accelerated Approval):**
  - Allows efficacy determined by *surrogate endpoints* "reasonably likely to predict clinical benefit."
  - Post-approval Ph 4 trials required to confirm clinical benefit for traditional approval.

- Is GFR 1 yr. post Tx a surrogate endpoint for 5 yr. graft & pt. survival?

- What are other more sensitive, specific endpoints for efficacy &/or safety?

  AJT 93:172, 2012; AJKD 57:466, 2011; AJKD 56:947, 2010
Data on New Drug Approvals by FDA from 2005 - 2012

- 188 novel drugs approved.
  - 20% for cancer, 14% for infectious diseases, 23% for cardiovascular disease, diabetes or hyperlipidemia.
  - Orphan status = 16.5%.
  - Accelerated Approvals = 11.7%.
  - Approval from a single pivotal trial = 36.8%.
  - Surrogate EP (SEP):
    - Primary EP = 48.9% of all trials.
    - For Accelerated Approvals = 95%.
    - Not yet for Tx trials.

Downing NS, et al. 2014. JAMA; 311: 368 - 377
Acceptance of SEPs as Primary EPs for Tx IS Accelerated Approval Trials Will Lower the Threshold for Showing ISD Efficacy Superiority vs. SOC ISDs

“My dad decided to make me more accessible”
## Definitions of Biomarkers (BMs) & SEPs


<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prognostic biomarker</td>
<td>Biomarker that forecasts the likely course of disease irrespective of treatment</td>
</tr>
<tr>
<td>Predictive biomarker</td>
<td>Biomarker that forecasts the likely response to a specific treatment</td>
</tr>
<tr>
<td>Clinical end point</td>
<td>Measurement providing information on how a patient feels, functions or survives&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surrogate end point</td>
<td>Measurement providing early and accurate prediction of both a clinical end point, and the effects of treatment on this end point</td>
</tr>
<tr>
<td>Validation</td>
<td>Confirmation by robust statistical methods that a candidate prognostic biomarker, predictive biomarkers or surrogate end point fulfills a set of conditions that are necessary and sufficient for its use in the clinic</td>
</tr>
</tbody>
</table>
• Recommendations:
  - Is the biomarker (BM) able to be accurately & precisely measured (*Analytical Validation*)?
  - Is the BM associated with the clinical EP (*Qualification*)?
  - What is the specific context of BM use (*Utilization*)?

• CDER process of BM qualification summarized.

• Presentation by Thomas Flemming:
  - BM hierarchy.
    - Clinical efficacy measures.
    - Validated SEPs.
    - Nonvalidated, reasonably likely to predict clinical benefit.
    - Correlates solely as a measure of biological activity.
• Recommendations to FDA for Accelerated Approvals:
  ➢ Expand its use to more indications (e.g., Tx).
  ➢ Present clear guidance to sponsors.
  ➢ Actively engage with the medical community & sponsors for guidance on SEPs.
FDA Safety & Innovation Act (FDASIA) 
Signed Into Law on July 9, 2012 (1)

• Expand use of Accelerated Approval beyond cancer & HIV/AIDS with revised EPs:

  ➢ For “serious or life-threatening disease or condition” where the drug “has an effect on a SEP that is reasonably likely to predict clinical benefit.”

  ➢ Evidence used to support a SEP: epidemiological, pathophysiological, therapeutic, or pharmacologic and biomarkers (BMs).
FDA Safety & Innovation Act (FDASIA) Signed Into Law on July 9, 2012 (2)

• FDA program required for development of SEPs & BMs.

“Targeted Drug Development: Why Are Many Diseases Lagging Behind?”
FDA White Paper
July, 2015

• A focus on rare, orphan diseases (e.g., Tx recipients):
  ➢ Need to understand causes, natural histories or how to intervene in progression to define BMs & drug targets.
  ➢ 50-60% of orphan drug approvals based on SEPs & Accelerated Approval (not yet for Tx).
  ➢ 80% use flexible trial designs.
  ➢ 66% approved from single trial.
  ➢ 25% use novel EPs.
A typical biomarker

- Patients who benefit from new therapy
- Patients who do not benefit from new therapy

Biomarker-defined subgroup
Prognostic and Predictive

- **PROGNOSTIC:** Biomarker-based test producing result associated with clinical outcome in absence of therapy (natural course) or with standard therapy all patients are likely to receive

- **PREDICTIVE:** Biomarker-based test producing result associated with benefit or lack of benefit (potentially even harm) from a particular therapy relative to other available therapy
  - Alternate terms: treatment-selection, treatment-guiding, treatment effect modifier

Prognostic vs. predictive: Importance of control groups

Prognostic but not predictive

(M = biomarker)

Prognostic and predictive

No survival benefit from new therapy

New therapy for all, or for M+ only?
Plasma IL-6 as a predictive biomarker for pazopanib in metastatic renal-cell cancer?

(Tran H et al., *Lancet Oncol* 2012;13:827-837)

**QUANTITATIVE INTERACTION**

- High plasma IL-6 concentration is prognostic for shorter PFS
- High plasma IL-6 concentration is predictive for improved relative PFS benefit from pazopanib compared to placebo

**Is IL-6 helpful for selecting therapy?**

<table>
<thead>
<tr>
<th>Interleukin 6</th>
<th>PFS (weeks)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pazopanib</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42.3</td>
<td>24.0</td>
<td>0.55 (0.38-0.81)</td>
</tr>
<tr>
<td>High</td>
<td>32.6</td>
<td>9.9</td>
<td>0.31 (0.21-0.44)</td>
</tr>
</tbody>
</table>

(Adapted from Figure 2 of Tran et al.)

(Randomized placebo-controlled phase 3 trial)
Biomarker-Stratified Design

- Reasonable basis for marker candidate (target gene or pathway)
- Allows maximum information
  - Controls for prognostic effect of marker
  - Directly compares new agent to control therapy in all patients
- Allows retrospective evaluation of markers measured by different method (e.g., protein, RNA, DNA) or alternative markers in pathway
- Variation: Standard therapy ± new agent
- Completely randomized design with retrospective marker evaluation is an option, but assay results might not be available for 100% of patients

Pathways at FDA to integrate biomarkers into drug development.

- **Diagnostic Biomarker**: COU: Patient Selection
  - COU: Stratify patients
  - COU: Enrich trials with patients likely to have disease

- **Prognostic Biomarker**: COU: Stratification
  - COU: Enrichment – Inclusion Criteria
  - COU: Enrichment – Companion Dx

- **Predictive Biomarker**: COU: Pharmacodynamic biomarker as an indicator of intended drug activity
  - COU: Efficacy response biomarker as a surrogate for a clinical endpoint
  - COU: Safety biomarker to monitor adverse effects on biology

**Biomarker Qualification Process**

**Initiation**
- Letter of Intent (LOI) received, go/no go decision, Biomarker Qualification Review Team (BQRT) formed, internal meeting, send briefing document specifications to submitter

**Consultation and Advice Stage**
- Briefing document received, reviewed, internal meeting, pre-meeting comments, face-to-face Meeting - Iterative process

**Review**
- Full submission package received, review by BQRT, internal meetings, request additional information (if needed), qualification recommendations

The biomarker qualification process.
“Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance & Utilization” (4)

- **Data submission & evidentiary considerations** for BMs:
  - Context of use (COU): a SEP?
  - Biological rationale, causal disease pathway & evidence that BM is pivotal in the pathway?
  - Relationships among BM, clinical outcomes & treatment?
  - Assay validation: accurate, precise, sensitive, specific, consistent, reliable, reproducible, robust?
Data submission & **evidentiary considerations** for BMs:

- Strength of BM & clinical outcome *(retrospective, prospective, registry or RCT)*?

- Data reproducibility for test & confirmatory datasets?

- Pre-specified statistics to show relationships for COU?

- Strength of evidence drives level of regulatory scrutiny *(next slide)*?
Level of Scrutiny by the FDA for Acceptance of Efficacy SEPs for Accelerated Approvals of Tx ISDs?
• **Statistical considerations** in qualification of SEPs:
  
  Ø More clarification needed.
  
  Ø Prentice criteria difficult to satisfy.
  
  Ø **First**, show BM changes caused by treatment correlate/predict changes in clinical outcome.
  
  Ø **Second**, using meta-analysis of RCTs show significant relationships between measurement effects for BM & clinical outcomes. “...more difficult than the first [step]”
“Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance & Utilization” (7)

Figure 6 Toward a multiple stakeholder framework for biomarker development.
BMIs of Immune-Mediated Injury to Renal Tx Presented in This Workshop as Potential Early Measures for Efficacy SEPs for Accelerated Approval Trials of ISDs to Decrease Renal Tx Failure

- **Tx Histopathology:**
  - Protocol Bx.
  - Bx for cause.

- **Anti-donor Ab:**
  - Pre-formed.
  - De novo.

- **Combination of BMs:**
  - Tx histopathology + decreased renal function.
  - Others?

- Others?
Hippocrates

"Life is short, the art is long, opportunity fleeting"
Efficacy SEPs: How to Solve the Problem of Heterogeneous Pathways Causing Tx Failure?


- **No ABMR lesions**
  - Banff 13: 28
  - Discrete ABMR lesions: 14

- **ABMR**
  - C4d+ chronic/active: 18
  - C4d+ acute/active: 6
  - C4d- chronic/active: 12
  - C4d- chronic/inactive: 6
  - C4d- acute/active: 2
Some Questions Relevant to FDA Acceptance of an Efficacy SEP for IS Trials in Renal Tx Recipients to Reduce Tx Failure

(1)

For Final Discussion Session

• What is the strength of evidence for **prognostic BMs** presented today?

  - For which BMs are the **measurement methods** sufficiently validated (accurate, precise, sensitive, specific, reliable, reproducible, robust)?

  - For which BMs (or combination of BMs) is the existing evidence the strongest / weakest for **predicting Tx injury progression & Tx failure under SOC ISDs**?
Some Questions Relevant to FDA Acceptance of Efficacy SEPs for IS Trials in Renal Tx Recipients to Reduce Tx Failure

(2)
For Final Discussion Session

• What is the strength of evidence for **prognostic BMs** presented today?

  ➢ For which BMs (or combination of BMs) does the existing evidence support their use for **enriching trials** for recipients at **highest risk of Tx failure** under SOC ISDs?

  ✓ Can BMs identify **specific donor/recipient phenotypes** & if so what are these?
Some Questions Relevant to FDA Acceptance of Efficacy SEPs for IS Trials in Renal Tx Recipients to Reduce Tx Failure

(3)

For Final Discussion Session

- What is the strength of evidence for **prognostic BMs** presented today?

  ➢ For which BMs is **more evidence required** to **predict Tx failure** under SOC ISD or to **enrich trials** for subjects at risk?

  ✓ What additional evidence is required & how, when & by whom will it be acquired?
Some Questions Relevant to FDA Acceptance of Efficacy SEPs for IS Trials in Renal Tx Recipients to Reduce Long-term Tx Failure (4)

For Final Discussion Session

• What is the strength of evidence for predictive BMs presented today?

  ➢ For which BMs are the measurement methods sufficiently validated (accurate, precise, sensitive, specific, reliable, reproducible, robust)?

  ➢ Are the incidences for these BMs/SEPs & the clinical outcomes sufficiently high for an acceptably powered trial with an acceptable number of subjects?
Some Questions Relevant to FDA Acceptance of Efficacy SEPs for IS Trials in Renal Tx Recipients to Reduce Long-term Tx Failure

(5)

For Final Discussion Session

• What is the strength of evidence for predictive BMs presented today?

➢ For which BMs (or combination of BMs) is the existing evidence (T. Flemming criteria) the strongest / weakest for SEP acceptance to detect ISD treatment effects of decreased Tx failure?
Some Questions Relevant to FDA Acceptance of Efficacy SEPs for IS Trials in Renal Tx Recipients to Reduce Long-term Tx Failure

For Final Discussion Session

• What is the strength of evidence for predictive BMs presented today?

➤ For which BMs above is more evidence required to predict IS treatment effects on SEPs of decreased Tx failure?

☑ What additional evidence is required & how, when & by whom will it be acquired?
86 DSA+ patients (ESOT: G. Boehmig, R. Oberauer, Med. Univ. Vienna)

- **No ABMR**
  - No ABMR lesions: 28

- **ABMR**
  - C4d+ chronic/active: 18
  - C4d+ acute/active: 6
  - C4d- chronic/active: 12
  - C4d- chronic/inactive: 6
  - C4d- acute/active: 2

Discrete ABMR lesions: 14

Banff 13
The Journey to Identify Efficacy SEPs for Accelerated Approval Tx ISD Trials:
Be Bold! Be Courageous!
Backup Slides

Citations for Tx BMs / SEP Publications: 2014 – 2003
Previous Meetings & Publications on Biomarkers & Surrogate Endpoints for Tx (1)

  ➢ Prognostic BMs.
  ➢ None sufficiently validated to guide clinical practice.

  ➢ Comprehensive review; prognostic BMs.
Previous Meetings & Publications on Biomarkers & Surrogate Endpoints for Tx (2)

  - Predictive rather than prognostic BMs or SEPs.

  - Primarily prognostic, some predictive data.
Previous Meetings & Publications on Biomarkers & Surrogate Endpoints for Tx (3)

  ➢ Application of T. Flemming’s SEP concepts for Tx trials.

  ➢ Prognostic rather than predictive BMs or SEPs.
Previous Meetings & Publications on Biomarkers & Surrogate Endpoints for Tx (4)

  
  - Consensus conference on development of SEPs for long-term Tx survival in collaboration with NIH & FDA. November 2001.

  
  - SEPs: renal function, Tx histology, alloresponses (e.g., DSA), safety, quality of life, combined EPs.
  - Brief overview.
Previous Meetings & Publications on Biomarkers & Surrogate Endpoints for Tx (5)

  - Statistics, validation, qualification; advanced for its time.

  - Main focus on predictive rather than prognostic EPs.
  - Advocates newer, earlier EPs to predict long-term survival.