Industry Panel Session

“What are the Challenges and Needs of Industry?”

Moderator:
Dr. John-Michael Sauer (C-Path)

Panelists:
Dr. Gary Friedman (Pfizer)
Dr. Dennis Andress (AbbVie)
Dr. Irene Nunes (Merck)
Dr. Frank Czerwiec (Otsuka)
Drug Development Tools for Kidney Disease

Industry Panel Introduction

Dr. Gary Friedman
Pfizer
## Economics of Pre- and Post-RRT Therapeutics

<table>
<thead>
<tr>
<th>COST of Pre-RRT Treatment</th>
<th>COST of Post-RRT Treatment</th>
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<tbody>
<tr>
<td>• Medication</td>
<td>• Medication</td>
</tr>
<tr>
<td>• Hospitalization</td>
<td>• Hospitalization</td>
</tr>
<tr>
<td></td>
<td>• Dialysis</td>
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<tr>
<td></td>
<td>• Transplantation</td>
</tr>
<tr>
<td></td>
<td>• Quality of Life</td>
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<td>• Quality of Life</td>
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*“mind the gap”*
USRDS and SRTR Data (2013): Global Imperative for NMEs to Preempt Renal Replacement Therapy
USRDS and SRTR Data (2013):
Rise of RRT End-Users / Insufficient Reversal of RRT Dependence

<table>
<thead>
<tr>
<th>Prevalent counts of reported ESRD:</th>
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<tbody>
<tr>
<td>all patients, U.S. and territories</td>
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<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
</tr>
<tr>
<td>Other urologic</td>
</tr>
<tr>
<td>Other cause</td>
</tr>
<tr>
<td>Unknown cause</td>
</tr>
<tr>
<td>Missing disease</td>
</tr>
<tr>
<td><strong>All</strong></td>
</tr>
<tr>
<td>Recovery of renal function</td>
</tr>
</tbody>
</table>

- Hemodialysis / Peritoneal Dialysis Annually: $40,000-$80,000 per patient
- To **STABILIZE** RRT Population ≡ **Double** the Rate of “Recovery of Renal Function”
- To **REDUCE** RRT Population ≡ **Triple** the Rate of “Recovery of Renal Function”

(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)
Prioritization of NME Development Resources

- **Chronic Kidney Disease**
  - Diabetes Mellitus
  - Hypertension
  - GN/NS (SLE, IgAN, MGN, MPGN, FSGS)
  - Cystic Renal Diseases
  - All others (AKI, vascular disease, neoplasia, infection, congenital)

- **Acute Kidney Injury**
  - Reversible
  - Non-reversible

(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)
**USRDS and SRTR Data (2013): Global Imperative for NMEs Prior to Renal Replacement Therapy (RRT)**

- **Economic impacts**
  - **IDDM / NIDDM**
    - Intensive insulin management; oral hypoglycemics, weight loss/bariatric surgery
    - Up to 35% progress to require RRT
  - **Hypertension**
    - Oral anti-HTN therapy, daily BP monitoring; <10% progress to require RRT
  - **Glomerular diseases—immunosuppression and/or extracorporeal therapies**
    - Reversible
    - Non-reversible
  - **Cystic Renal Disease co-morbidities**
    - Renal cyst infection and/or hemorrhage; Renal cystectomy; Nephrectomy
    - Hepatic cyst formation & hepatic parenchymal loss
  - **AKI**
    - ICU care
    - <5% require permanent RRT

(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)
USRDS and SRTR Data (2013):
Renal Replacement Pre-transplantation driven by patients <50 years old
Post-transplant costs driven by co-morbidities in patients <50 years old

- Post-Transplant Economic impacts
  - Organ Rejection
  - IDDM / NIDDM
  - Hypertension
  - Hyperlipidemia
  - Recurrent Disease
  - Cancer
  - Infection

(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)
## Unmet Needs in Kidney Disease: Disease-specific Outcomes

<table>
<thead>
<tr>
<th>DISEASE ENTITIES</th>
<th>CLINICAL &amp; PATIENT REPORTED OUTCOMES</th>
</tr>
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<tbody>
<tr>
<td>• AKI</td>
<td>• Proportion of subjects without further functional loss;</td>
</tr>
<tr>
<td></td>
<td>• Proportion of subjects with reversal of functional loss;</td>
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<td></td>
<td>• Proportion of subjects relegated to RRT</td>
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<tr>
<td>• Diabetes Mellitus</td>
<td>• Delay time to renal functional decline by NN% from baseline;</td>
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<td></td>
<td>• PRO/QoL</td>
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<tr>
<td>• Hypertension</td>
<td>• % time with adequate BP control vs. baseline;</td>
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<tr>
<td></td>
<td>• % increase of proteinuria vs. baseline;</td>
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<td></td>
<td>• PRO/QoL</td>
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<tr>
<td>• Glomerular Diseases (FSGS, SLE, IgAN, MGN)</td>
<td>• Proportion of subjects without further functional loss;</td>
</tr>
<tr>
<td></td>
<td>• proportion of subjects with reversal of functional loss;</td>
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<td></td>
<td>• Proportion of subjects reaching CKD 5;</td>
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<tr>
<td></td>
<td>• PRO/QoL</td>
</tr>
<tr>
<td>• Cystic Kidney Diseases</td>
<td>• Renal volume stabilization</td>
</tr>
<tr>
<td></td>
<td>• Proportion of subjects without further functional loss;</td>
</tr>
<tr>
<td></td>
<td>• Proportion of subjects with reversal of functional loss;</td>
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Industry Drivers to Address Unmet Needs in Kidney Disease

- Pharma Internal Resourcing Competition
- Scientific Advice
  - Unmet medical need
  - Economic assessment
- Biostats Collaboration
  - Optimize design
  - Regulatory & Industry collaboration
- FAP
- M4 Interim Analysis
  - Efficacy
  - Safety
- M8 Interim Analysis
  - Efficacy
  - Safety
- M12 Interim Analysis
  - Efficacy
  - Safety
- IND Submission
  - Efficacy
  - Safety
  - REMS
- Post-Approval Registry
  - Efficacy
  - Safety
  - REMS
Biomarker Goals—Industry Needs:

Balance Benefit/Risk: Efficacy/Safety Assessments

SAFETY

• Current PSTC and SAFE-T outputs may provide sufficient starting point.

• Accumulation of data from consortia members and academia may further flesh out/refine utility

• Timely safety decisions to meet “Early Development” needs

EFFICACY

• Serum creatinine, Alb/Cr ratio, eGFR shift tables have been “industry standard”

• Limited success moving NMEs forward to date

• Resources dedication to AKI and CKD NME development programs more likely with “more proximal” biomarkers of efficacy demonstration
Renal Biomarkers: Understanding the Issues

Dr. Frank Czerwiec
Vice President, Global Clinical Development
Otsuka Pharmaceutical
Using Biomarkers for CKD Treatments: Issues

• Kidney-specific issues:
  - Discrete and complex filtration units
  - Limited repair/regeneration (inflammation/scarring)
  - Damage control through redundancy (delays detection)

• Efficacy biomarker (surrogate endpoint) issues:
  - Complicated validation prolonged by need for multiple therapies
  - Dissociated effects on biomarker and on outcome (especially for early markers)
  - Confounding off-target effects

• Treatment issues:
  - Early treatments (e.g., HbA1c control) take many years to detect renal outcomes (UKPDS-9 years for SCr Doubling, DCCT/EDIC-26.5 years for persistent CKD-3)
  - Few treatments improve renal outcomes in late disease (e.g., ACEi or ARB)

• Harmonization issues:
  - Understanding the relationship of biomarkers and accepted outcomes
  - Harmonized use of biomarkers
“Many people who receive a serious medical diagnosis dream about heading off on a global adventure.”

“Dr. Riordan said he didn’t see any reason to stop me from going because I wasn’t actively sick.”

eGFR = 11 mL/min/1.73m²
Unanticipated “Off-target” Effects can Dissociate Biomarkers from Later Disease Outcomes

- Everolimus is often used as an anti-rejection agent for transplantation
- Early evidence suggest it is less nephrotoxic than calcinurin inhibitors in CKD-1
- Recent evidence in oncology suggests it is associated with AKI in CKD 2-4
- Off-target effects may explain everolimus’ “dissociation” of eGFR and TKV in ADPKD: “Unexpectedly, a significant reduction in the TKV (P = 0.02) coincided with a significant worsening of renal function and a drop in estimated GFR (P = 0.004) after 1 year of treatment with everolimus ... Among male patients with ADPKD who had an estimated GFR of less than 60 ml per minute, those in the everolimus group had a significantly more rapid decline in the estimated GFR than did those in the placebo group. This was not seen among male patients with an estimated GFR of 60 ml per minute or more ... “ G. Walz 2011 NEJM Letter

Figure 2 Incidence of AKI according to baseline eGFR categories in the RCC group. The incidence of all-cause AKI and everolimus-associated AKI increased progressively with decreasing eGFR (P = 0.029 and P = 0.004 for trend, respectively). S.H. Ha 2014 BMC Cancer
DCCT-EDIC Trials: Nephropathy Results over 20 Years

I.H. de Boer, et al., 2011 NEJM
Relationship of Outcomes and Biomarkers: Understanding Clinical Interpretability

- **RENAAL Trial**¹: (N=1513, age 31-70 yrs, NIDDM, mean SCr=1.9 mg/dL, losartan vs. placebo)
  - ↓16% Dbl SCr/ESRD/Death

- **IDNT Trial**²: (N=1715, 30-70 (̄x=59) yrs, NIDDM, SCr 1.0 ♀, 1.2♂-3.0 mg/dL, ̄x=1.67, irbesartan vs. placebo)
  - ↓23% Dbl SCr/ESRD/Death

- **AASK Trial**³⁴: (N=1094, 18-70 (̄x=54) years, HTN, eGFR 20-65 mL/min/1.73m², ̄x= 46, ramipril vs. amlodipine)
  - ↓38% Dbl SCr/ESRD/Death

Relationship of Outcomes and Biomarkers: Understanding Clinical Interpretability

- **RENAAL Trial**\(^1\): (N=1513, age 31-70 yrs, NIDDM, mean SCr=1.9 mg/dL, losartan vs. placebo)
  - ↓16% Dbl SCr/ESRD/Death → 0.8 mL/min/1.73m\(^2\)/year difference
    - 15% reduction in eGFR decline (4.4 vs. 5.2 mL/min/1.73m\(^2\)/year)

- **IDNT Trial**\(^2\): (N=1715, 30-70 (\(\bar{x}=59\)) yrs, NIDDM, SCr 1.0♀, 1.2♂-3.0 mg/dL, \(\bar{x}=1.67\), irbesartan vs. placebo)
  - ↓23% Dbl SCr/ESRD/Death → 1.0 mL/min/1.73m\(^2\)/year difference
    - 15% reduction in Creatinine clearance decline (5.5 vs. 6.5 mL/min/1.73m\(^2\)/year)

- **AASK Trial**\(^3,4\): (N=1094, 18-70 (\(\bar{x}=54\)) years, HTN, eGFR 20-65 mL/min/1.73m\(^2\), \(\bar{x}= 46\), ramipril vs. amlodipine)
  - ↓38% Dbl SCr/ESRD/Death → 1.16 mL/min/1.73m\(^2\)/year difference
    - 36% reduction in eGFR decline (chronic slope = 2.07 vs. 3.22 mL/min/1.73m\(^2\)/year)

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Harmonizing Approaches to Efficacy Biomarkers

• 2014 EU Guideline for products to prevent/slow progression of CRI
  “Recommendations are given regarding assessment methods to be used in relation to selected endpoints, strategy and design of clinical trials, criteria for the choice of comparator, study duration, factors confounding the interpretation of study results, specific aspects to be considered for paediatric and elderly patients, and for safety assessment, focusing on overlapping safety signals and encouraging broader exploration of more sensitive tools, namely biomarkers.”

• 1998 FDA Evidence for Effectiveness Guidance:
  “A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). … the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.”

• 2012 Everolimus in Tuberous Sclerosis Complex renal angiomyolipoma
  Approved for “adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.”