Paris NASH Meeting

International Think Tank

September 7 & 8, 2023

9th edition

The DOOR is Open:
Assessing Multiple Outcomes in Phase 3 Trials

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Paris NASH Meeting

International Think Tank

Conflict of interest disclosure

- Grants: from NIAID, NCI, NHLBI of the NIH and the CDC.
- Royalties: Chapman & Hall/CRC Press.
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Complexities in NASH Clinical Trials

- Several important multi-organ clinical and other events
  - Death
  - CV
  - CKD
  - New onset diabetes
  - Cancer

- Critical to recognize for clinical decision-making that some events are more important than others
  - Death is more important than a non-fatal event
  - Events w/ disabling sequelae are more important than those w/ non-disabling sequelae
  - Events w/ permanent sequelae are more important than those w/ transient sequelae
  - More bad events is worse than fewer

Totality of Evidence and the Challenges in Benefit:risk Evaluation

- Typical benefit:risk analyses
  - Compare interventions for each efficacy and safety outcome
  - Combine these effects

- These analyses
  - Fail to incorporate associations between outcomes
  - Fail to recognize the cumulative nature of outcomes on individual patients
  - Suffer from competing risk complexities during interpretation of individual outcomes, and
  - Since efficacy and safety analyses are often conducted on different populations, generalizability is unclear.

Question 1

- We define analysis populations
  - Efficacy: ITT population
  - Safety: safety population

- Efficacy population ≠ safety population

- We combine these analyses into benefit:risk analyses

- To whom does this analysis apply?

Question 2

- Suppose we measure the duration of hospitalization
- Shorter duration is better … or is it?
- The faster the patient dies, the shorter the duration
- Interpretation of an outcome needs context of other clinical outcomes for the same patient
- Why do we analyze them separately?

Question 3

- Suppose a loved one is diagnosed with a serious disease
- You are selecting treatment
- 3 treatment options: A, B, and C
- 2 outcomes, equally important
  - Treatment success: yes/no
  - Safety event: yes/no

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

They all have the same success rate.

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

They all have the same success rate.

A has the lowest safety event rate.

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

Which treatment would you choose?

They all have the same success rate.

A has the lowest safety event rate.

B and C are indistinguishable.

RCT Comparing A, B, and C
Analysis of Outcomes

A (N=100)	B (N=100)	C (N=100)
Success: 50%	Success: 50%	Success: 50%
Safety event: 30%	Safety event: 50%	Safety event: 50%

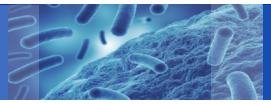
Which treatment would you choose?

They all have the same success rate.

A has the lowest safety event rate.

B and C are indistinguishable.

Choose A…right?



Our culture is to use patients to analyze the outcomes.

Shouldn’t we use outcomes to analyze the patients?

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

Safety event: 30%

		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

Safety event: 30%

		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

Safety event: 30%

		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0

Analysis of Patients: 4 Possible Outcomes

A (N=100)

Success: 50%

Safety event: 30%

		Success +	Success -
SE	+	15	15
	-	35	35

B (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	50	0
	-	0	50

C (N=100)

Success: 50%

Safety event: 50%

		Success +	Success -
SE	+	0	50
	-	50	0

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
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Taylor & Francis
Taylor & Francis Group

Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes: A Step Toward Pragmatism in Benefit:Risk Evaluation

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[a]Department of Biostatistics, Harvard University, Boston, MA, USA; [b]Center for Biostatistics in AIDS Research, Harvard University, Boston, MA, USA; [c]National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), Bethesda, MD, USA.

Scott's father (a math teacher) to his confused son many years ago:

"The order of operations is important…"

Desirability Of Outcome Ranking (DOOR)

- A patient-centric paradigm for the design, monitoring, analyses and reporting of clinical trials based on benefit:risk

- Addresses noted challenges

Before we analyze several hundred patients,

we must understand how to analyze one.

DOOR: A Brief Outline

- Use outcomes to analyze patients
  - Construct ordinal DOOR outcome based on the *patient journey*

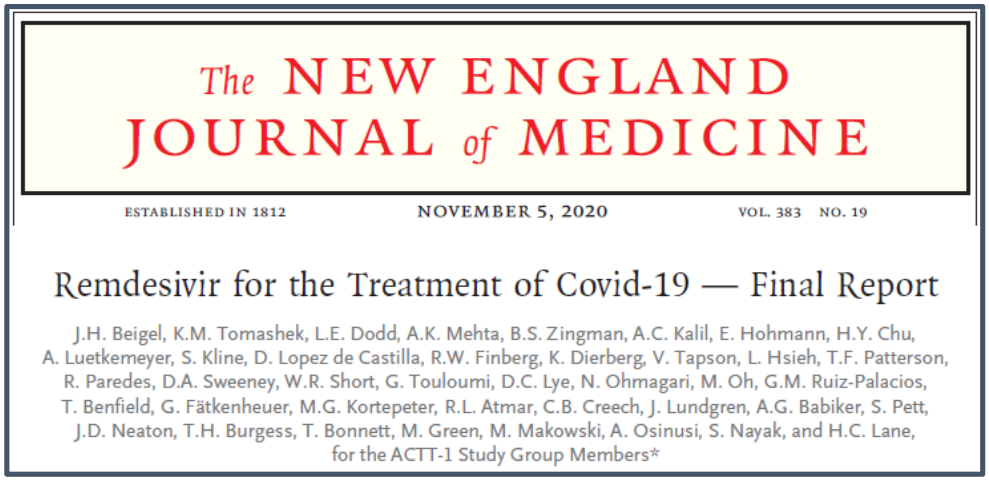
- Two complimentary analyses
  1. Rank-based
     - Estimating the DOOR probability: the probability that a patient from treatment has a more desirable outcome than a patient on control
       - 50% implies equivalence
       - Intuitively attractive
  2. Partial credit (score based analyses)

- Analyze individual outcomes for comprehensive assessment

Adaptive Covid-19 Treatment Trial (ACTT-1)

- No known efficacious treatments for COVID-19 at the time

- ACTT-1
  - Randomized double-blind placebo-controlled trial of IV remdesivir in hospitalized adult COVID-19 patients w/ LRTI
  - N=1062



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ACTT-1

- Important events
  - Death
  - Hospitalized with invasive mechanical ventilation / ECMO
  - SAE that is not resolved or resolved with sequelae

	Treatment	
DOOR (Day 29)	**Remdesivir (N=541)**	**Placebo (N=521)**
1. Alive: 0 of the other events above		
2. Alive: 1 of the other events above		
3. Alive: both of the other events above		
4. Death		

ACTT-1

- Important events
  - Death
  - Hospitalized with invasive mechanical ventilation / ECMO
  - SAE that is not resolved or resolved with sequelae

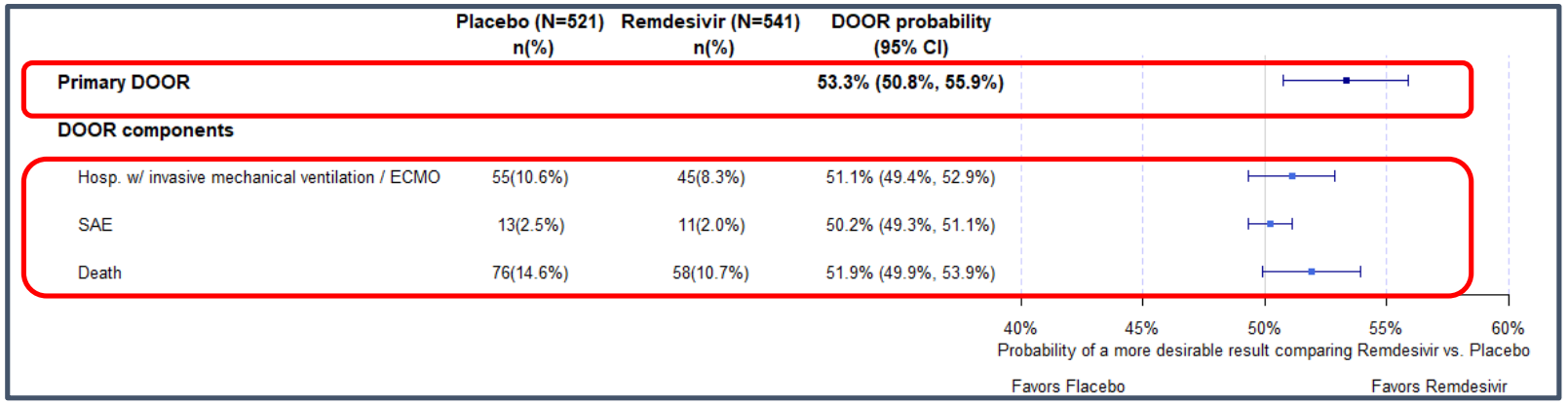
	Treatment	
DOOR (Day 29)	**Remdesivir (N=541)**	**Placebo (N=521)**
1. Alive: 0 of the other events above		382 (73.3%)
2. Alive: 1 of the other events above		57 (10.9%)
3. Alive: both of the other events above		6 (1.2%)
4. Death		76 (14.6%)

- Will there by a northward migration to more desirable categories with treatment?

ACTT-1

- Important events
  - Death
  - Hospitalized with invasive mechanical ventilation / ECMO
  - SAE that is not resolved or resolved with sequelae

	Treatment	
DOOR (Day 29)	**Remdesivir (N=541)**	**Placebo (N=521)**
1. Alive: 0 of the other events above	433 (80.0%)	382 (73.3%)
2. Alive: 1 of the other events above	42 (7.8%)	57 (10.9%)
3. Alive: both of the other events above	8 (1.5%)	6 (1.2%)
4. Death	58 (10.7%)	76 (14.6%)


Placebo (N=521) n(%)
Remdesivir (N=541) n(%)
DOOR probability (95% CI)
Primary DOOR
53.3% (50.8%, 55.9%)
DOOR components
Hosp. w/ invasive mechanical ventilation / ECMO
55(10.6%)
45(8.3%)
51.1% (49.4%, 52.9%)
SAE
13(2.5%)
11(2.0%)
50.2% (49.3%, 51.1%)
Death
76(14.6%)
58(10.7%)
51.9% (49.9%, 53.9%)
40%
45%
50%
55%
60%
Probability of a more desirable result comparing Remdesivir vs. Placebo
Favors Placebo
Favors Remdesivir

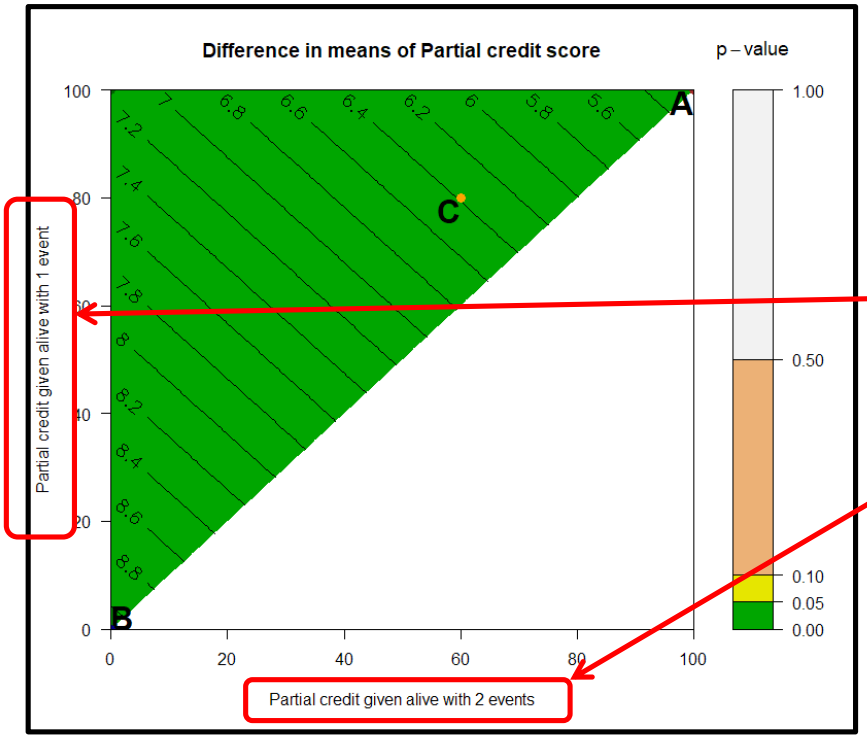
PARTIAL CREDIT

	Score
1. Alive: 0 of the events	100
2. Alive: 1 of the events	Partial credit
3. Alive: both of the events	Partial credit
4. Death	0

Partial credit can be used to account for:

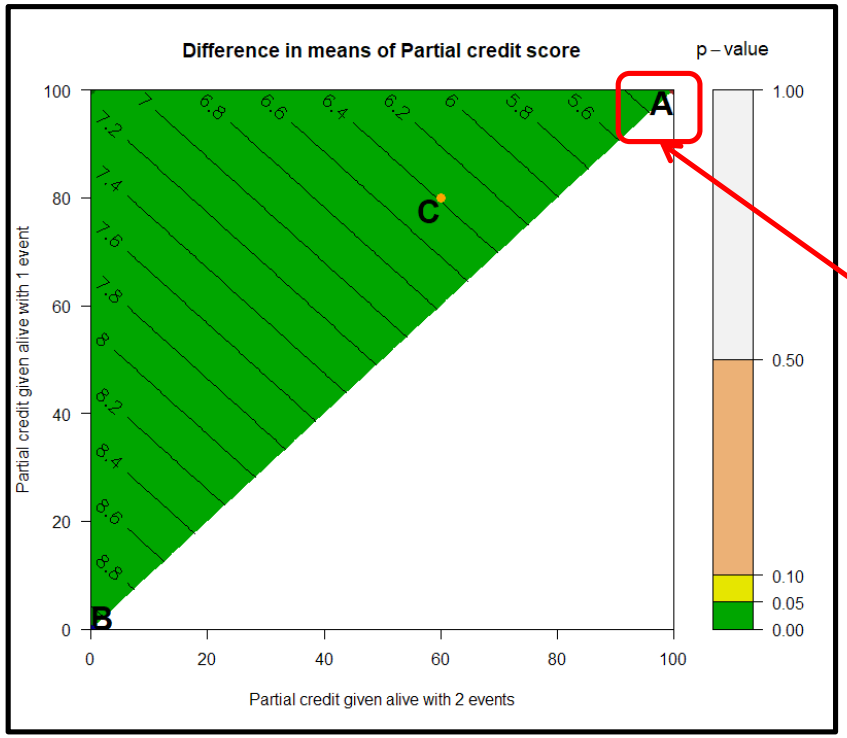
1. **Strategic distancing between steps in a calculated way**
2. **Personalized perspectives among patients / clinicians regarding the desirability of the categories**
3. **Robustness analyses**

Contours of Effects as Partial Credit Varies



Category	Credit
Alive; 0 event	100
Alive; 1 event	Partial credit
Alive; both events	Partial credit
Death	0

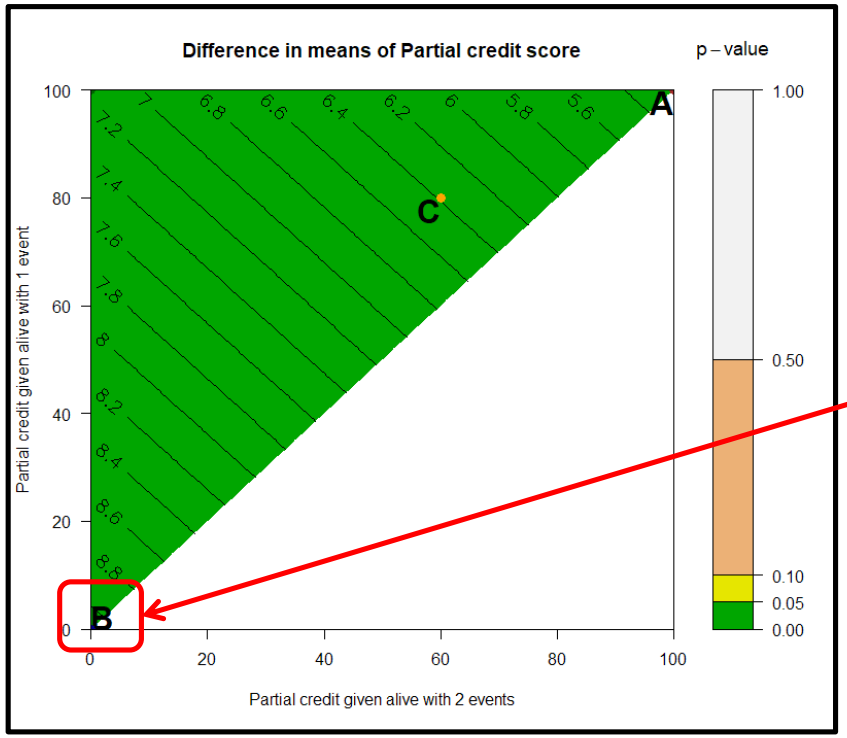
Survival



Category	Credit
Alive 0 events	100
Alive; 1 event	100
Alive; both events	100
Death	0

Remdesivir Advantage ≈ 5.2%

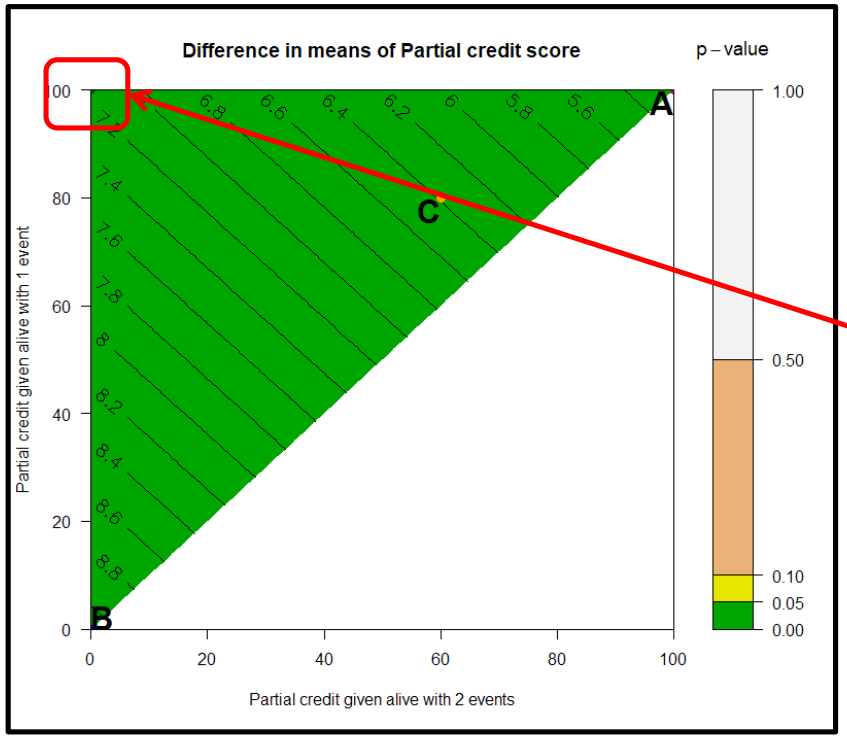
Alive; 0 Events



Category	Credit
Alive; 0 events	100
Alive; 1 event	0
Alive; both events	0
Death	0

Remdesivir Advantage ≈ 9.0%

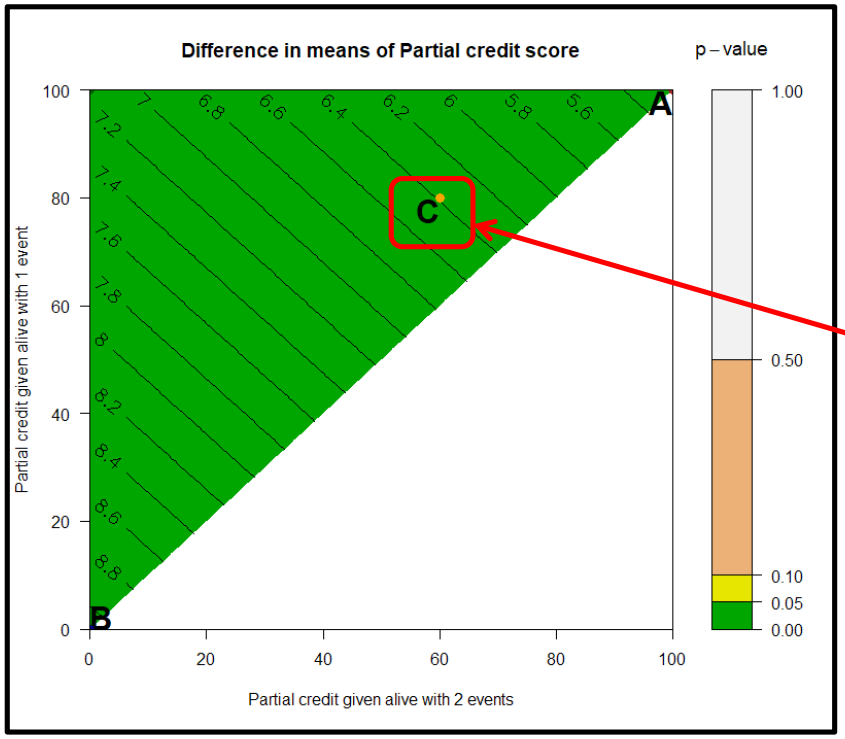
Alive with 0 or 1 Events



Category	Credit
Alive; 0 events	100
Alive; 1 event	100
Alive; both events	0
Death	0

Remdesivir Advantage ≈ 7.2%

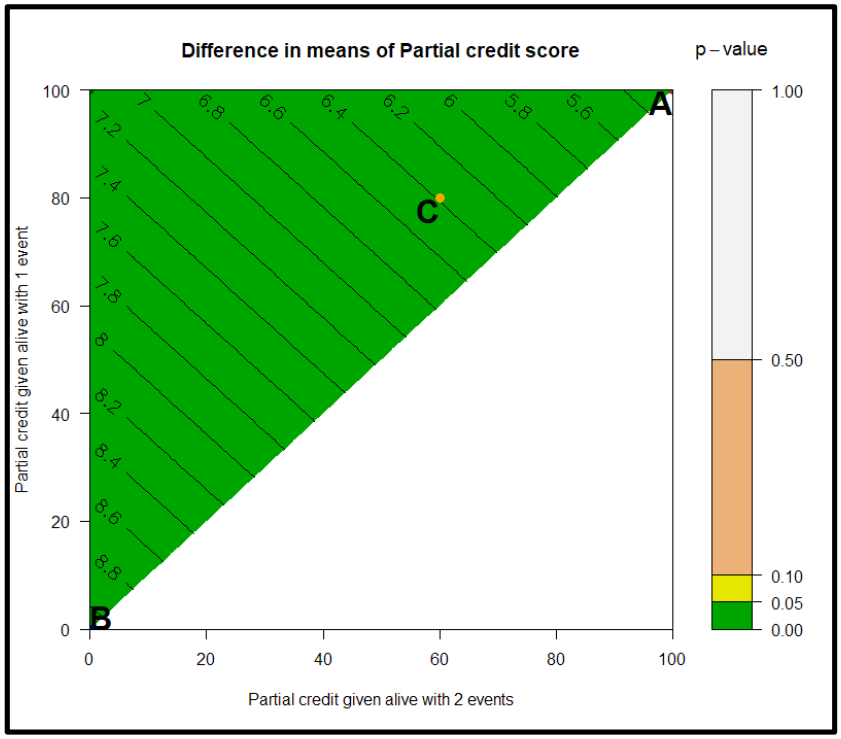
Compromise



Category	Credit
Alive; 0 events	100
Alive; 1 event	80
Alive; both events	60
Death	0

Remdesivir Advantage ≈ 6.4%

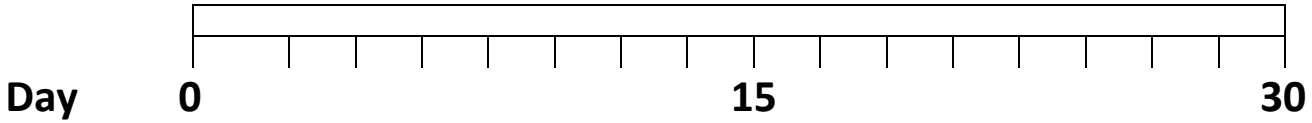
Robustness



- Numeric results vary by partial credit grading key, though robustness is demonstrated as green color indicates statistical significance everywhere

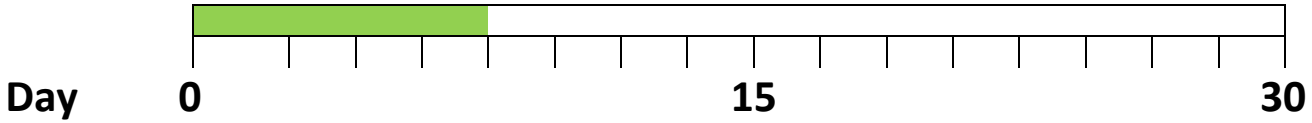
Anthology of Patient Stories

The Patient Story



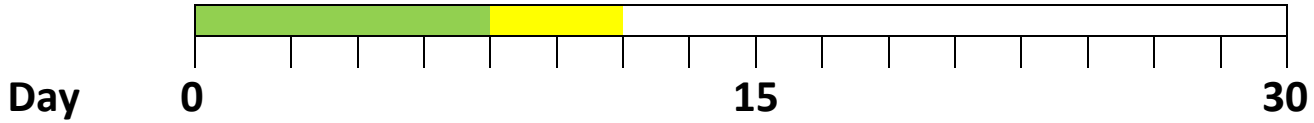
Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

The Patient Story



Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

The Patient Story

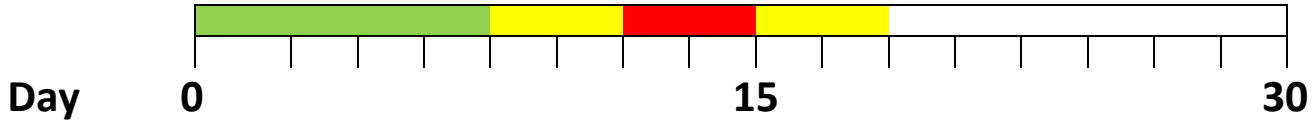


Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

The Patient Story

Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

The Patient Story

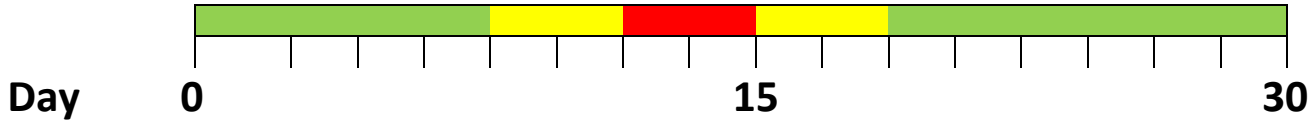


Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

The Patient Story

Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

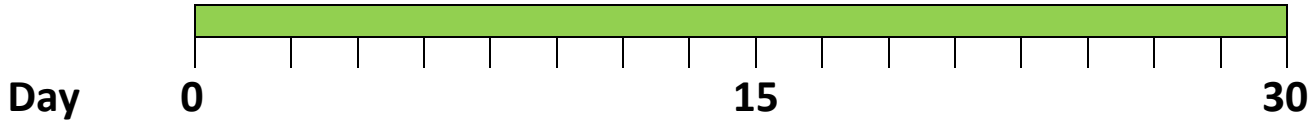
The Patient Story



Alive with 0 events	
Alive with 1 event	
Alive with 2 events	
Death	

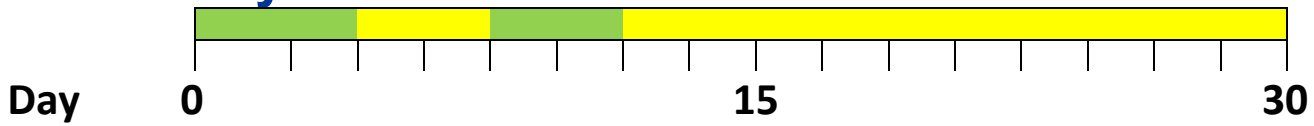
The Trial Anthology: A Collection of Patient Stories

Saul Goodman



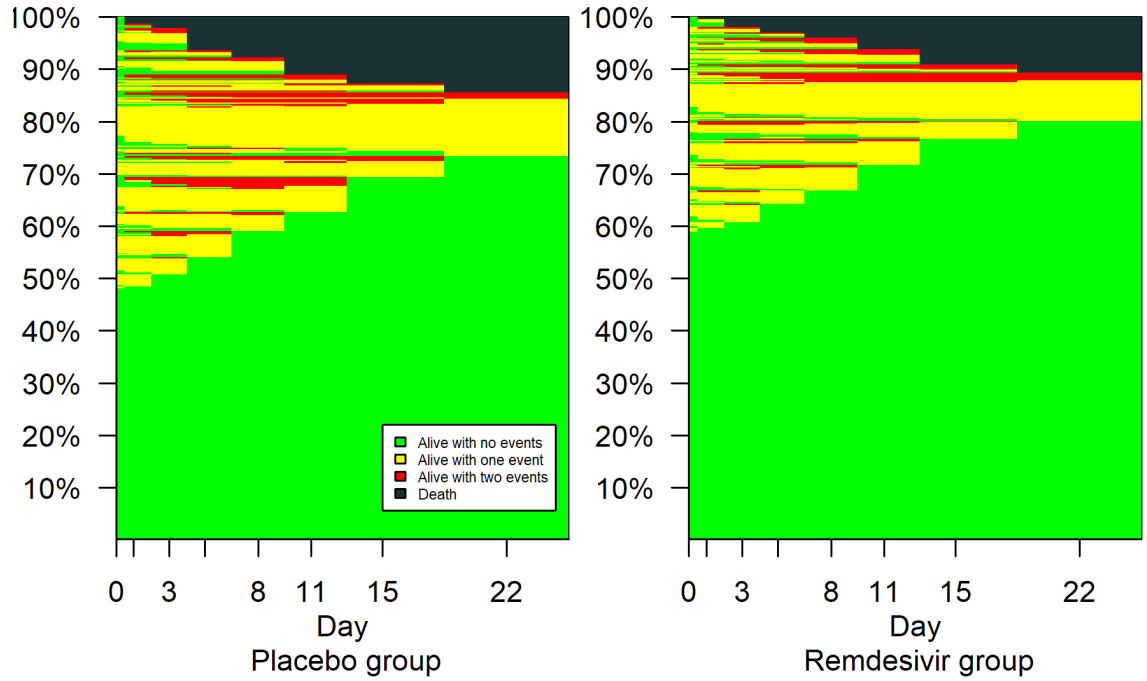
Ita Lendswell

Nori Kovery

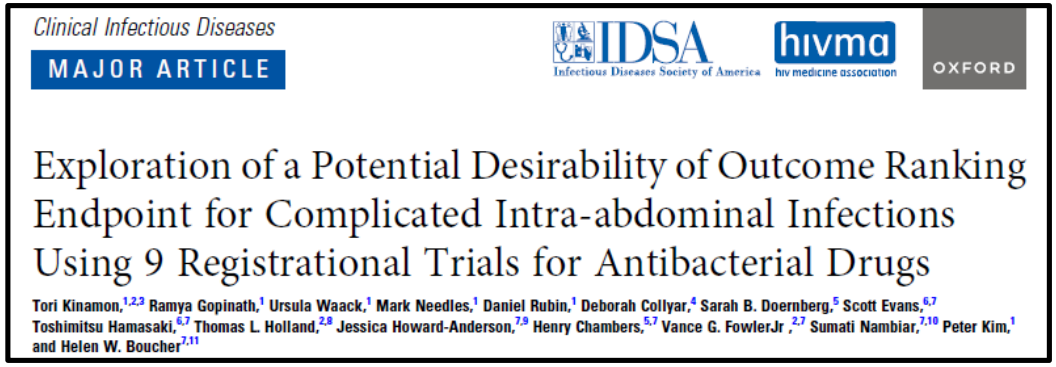


Statistician Marge N. O’vera

The Trial Anthology of Patient Stories



- Mortality at Day 29: 14.6% in placebo; 10.7% in Remdesivir
- No events at Day 29: 73.3% in placebo; 80% in Remdesivir
- No events in all time intervals: 48% in placebo; 58.8% in Remdesivir



- Council for International Organizations of Medical Sciences (CIOMS) in Geneva is expected to recommend regular including of DOOR in trial protocols to enhance benefit:risk assessment

A DOORable NASH Trials?

- Important events
  - Death
  - CV event
  - CKD
  - New onset diabetes
  - Severe toxicities from therapy, e.g., requiring dialysis

	Treatment	
DOOR	**Treatment**	**Control**
1. Alive: 0 events		
2. Alive: 1 event		
3. Alive: 2 events		
4. Alive: >2 events		
5. Death		

Freely-available Online Analysis Tool

https://methods.bsc.gwu.edu/

- Summary tables and graphics
- FDA involvement with approving this as a regulatory science tool
- Design tool in development

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Conclusions

- The effects of interventions are multidimensional
- Use outcomes to analyze patients rather than patients to analyze outcomes
  - A closer reflection of the effects on patients
- DOOR
  - Effective tool for evaluating totality of patient-centric effects (benefit:risk)
  - May be tailored for NASH
  - Analysis of individual components is part of comprehensive DOOR analyses
  - May be sensitive due to recognition of finer gradations of patient response

Paris NASH Meeting

Significant Contributors (p<0.001)

- Toshi Hamasaki
- Dean Follmann
- Dan Rubin
- Guoqing Diao
- Weixiao Dai
- Antibacterial Resistance Leadership Group
- ACTT-1 Investigators

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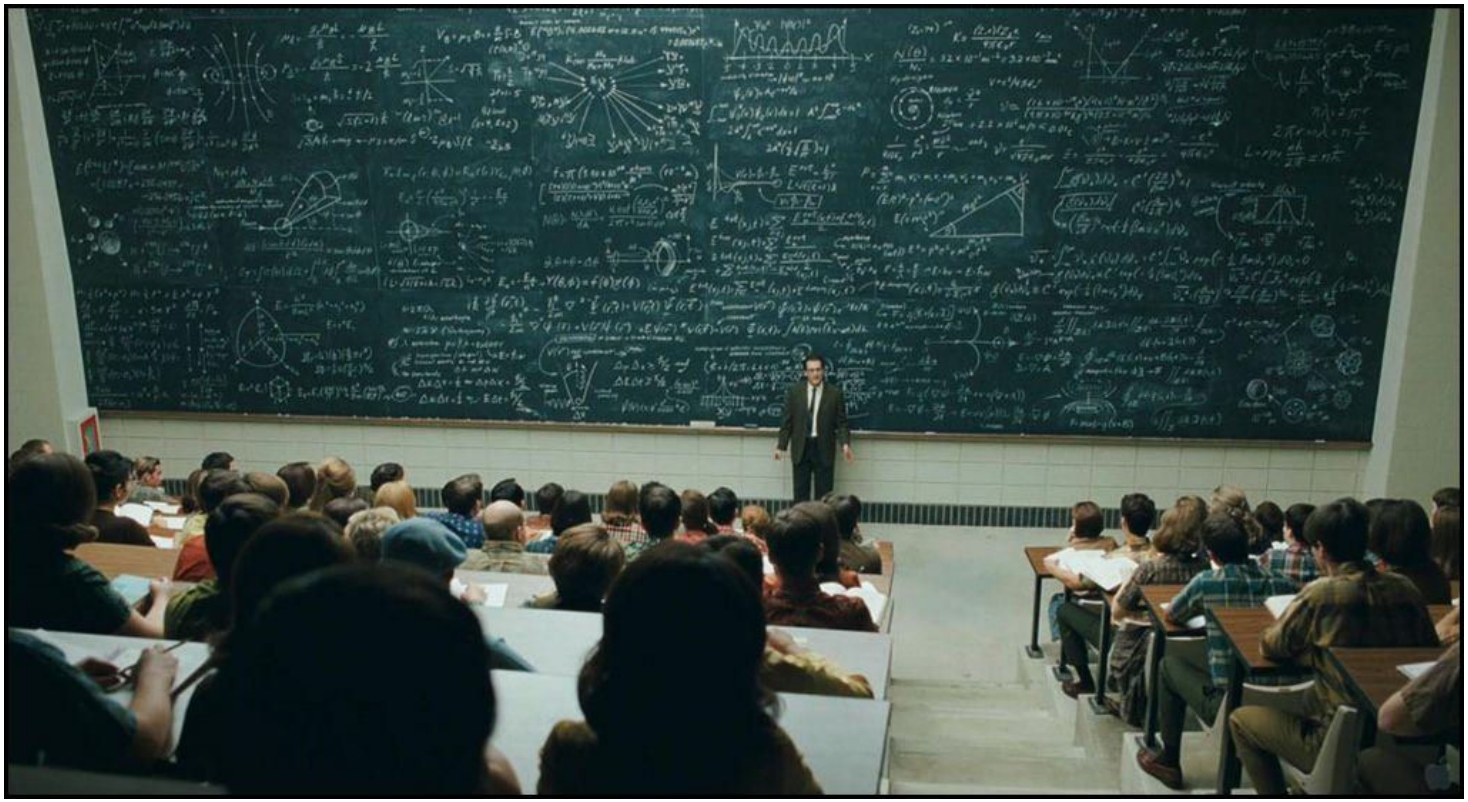

I know that you will enthusiastically applaud now…

Because you are so relieved that it is over.

Thank you.

International Think Tank

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