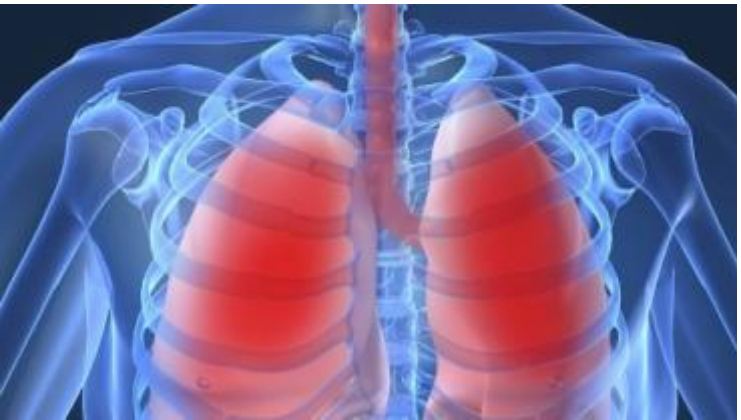
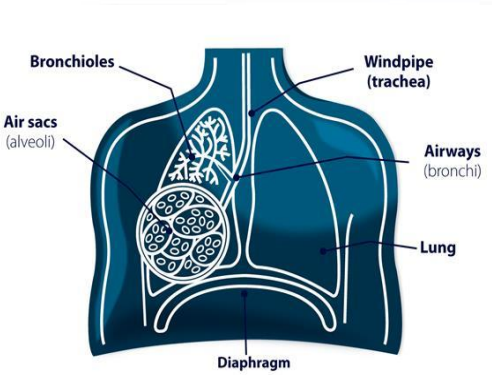
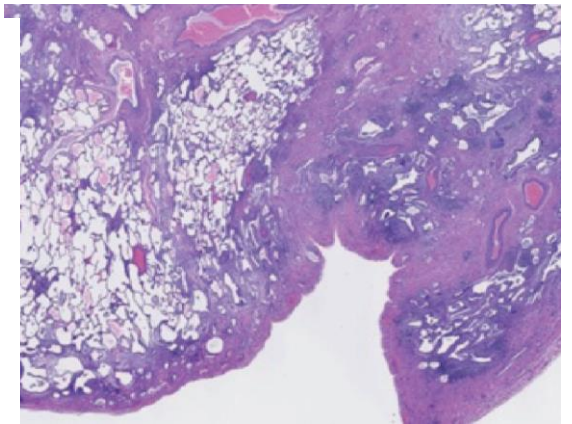
Clinical Development Challenges in Idiopathic Pulmonary Fibrosis

Friday 13th November 2015
Andy Kenwright, Roche Products Ltd







Acknowledgements and Disclaimer

- Thanks to all our IPF clinical development team and particularly Rhian Jacob & Bernie Surujbally from Statistics, Astrid Scalori, Janusz Kaminski and Jeannie Hou

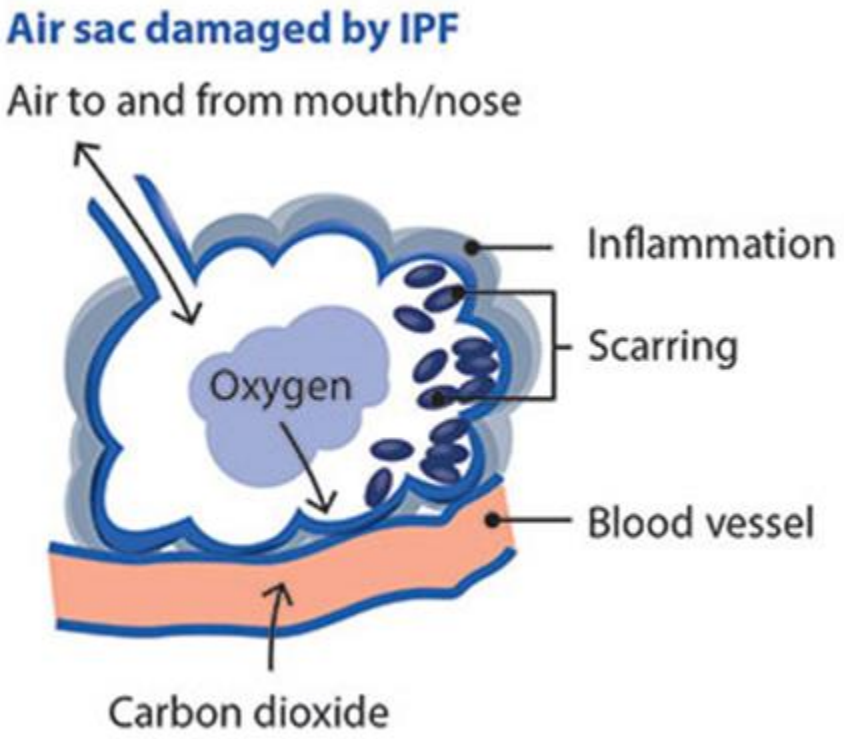
- All statements, thoughts, musings and recollections are my own views and do not necessarily reflect those of Roche Products Ltd

Roadmap

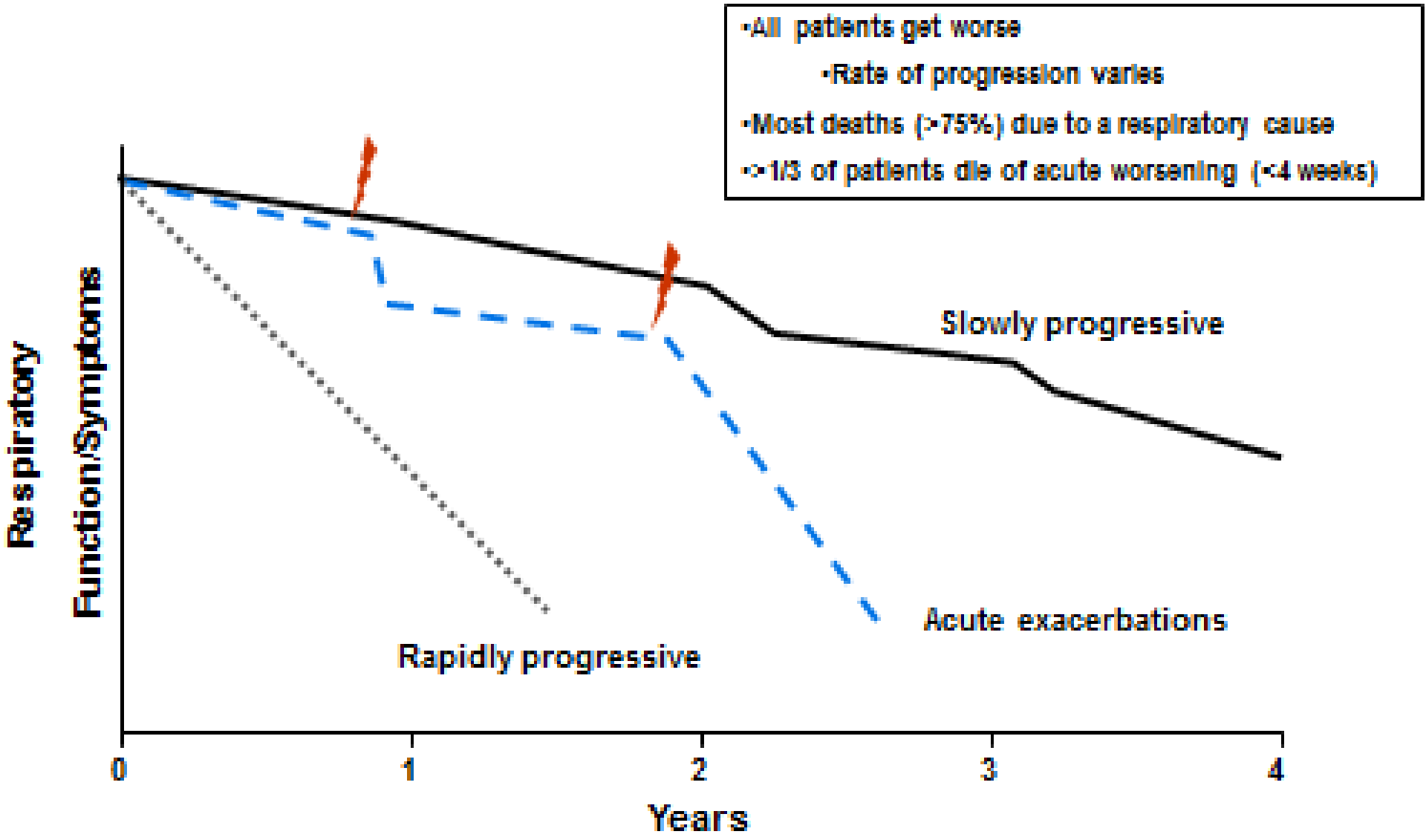
- What is IPF ?
- IPF Treatment Paradigms
- Endpoint and Design Challenges in Designing IPF Trials
- Dynamic Evolution of Development Plans
- Take-home Messages
- The Future

What is Idiopathic Pulmonary Fibrosis ?

- The most common form of Interstitial Lung Disease - 5,000 cases every year in the UK, men account for 6 out of 10 cases
- A fatal disease of unknown origin causing progressive scarring (fibrosis) of the lungs
- Median survival time of 2-3 years, progression leads to lung transplant or death
- Symptoms of shortness of breath and dry cough
- Still significant unmet need despite licensed treatments

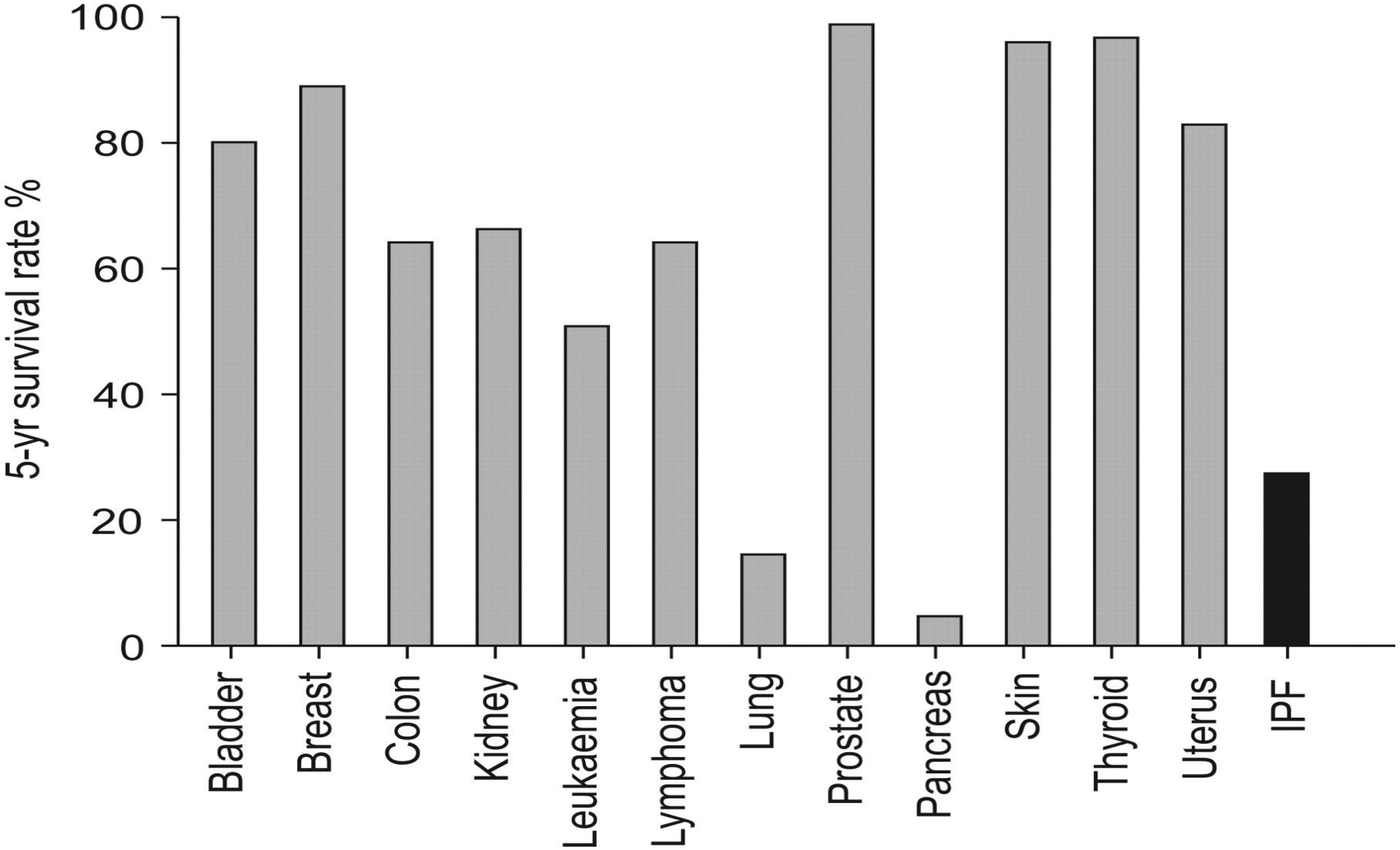


Clinical Course



Prognosis

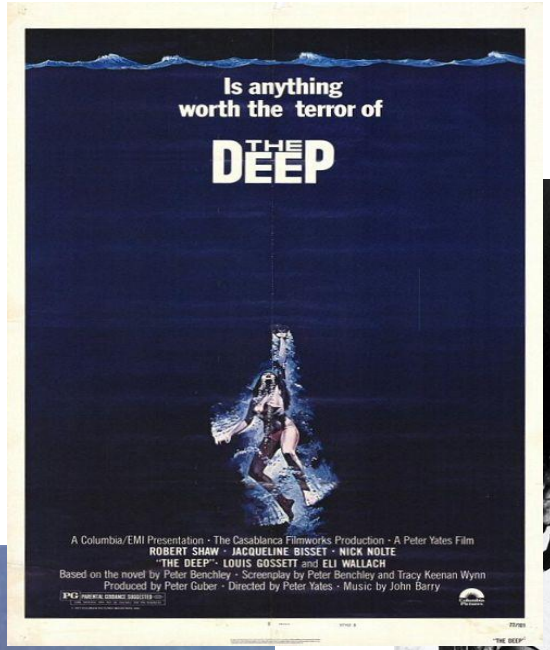
Comparison of the 5-year Survival Rate for Idiopathic Pulmonary Fibrosis (IPF) and Different Forms of Cancer

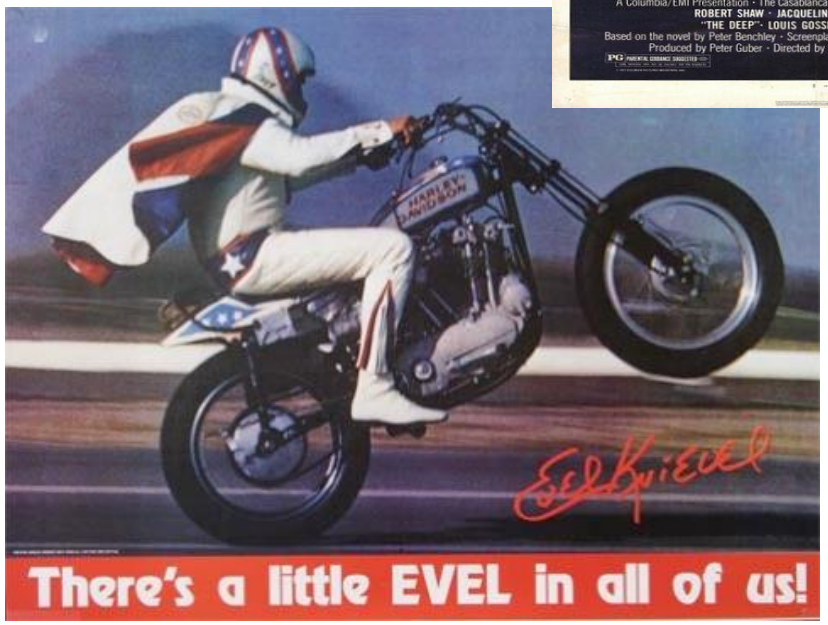


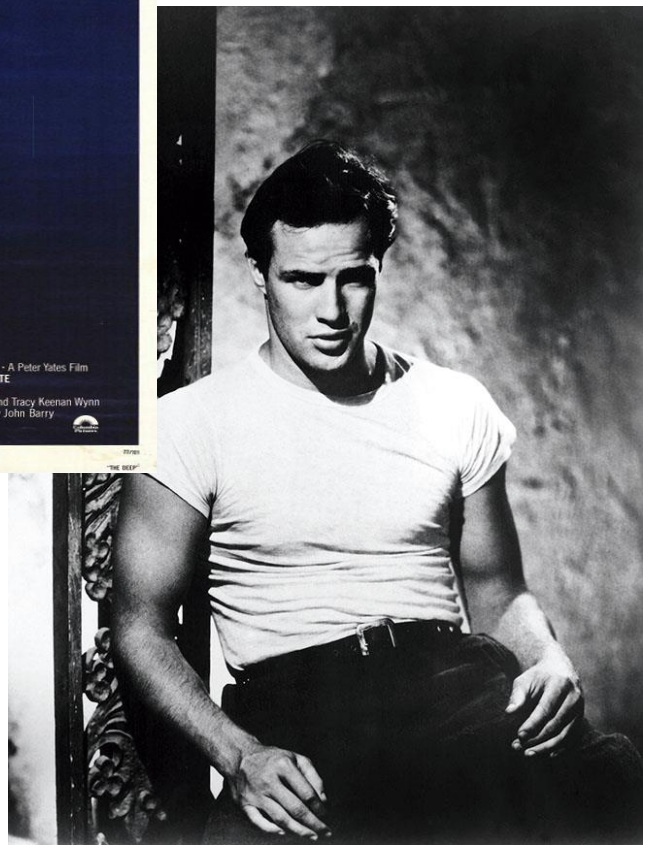
Current Status of Treatments

- A slowing of the decline in lung function is currently best case
- Mode of actions to reverse Fibrosis are not yet known
- Licensed treatments now available to slow progression – Ofev (nintedanib) and Esbriet (pirfenidone)
- Some good news: treatment rates are increasing, and patients are being diagnosed earlier
- Within 10 years expect new compounds to further slow disease progression

Famous Faces, a Less Famous Disease







Design Challenges (Phase II & Phase III)

- RETENTION - Patients will feel worse on treatment in the short/medium term
- MONO VS COMBO - Placebo without background standard of care treatment now unlikely
- SAFETY PROFILE - In combination therapy any additive side effects or increasing the range of side effects may lead to further drop-outs
- ADD ON EFFICACY - Demonstrating further improvement over effective SoC is difficult without MOA to reverse disease course (i.e. restore normal lung architecture)
- FAST PACED - changing external &internal landscape – think on your feet and adapt as new treatments change the regulatory picture
- WHAT IS OUR Probability of Success ? - a natural desire for interim readouts and data driven conditional probability of success; combination therapy makes these more challenging

Characteristics of the Ideal IPF Primary Endpoint

- Primary endpoints for IPF should be clinically meaningful i.e. directly inform how a patient feels, functions, or survives
- Endpoint should be well-defined, reliable, measurable, interpretable, and sensitive to effects of the intervention
- No validated measures of symptoms, health/functional status exist
- Validation of a surrogate endpoint requires substantial evidence that the effect of an intervention on a clinically meaningful endpoint is reliably predicted by effect of intervention on surrogate endpoint
- Currently no validated surrogate endpoints in IPF (although FVC considered approvable endpoint)

Potential Endpoints in IPF Trials

Endpoint	Pros	Cons
Mean FVC Change	•Smaller sample size needed •May be accepted if other indices are supportive •Most common endpoint used •Objective/easy to standardize	•Not recommended by FDA •No established MID
Proportion with at least 10% FVC decline	•Believed to be a predictor of mortality •More clinically significant than FVC •Objective/easy to standardize	•May be more driven by those with exacerbations
6MWD	•May be combined with 02 requirement •Endpoint used in other lung diseases (e.g. PAH) as labeling claim	•High measurement variability •Unclear regulatory viability
QoL	•Easy to measure •Smaller sample size needed	•Minimal data on MID •Preferred tool not established •Unclear regulatory viability
Fibrosis on HRCT	•Believe to be a predictor of mortality	•No established scoring system •Difficult to standardize •Unclear regulatory viability
Disease Progression Composite	•Recommended endpoint by FDA •Clinically significant	•Ideal composite makeup not established •Larger trials needed •Usually driven by FVC component
Mortality	•Recommended endpoint by FDA •Most robust endpoint from regulatory standpoint	•Long, expensive study •May be harder to show benefit

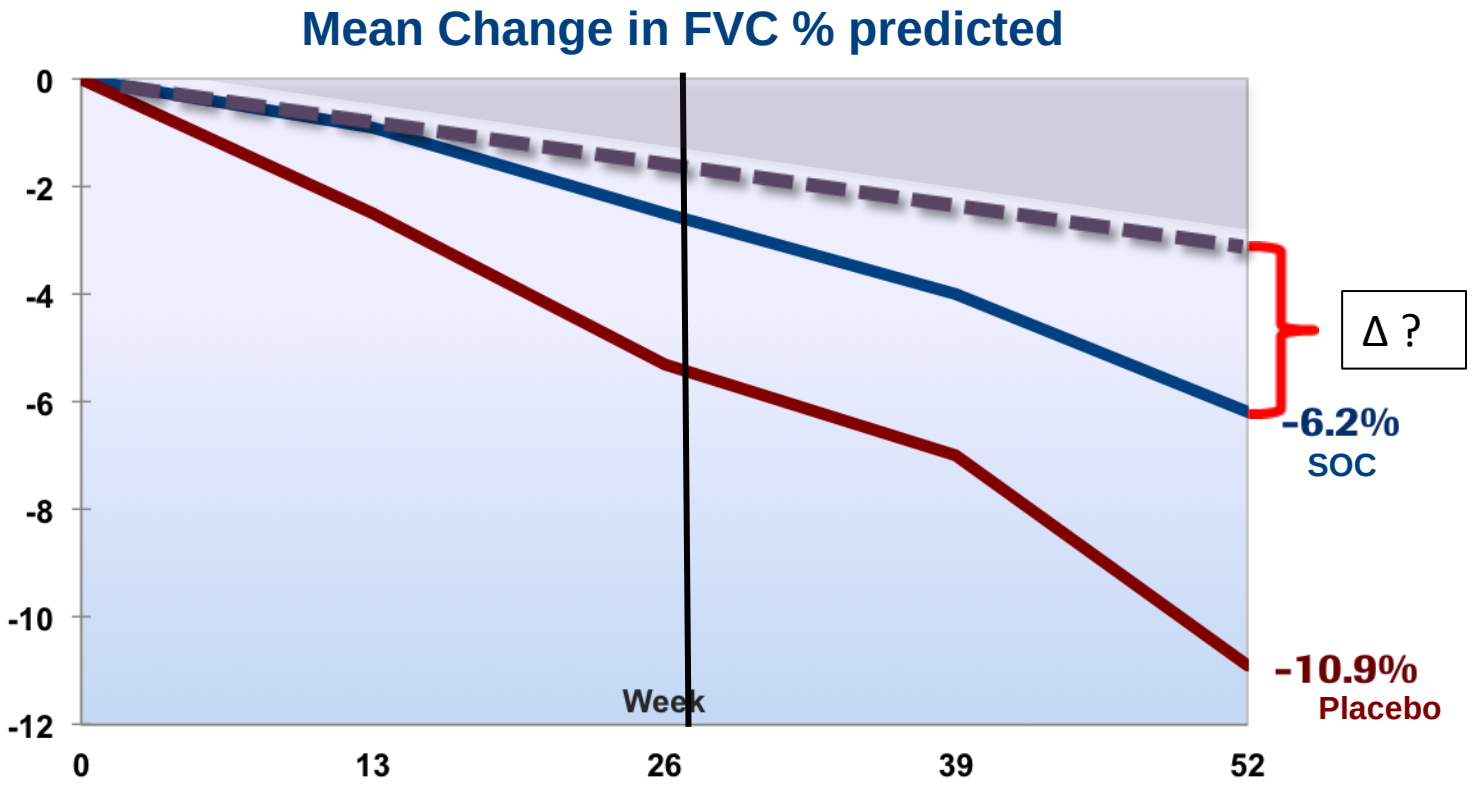
Forced Vital Capacity Recommended as Primary Endpoint for any "Best-in-Class" goal

FVC

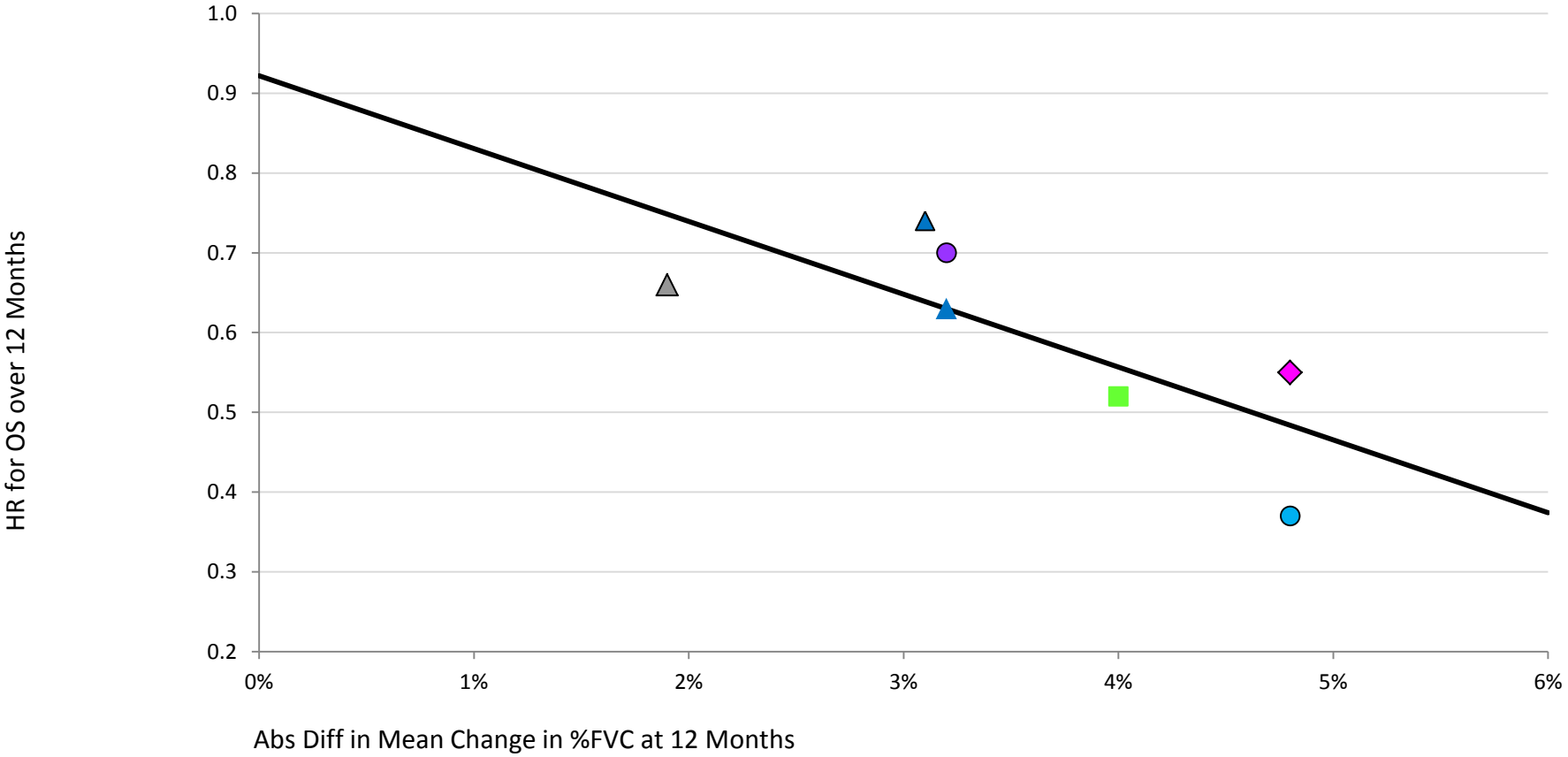
The most statistically efficient endpoint available and is accepted by the scientific community and health authorities as being a surrogate for mortality

- Change in %FVC at 12 months is the optimal test parameter and treatment duration
- 3% delta is minimum difference considered clinically meaningful

Narrow Potential "Window" for Add-on Therapy



Evolving and Convincing Evidence of Relationship Between Reduction in FVC Decline and Improvement of All-Cause Mortality (Points on plot are study results)



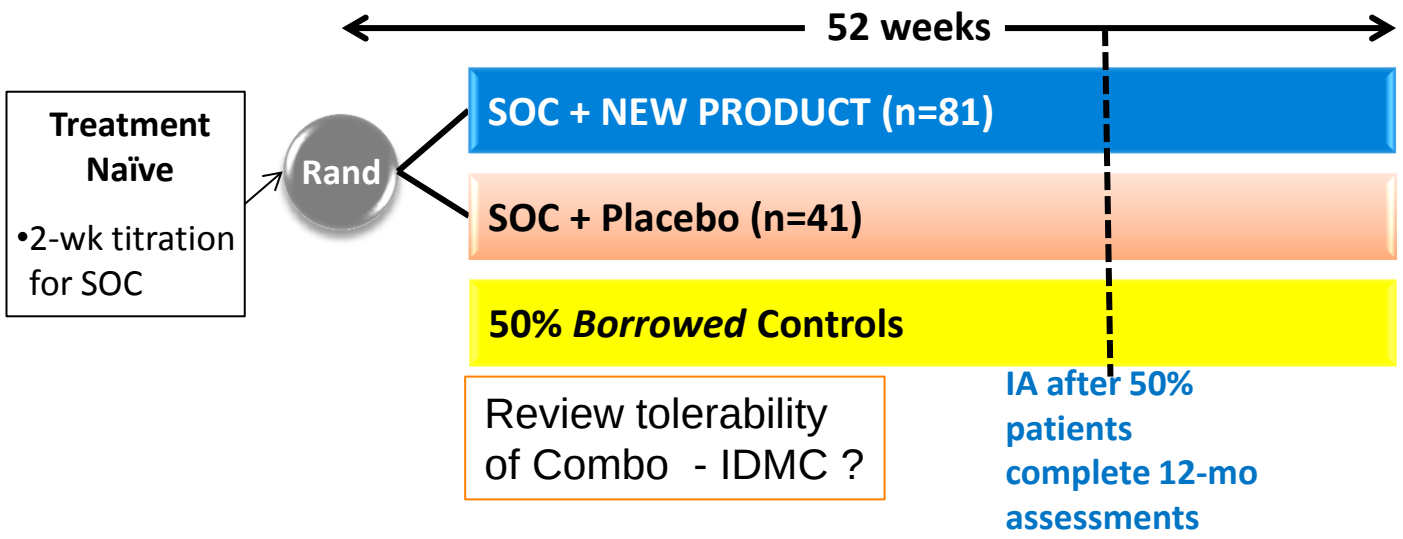
"The relationship between FVC and mortality trends in both sets of clinical trials strengthened our ability to rely on FVC as a clinically relevant efficacy measure in IPF." US FDA perspective (Karimi-Shah et al, NEJM 2015)

Dynamic Evolution of Clinical Development Plans

Planning phase II and III studies in IPF changed dramatically with:

- Evolving treatment: new “standard of care” evolves quickly in a competitive environment
- Regulators respond to primary and secondary endpoints choices
- Scientific Advisory Board (non Agency)
- “Competitor” drug filing results
- Evolving biomarker information
  - On investigational drug
  - On “standard of care” drug
  - In the general disease area

Phase II Evolution - from a simple 2 arm monotherapy study into less Simple : Combination



- ***Primary:***
  - Superiority of New Product+SOC over SOC alone on Change in %FVC at 52 weeks
  - ~80% power to demonstrate a 4% absolute reduction in mean change in %FVC using rank ANCOVA at 1-sided 0.1 alpha (assume mean rank diff=0.10, SD=0.29)
  - Interim futility analysis after 50% patients complete the study

- ***Secondary:***
  - All-cause mortality
  - PFS, 6MWT Distance, USCD SOBQ score
  - Safety
  - Explore prognostic and predictive biomarkers

Borrowing Standard of Care Placebo Data

- Informative Prior: a meta-analysis was carried out on three published Phase 3 trials to estimate the overall mean SOC response for change from baseline in %predicted FVC at Week 52 - A classical Random Effects Restricted Maximum Likelihood (REML) model gives mean estimate
- Bayesian Hierarchical Model was proposed to estimate the primary endpoint, incorporating an informative prior for the SOC treatment response
- Model used to describe the data:

$$Y_i \sim \beta_0 + \sum_j \beta_{[j]} x_{[j]}(i) + \beta_{cov} x_{cov}(i) \quad (1)$$

$$\sum_j \beta_{[j]} = 0 \quad (2)$$

i= 1 to total number of patients, j=1 for SOC, j=2 for Combination drugs

- Estimated that we could borrow all our placebo data, but opted for 50%

Interim Analysis – Operating Characteristics For 50% Patients at 12 months
(No Borrowing)

Predictive Probability used to determine efficacy or futility using cut-offs:

- **62% probability of correctly claiming futility when True Value of Delta=0**
- End of Study Success Criteria:
  - **C1:** 90% probability that New Drug+SOC is better than SOC (delta > 0)
  - **C2**: 25% probability that the effect of New Drug+SOC over SOC is 2.5
  - Efficacy: > 80% predictive probability – so > 80% probability that the End of Study C1 (and C2) rules will be met, conditional on the observed interim results
  - Futility < 20% predictive probability – so < 20% probability that the End of Study rules will be met, conditional on the observed interim results

Operating characteristics for Interim (N=33 per group) using Predictive Probability (PP) – Non-Informative Prior

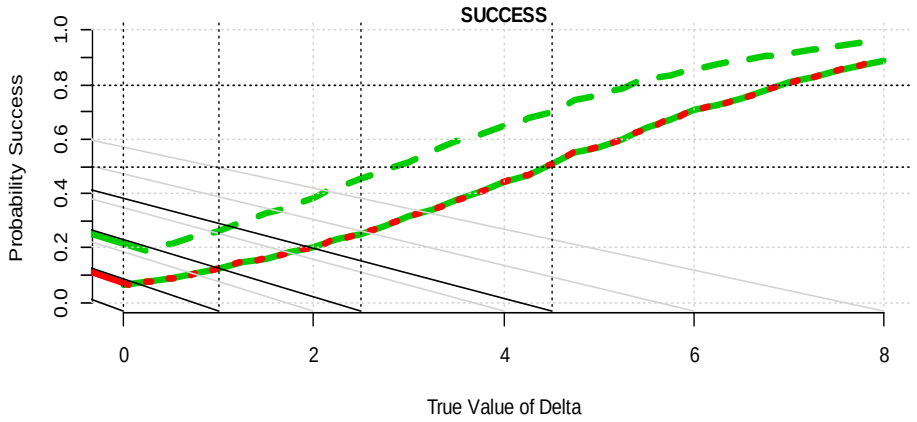
OC at INTERIM

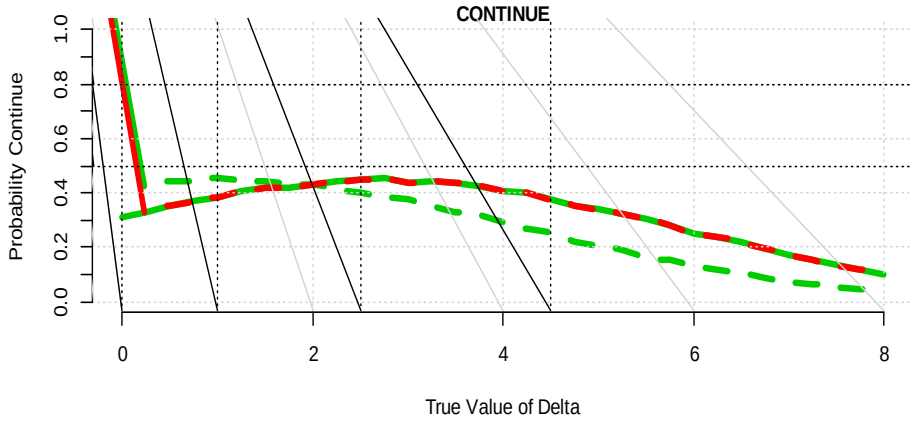
Pred Probs defining Futility/Success: 0.2 / 0.8
Criterion 1: Prob > 0.9 that delta > 0 (solid line)
Criterion 2: Prob > 0.25 that delta > 2.5 (dashed line)
Both criteria: broken red line (may overlap Criterion 1 or 2)

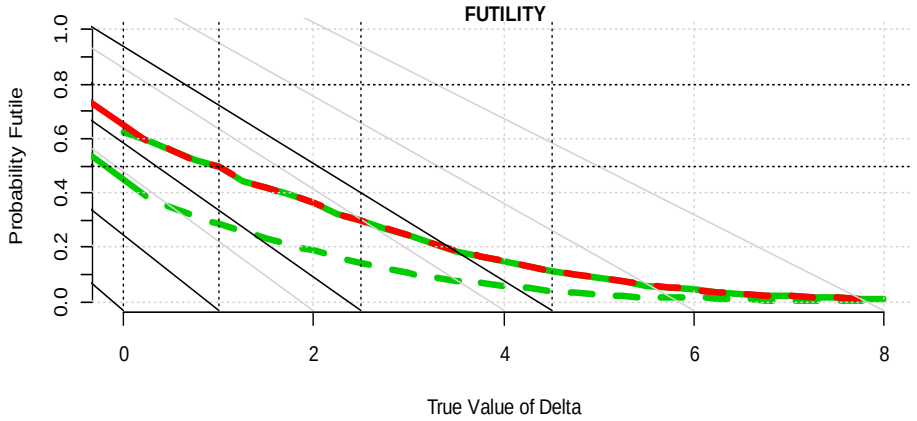
Interim N. Control: 33 of 66, Active: 33 of 66

Prior for Control Mean: N(mean= 0, sd= 12000)
Prior Effective N (Controls) = 1e-06

sigma = 12, Effect's PostSD@int = 3







Other Debates Along the Way

- Analysis
  - Rank ANCOVA vs parametric ANOVA vs % of patients with FVC<10% etc
  - Scientific advice: threw up many demands eg for “slopes analysis” (we proposed a mixed model approach)
- Missing Data Handling Methods
  - Imputation for death or transplantation
    - 0 for RANK ANCOVA (with adjustment for time of death/transplant)
    - 30% FVC if use parametric ANCOVA
  - Plus Maximum Likelihood methodologies
  - And potential for use of MI and random effects pattern mixture model
- Populations
  - Treatment Naïve or a mix (borrowing complicates matters)
  - Degree of severity of disease

Take-homes

- Gaining a picture of ALL stakeholder's needs is vital – from patients to payers via KOLs, safety scientists and regulators
- Immerse yourself in the physiology and medicine, try to become as expert as the KOLs – we are **statistical scientists**
- Be BRAVE in proposing novel designs/analyses and be ready to convince, negotiate and debate the benefits and risks
- There is a race to develop new treatments and like a MOTOGP rider, the pace is FAST when your knees and elbows are skimming the racetrack – but looks slower from the helicopter view
- The future is not idiopathic – it's baseline is today

The Future

- Understanding the Disease
  - Increased investigational activity is rapidly informing our understanding of IPF
- Novel endpoints
  - Exacerbation definition/symptom scores/exercise capacity/imaging modalities
  - IPF-specific PRO's ?
- Combination Therapy
  - Multiple combination therapy seems likely (side effect profiles..)
- Individualised Therapeutic Regimens
  - Patient segmentation (biomarkers, gene signatures)
  - Shorter pivotal trials using biomarkers (e.g., imaging)

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