

Data Monitoring of the First Remdesivir Trial on COVID-19 During Pandemic Crisis

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Perspective

- We live at a historical time to witness the worst disaster in the century
- Global (6/20):
 - > 8.8M Infected
 - > 465,000 Deaths
- In US
 - > 2.3M infected
 - > 121,000 deaths
- This is a documentary talk



About DSMB experience

- Medical journals (and the public) focus on the final results
We statisticians also examine the process which derives the results.
- Generally, DSMB functions are well known (ICH and FDA guidance), although some variation exists for each DSMB.
- DSMB meetings seem mystic to non-members/participants; closed meeting minutes often untold – only accessible later to the sponsor or regulatory agencies if requested.
- There are books about DSMBs -- covering principles or pieces of discussion items. Never a full process/story telling.
- This is a unique experience: for remdesivir trials on COVID-19, research teams faced many unknowns, pressures and close scrutiny at an urgent time. (Note: The NIAID-led ACTT-1 had no interim meeting of the DSMB – probably due to logistic reason.)

Outline

- Overview of trial design
 - Patient population
 - Endpoint
 - Sample size
- DSMB
 - Debate
 - Highlight of the Charter – data monitoring plan
 - Each of the meetings – chronologic order
 - Use of DDM system

The First Remdesivir Trial on COVID-19

- Novel coronavirus (nCoV-2019) outbreak in Wuhan in late 12/2019, then became epidemic in China mid 1/2020
- NEJM (1/31/2020): *“First (confirmed) case of nCoV-19 in US”*
 - After 6 days (in hospital) of continuing worsening, treated with remdesivir (compassionate use) on Day 7, started improvement on Day 8 → recovering
- Remdesivir was tested for treating Ebola and MERS (phase II trials in 2016-8)
- In record time, Chinese investigators initiated the first Remdesivir trial (2/3/2020)
 - *A Phase 3 Randomized, Double-blind, **Placebo-controlled**, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With **Severe** 2019-nCoV Respiratory Disease. PI: Cao Bin. (ClinicalTrials.gov: NCT04257656)*
 - *A second trial was on “mild-moderate” patients (2/6/2020)*
 - “COVID-19” -- WHO formally named it on February 11, 2020

Investigators team

Sponsor: Institute of Respiratory Medicine, Chinese Academy of Medical Science

- PI: Wang Chen, MD
- Co-PI: Cao Bin, MD
- Sites: 10 hospitals in Wuhan City
- CRO: Tigermed Consulting, Hangzhou
- eDMC and DDM system provider:
CIMS Global, Somerset, NJ



Outline of Protocol: Patient inclusion (main points)

- aged ≥ 18 years,
 - RT-PCR positive for SARS-CoV-2,
 - had pneumonia confirmed by chest imaging,
 - had oxygen saturation $\leq 94\%$ on room air, or $PAO_2/FIO_2 \leq 300$ mm Hg,
- and
- were within 12 days of symptom onset
 - did not receive other treatment except for allowed SOC

(Red items above were the requirement to distinguish “severe” from “mild-moderate” cases)

Outline of Protocol: Primary endpoint

Time-to-clinical-improvement (TTCI): from randomization to first time having 2-point decline or alive discharge of the 6-point ordinal scale:

1—discharge (alive)

2—hospital admission, not requiring supplemental oxygen

3—hospital admission, requiring supplemental oxygen (**but not HFNC or NIMV**)

4—hospital admission, requiring high-flow nasal cannula (HFNC) or noninvasive mechanical ventilation (NIMV)

5—hospital admission, requiring extracorporeal membrane oxygenation (ECOM) or invasive mechanical ventilation (IMV)

6—death

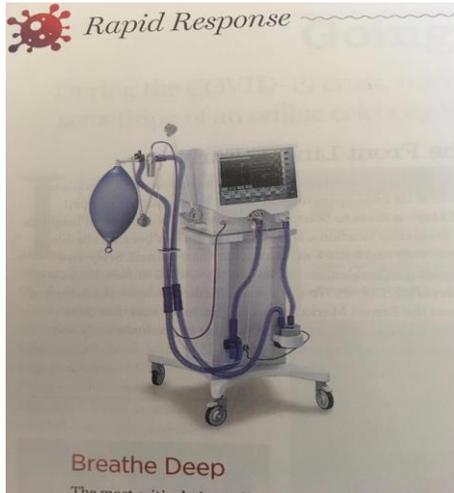
Scale 3—Hospitalized, requiring supplemental (low flow) oxygen (but not HFNC or NIMV)

Scale 4:

High-flow nasal cannula (HFNC) ;

Noninvasive mechanical ventilation (NIMV)

Ventilator: Most critical equipment for severe COVID cases



Scale 5:

Extracorporeal membrane oxygenation (ECMO) ;

Invasive mechanical ventilation (IMV)

ECMO: Technology to help COVID patients when ventilators can't

Invasive machine, oxygenates blood using a complex circuit of pumps, tubes, filters and monitors



Web photos

Outline of Protocol: Remdesivir IV treatment

- Day 1: 200 mg,
- Day 2-10: 100 mg
- Follow up \leq Day 28
- Time points for data report:
Days 3, 5, 7, 10, 14, 21, 28

How does Gilead's experimental drug remdesivir work against the coronavirus?

- <https://www.statnews.com/2020/05/04/how-gilead-drug-remdesivir-works-against-coronavirus/?jwsourc=cl>



Alex Hogan @hoganalex
May 4, 2020

Outline of Protocol: Sample size and power

Based on TTCl:

- **Total of 325 events to provide 80% power** under a one-sided type I error of 2.5% if the hazard ratio (HR) comparing remdesivir to placebo is 1.4, corresponding to a shorten of TTCl of 6 days, assuming TTCl = 21 days on placebo
- Total number of **patients planned = 453** (2:1 randomization -- rem:plb; stratified by the baseline ordinal scale)

DSMB

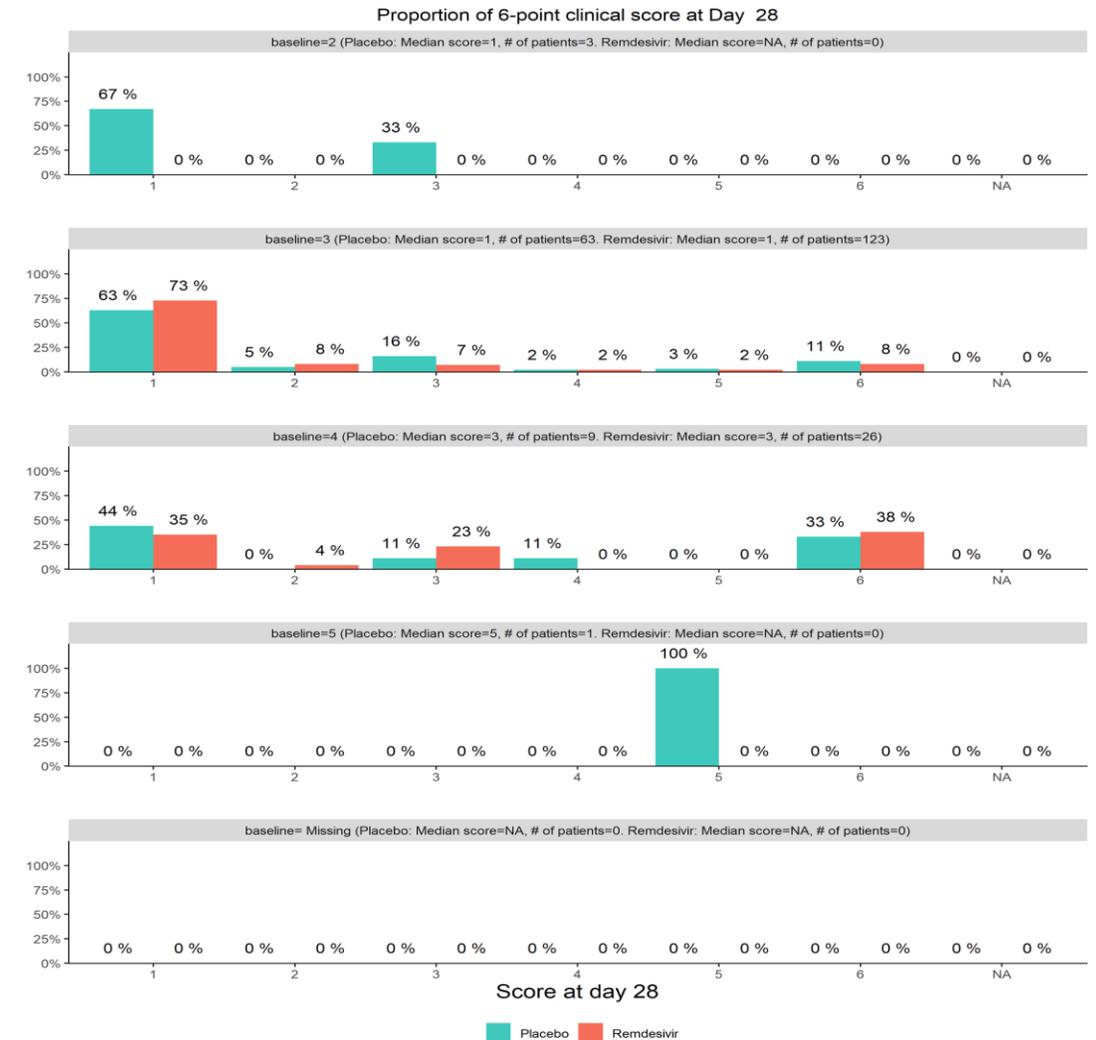
- Prior to DSMB Debate:
 - With rapid enrollment, is it necessary and feasible to have a DMC?
 - YES. Remdesivir was an investigational drug. ICH and Chinese Regulation require DMC to protect patients' interest and research integrity
 - Real Challenge: How to monitor data efficiently and scientifically sound?
 - Use eDMC system for data management + DDM for data analysis
(Previous talk By Tai Xie)
- **Kick-Off meeting (2/11/2020)**
 - Composition: 5 members; supported by 2 independent statisticians
 - Brief review of the study protocol and status of enrollment (n=136 severe cases already randomized)
 - Discuss and approve Charter: what data to review and how (next slide); meeting frequency – weekly in principle

What data to review

- Key patients baseline characteristics, especially
 - Time from symptom onset to study entry
 - Oxygen saturation level
- Key Safety data: AEs, and labs -- especially liver function; Mortality
- Debate on Efficacy endpoint
 - Protocol primary endpoint: TICI (from WHO blue print on influenza)
 - DSMB questioned about TICI (censoring death at Day 28)
 - Need to consider the competing risk of death
 - 6-point scale could decline (improve) and rise (worsen) again
 - Instead, DSMB decided to monitor the distribution of the 6-point scale directly (next slide). But kept the protocol's plan on 1 interim analysis for TICI.

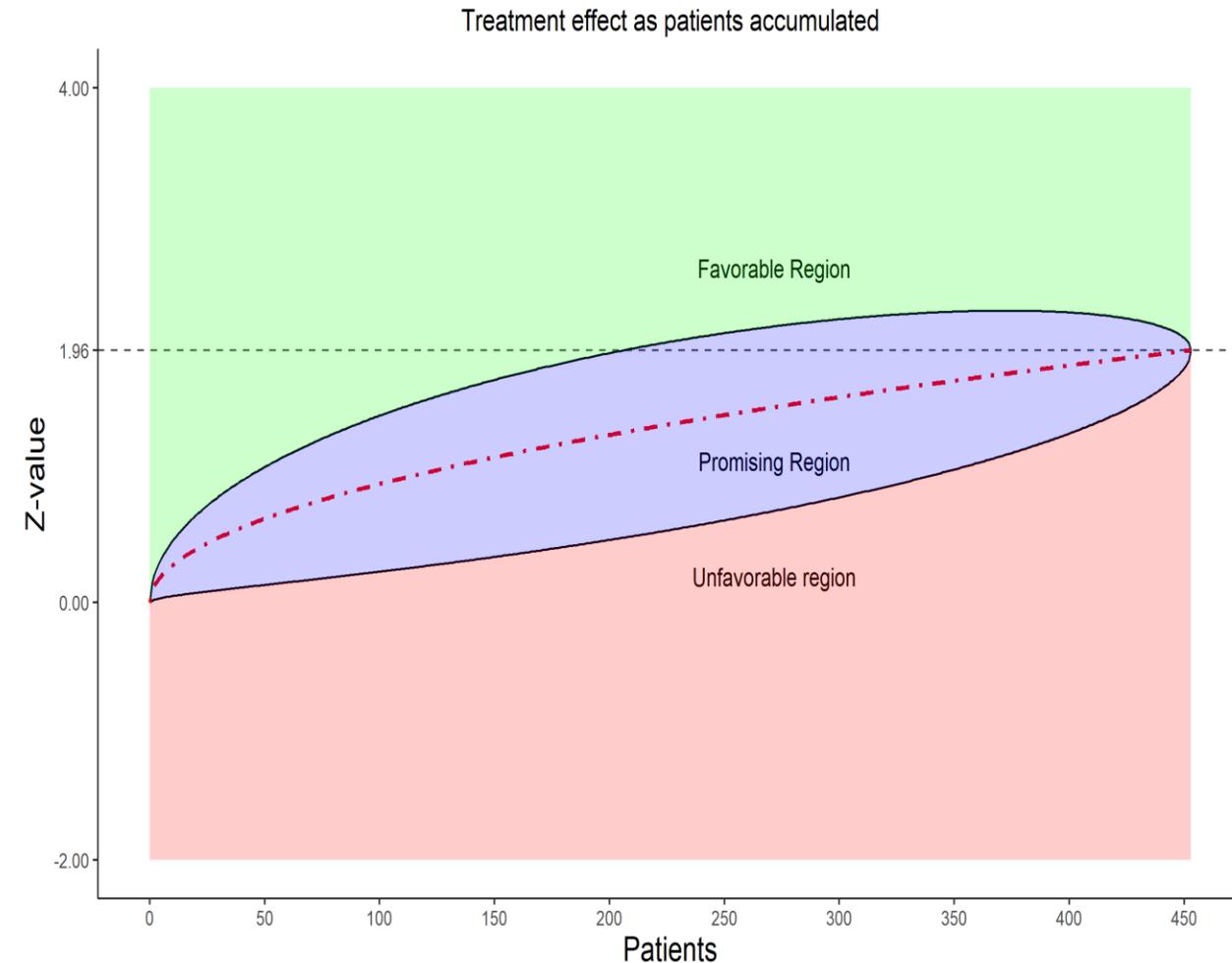
Analysis of the distribution of the 6-point ordinal category scale

- Baseline-stratified Wilcoxon-Mann-Whitney Rank Sum Test (with ties)
- Display z-statistic on the DDM “radar” screen as patients accumulate (next page)
- Focus on Day 7, 14, 21, 28 (protocol pre-specified timepoints)
- If necessary, protect overall alpha by Hochberg stepwise procedure
- When see “signal”, will trigger TICI analysis
 - Protect overall alpha by Pocock-type alpha-spending function



Footnotes: Number of patients in each group: Placebo= 76 , Remdesivir= 149 .
Median score in each group: Placebo= 1 , Remdesivir= 1 .

DDM “radar” screen with regions by conditional power (CP)



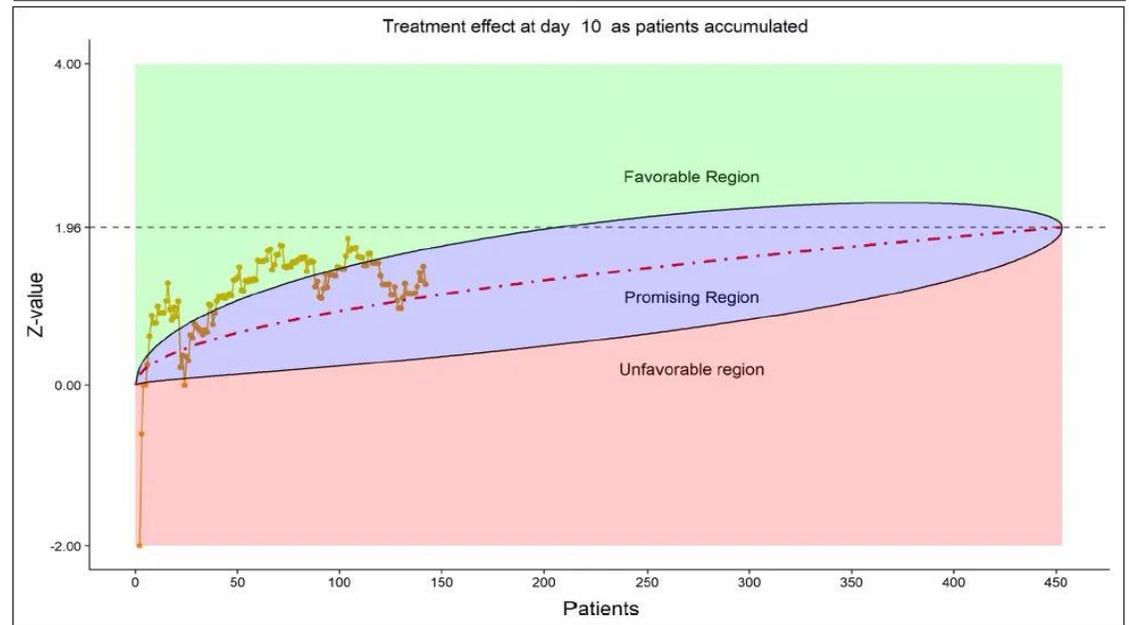
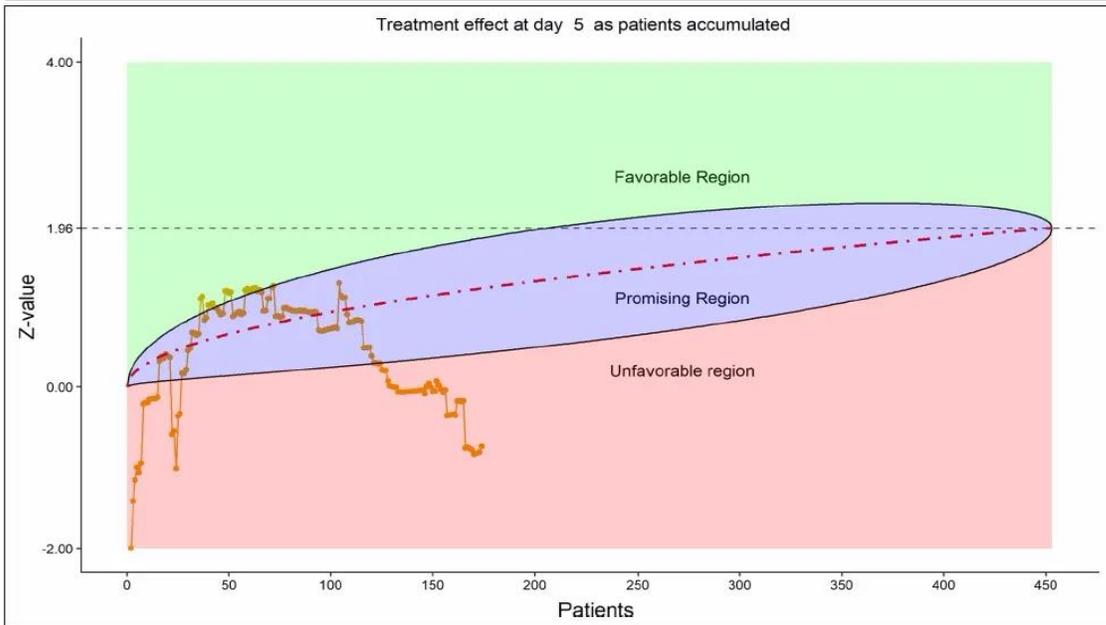
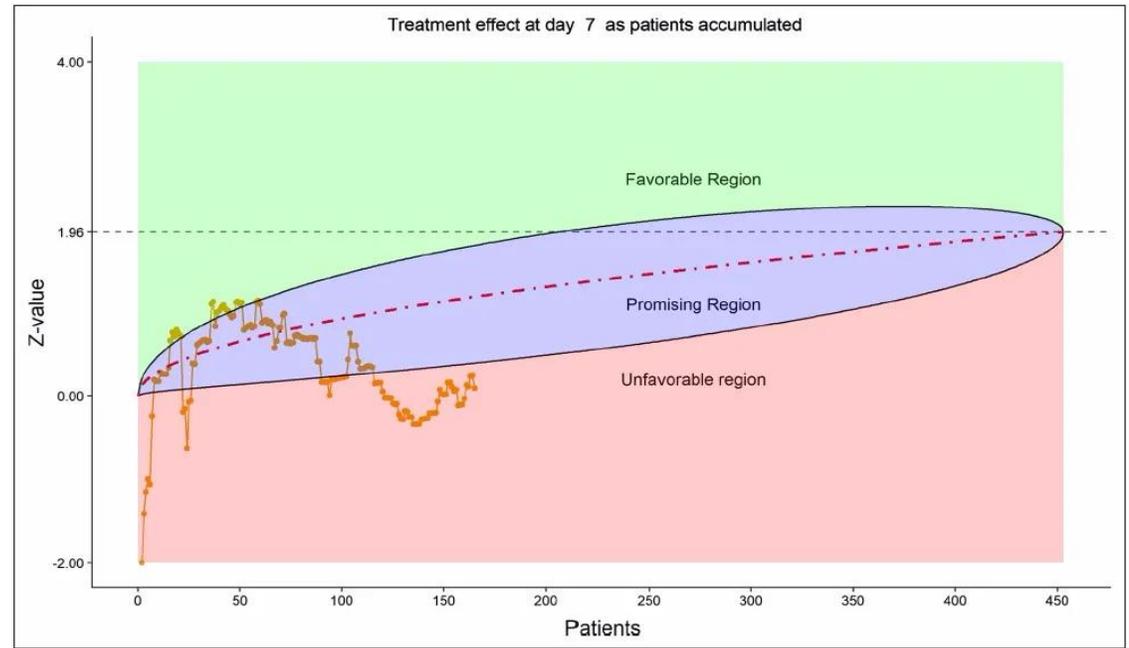
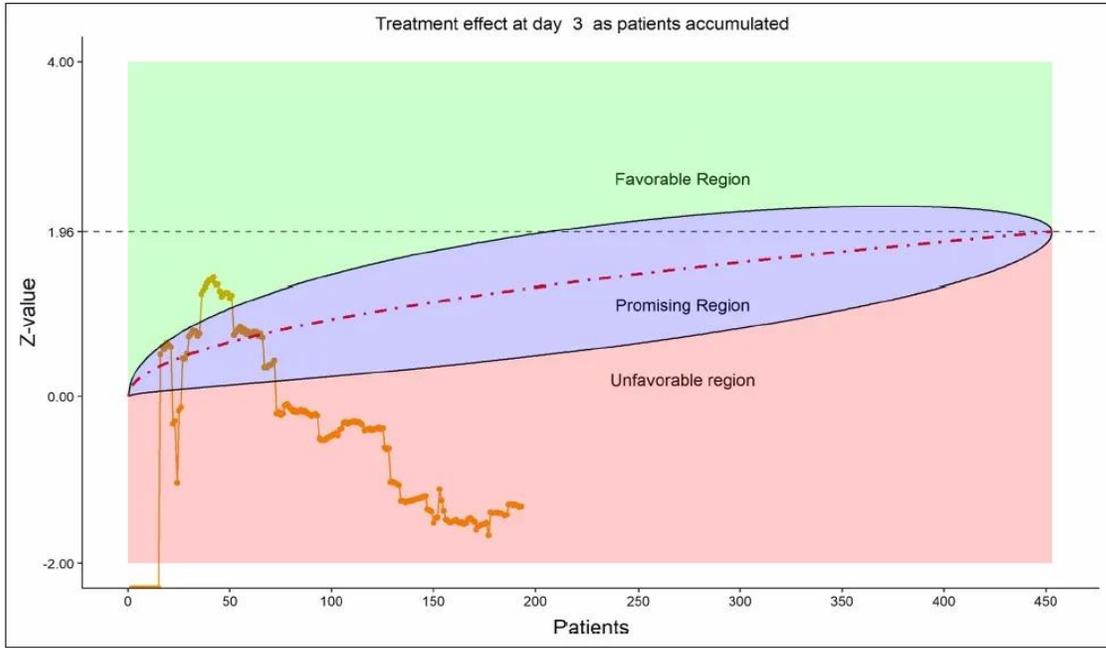
- **Green:** “Favorable” region
 $CP \geq 90\%$
- **Purple:** “Promising” region
 $5\% \leq CP < 90\%$
- **Red** dotted line: $CP=50\%$
- **Pink:** “Unfavorable” region
 $CP < 5\%$

$$CP = P(Z_{final} > 1.96 | Z_{current})$$

First Data Review (2/22/2020)

- N = 215; Majority 83% baseline scale=3
- DDM “radar” Screen: Days 3, 5, 7, 10
 - Remdesivir not effective early on – no quick efficacy
 - Day 10 started to show some hope
- Without safety concern, recommended to continue (with note)
- Note: At this time COVID-19 epidemic in Wuhan was slowing down, and many other studies also started in the region in February, competing for the patient resources. Facing the decline of enrollment, DSMB recommended the investigators to consider enhancing their enrollment effort and to the trial sponsor to re-evaluate the planned time-line for study completion date (the original projection date was April 27, 2020).
- Aside: On 2/21, NIAID launched ACTT, similar sample size with 8-point scale as primary endpoint

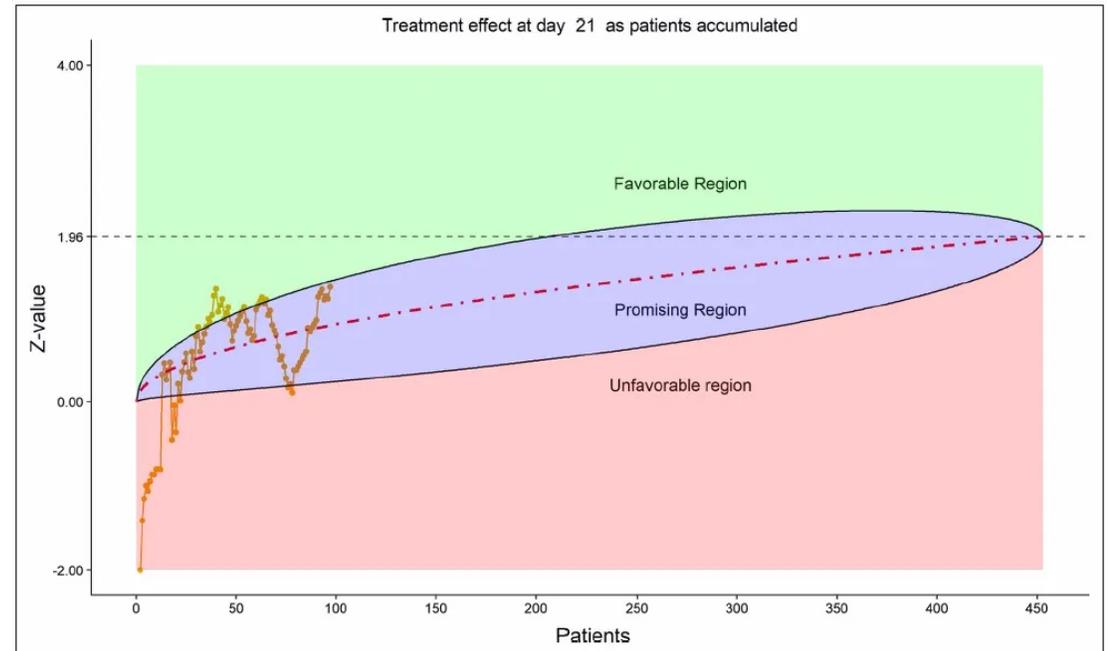
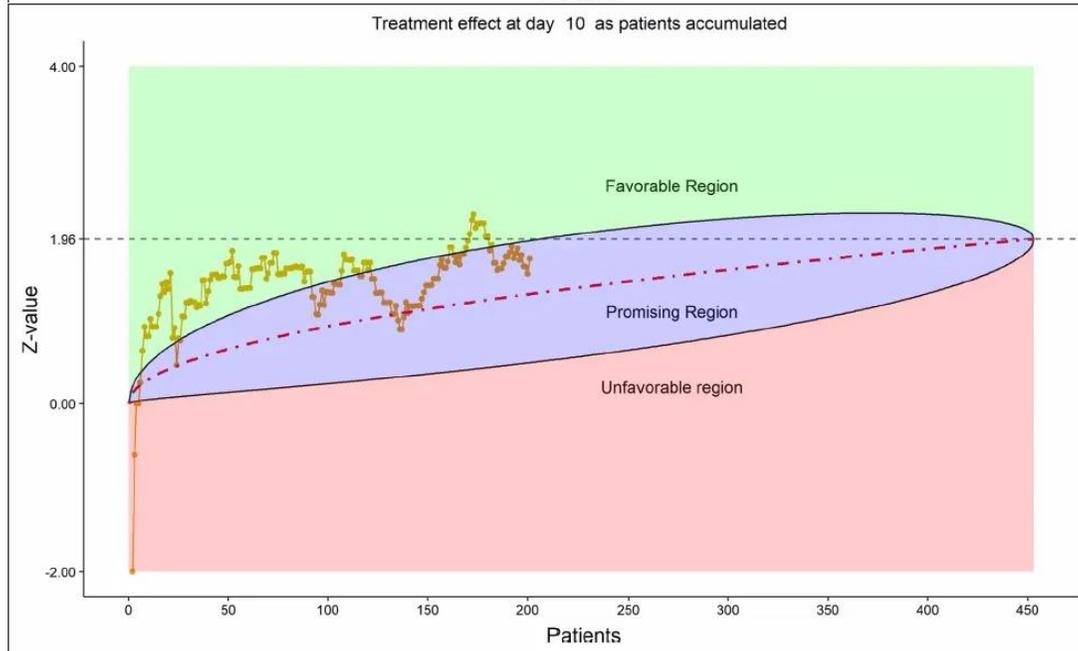
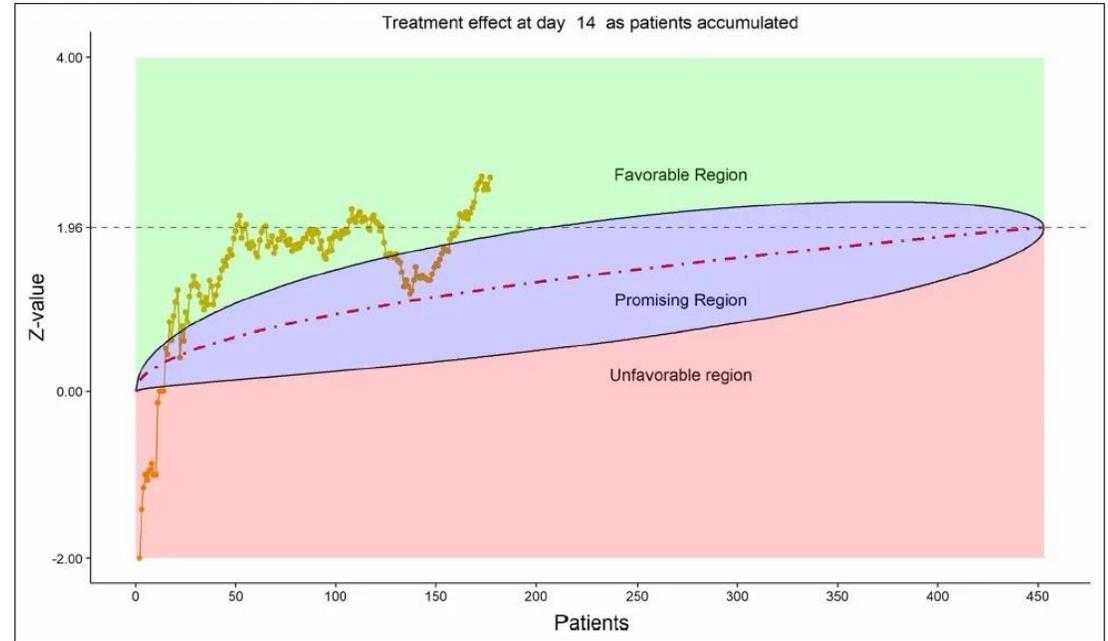
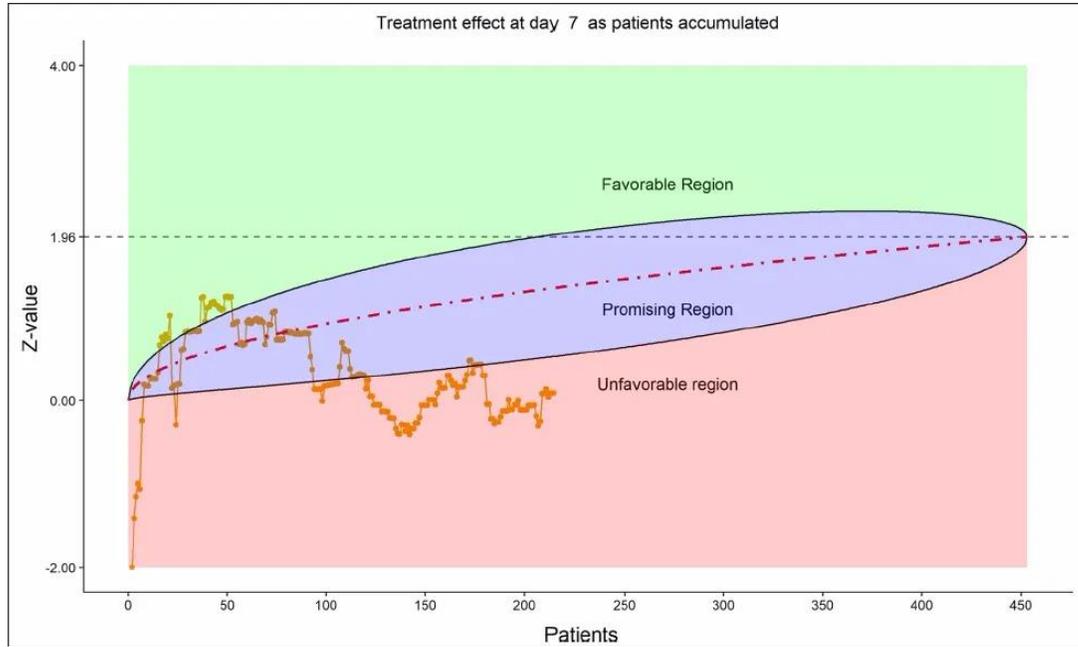
First Data Review (2/22/2020)



Second Data Review (2/29/2020)

- N =228; (Only enrolled 13 patients in a week)
- More patients accumulated data on Days 10 and 14
- DDM “radar” screen:
 - Day 14 entering the “favorable” region, DSMB was enthusiastic, requested K-M plot for TTCl endpoint at next meeting
 - Day 21 in “promising” region, but only ~ 100 patients
- Total deaths = 24 (10.53% mortality), evenly split between groups.
- DSMB Recommendation: Continue the trial, urge sponsor to re-evaluate the time-line for study completion date and the original planned interim analysis strategy on TTCl
- Aside: To reach 453 patients and to complete the 28 days study by 4/28, must randomize 7-8 patients/day on average in March

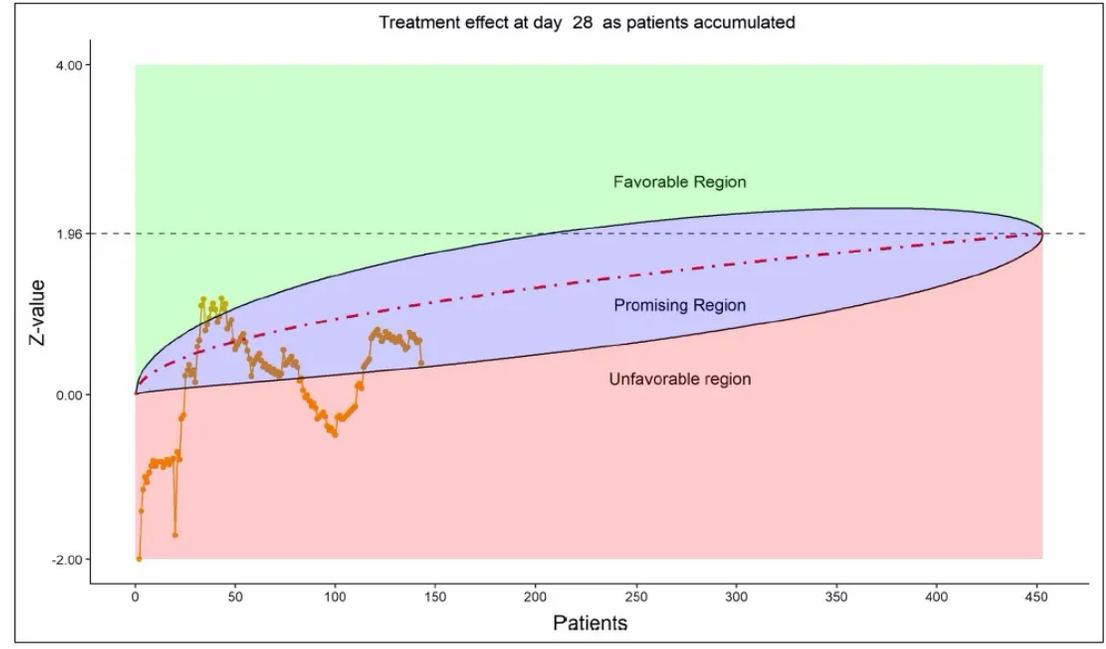
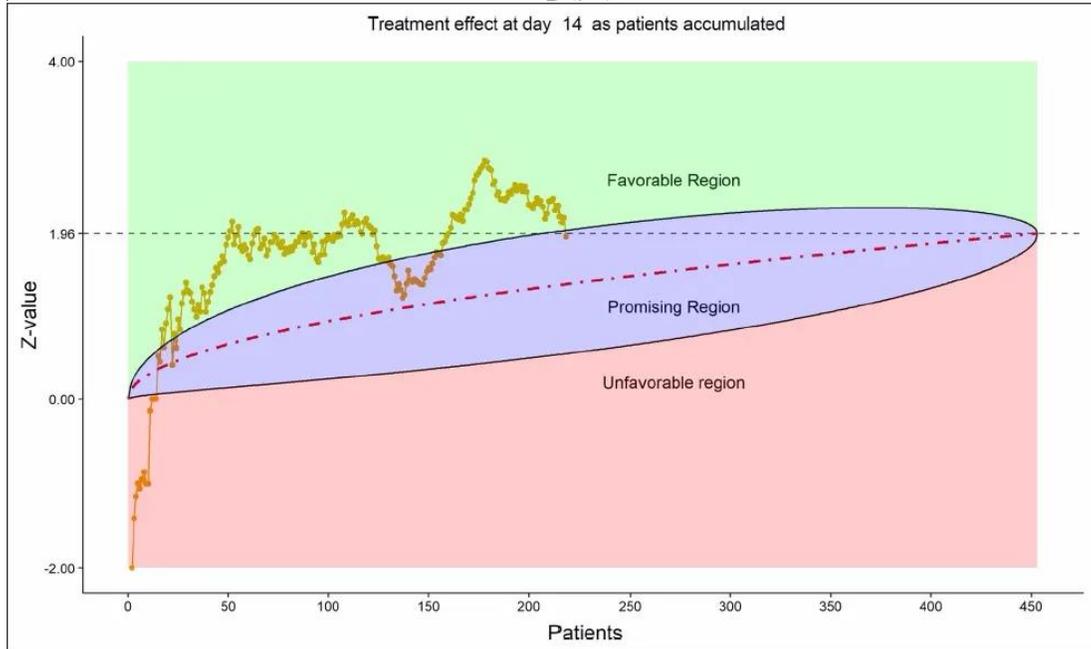
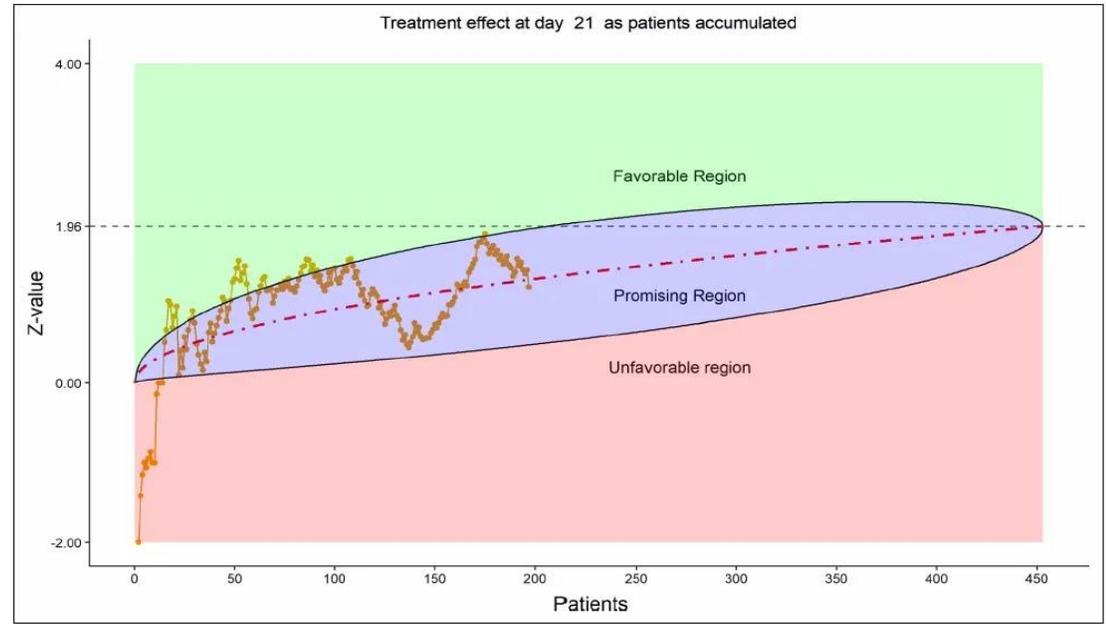
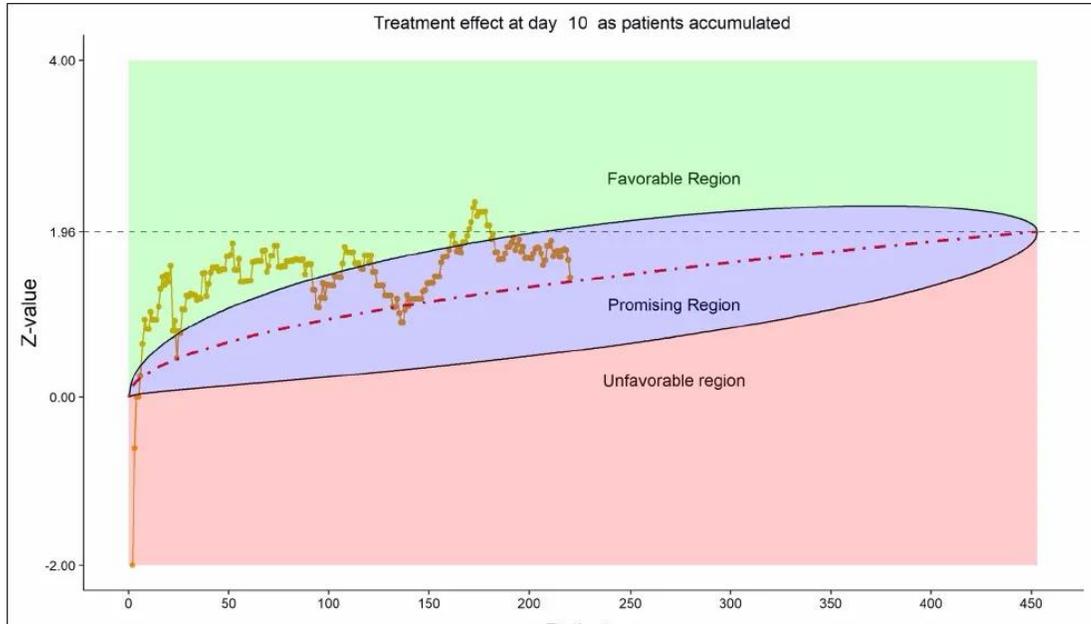
Second data review (2/29/2020)



Third Data Review (3/8/2020) – the inflection point

- N =235; (Only enrolled 7 patients in a week)
- More patients accumulated data on Days 10, 14 and 21.
- DDM “radar” screen: Day 10, 14, 21, 28 --- disappointing trend
 - Day 14 did not remain in the favorable region – moving downward
 - Day 21 did not rise, moving downward to touch 50% CP
 - Day 28 did not rise above 50% CP
- Hospital discharge rate: 38% (rem) vs. 44% (placebo)
- Mortality rate = 11.7%, comparable between the two groups
- Median TTCl: 23 days (rem) vs. 24 days (placebo)

Third data review (3/8/2020)



- Sponsor: COVID-19 cases continue to decline in Wuhan, investigators not able to enroll new patients to reach the protocol-planned number by the target time
- DSMB recommendation: Consider expanding the study to other cities in China or to other countries.
- Otherwise, sponsor needs to revise the protocol:
 - (a) Change the planned sample size for the declining enrollment reason;
 - (b) Cancel the scheduled interim analysis of TTCl;
 - (c) Continue the trial till all randomized patients finish 28 days follow-up;
 - (d) Prepare the final DSMB review meeting at the end of March

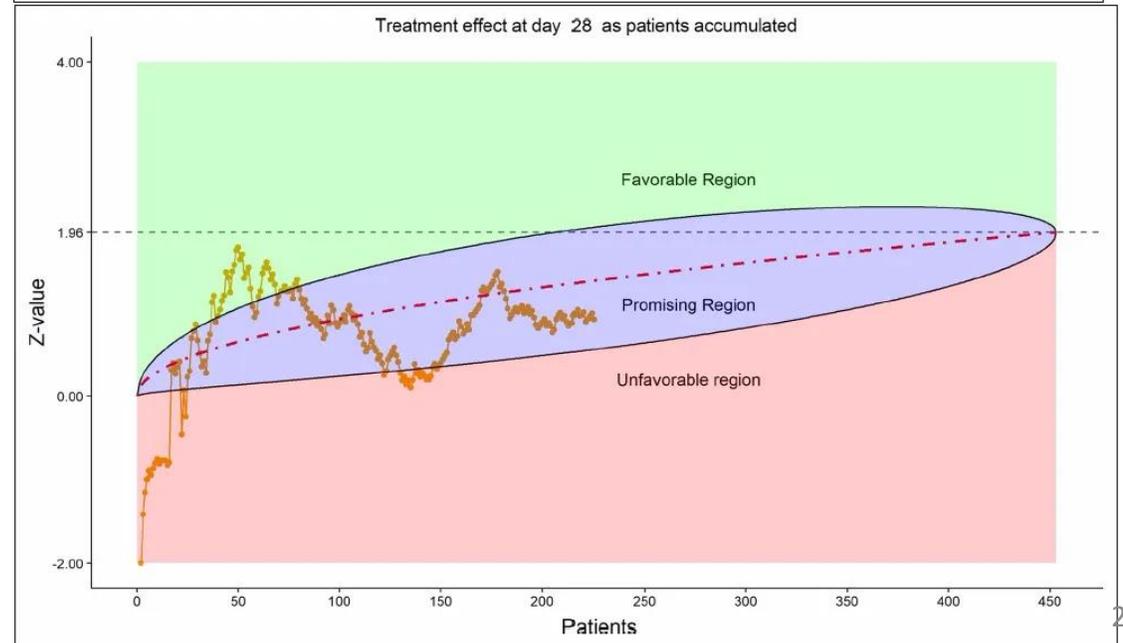
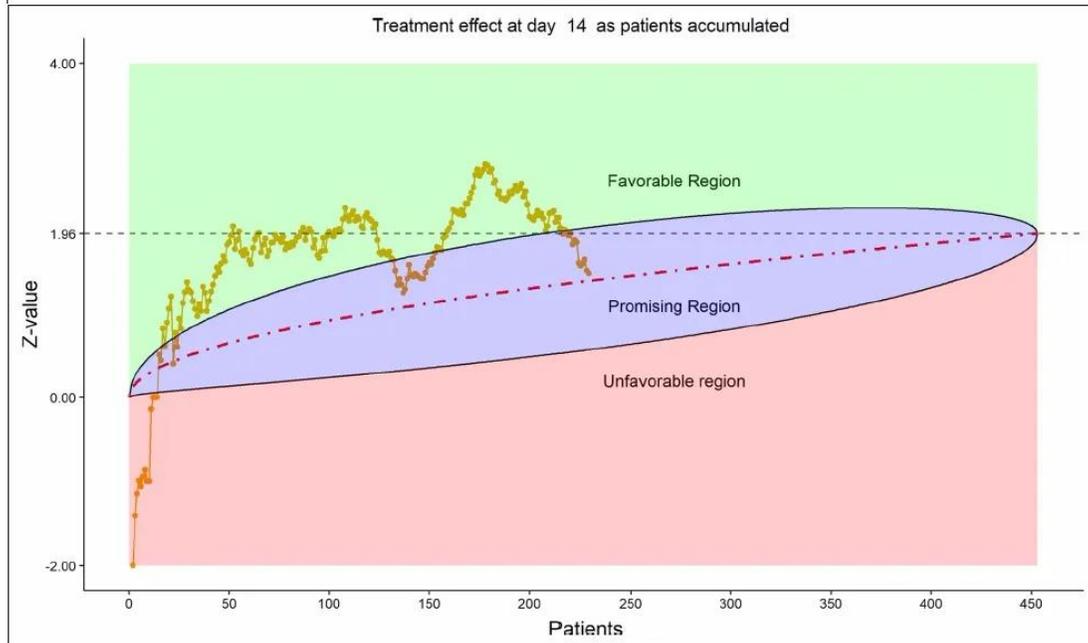
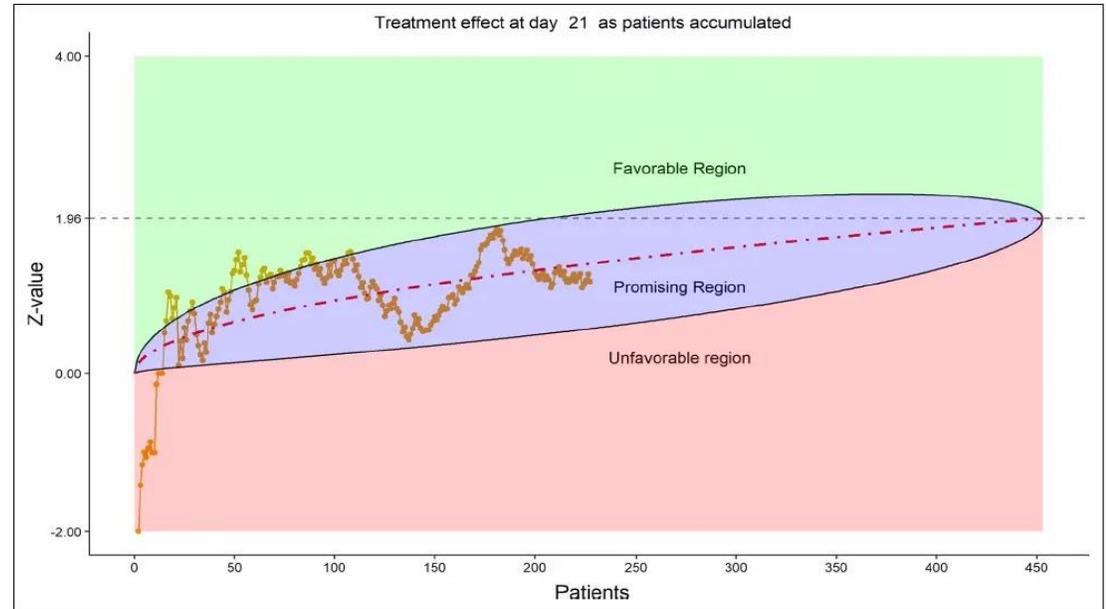
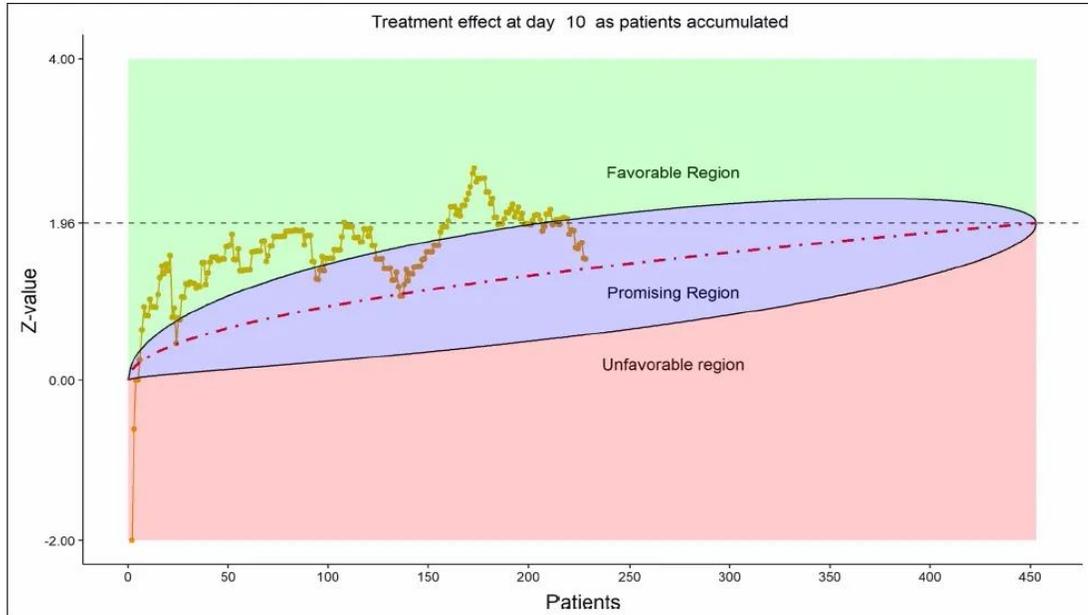
Aside: On 3/3, Gilead Science launched two clinical trials of remdesivir:

- For the moderate cases, primary endpoint: time to discharge in 5 to 10 days.
- For the severe cases, primary endpoint: proportion of participants with normalization of fever and oxygen saturation through Day 14.
- On 3/11, WHO declared COVID-19 outbreak a pandemic.

Fourth (last) Data Review (3/29/2020)

- N =237 (Only enrolled 2 patients in 3 weeks), but more patients reached Day 21 and Day 28
- Sponsor accepted DSMB's last recommendations of revising the protocol
- DDM "Radar" Screen: Day 10, 14, 21, 28 – trends were same as before
- Hospital discharge rate: 68% (rem) vs. 74% (placebo)
- ITT mortality rate: 15% (rem) vs. 14% (placebo)
- Median TTCl: 22 days (rem) vs. 24 days (placebo)

Fourth (last) data review (3/29/2020)



Discussion

- Regarding the trial, it well-designed, carefully conducted and managed despite the urgent nature in which it was put forth and conducted. It was unfortunate for shortening the trial, but good for the disease under control quickly.
- Regarding remdesivir effect in this trial, it was rather limited to “moderately severe” patients (baseline scale=3); little effect for critically severe patients; no early effect; best improvement was on Day 14.
- NIAID and Gilead trials later changed their study follow-up to 28 days.
- Regarding DDM, it is an efficient system, enabled DSMB to conduct (weekly) data analyses and to visualize the trajectory rapidly in the emergent situation. Hope our experience may help other on-going COVID trials.
- Some technical question remains: How can the process of observing the trajectory of a secondary endpoint for triggering the primary endpoint analysis be formally taken into account in the group sequential boundary? (Research on progress)

Acknowledgement

- DSMB members: Jieming Qu (Chair, Shanghai Ruijin Hospital), Weichung Joe Shih (Rutgers University School of Public Health), Robert Fowler (University of Toronto), Rory Collins (University of Oxford), Chen Yao (Peking University).
- Independent statisticians: Bin Shan (Tigermed CRO), Xiaoyan Yan (Peking University).
- eDMC Programmers: Peng Zhang, Emy Wang (CIMS Global).



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Articles

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ORIGINAL RESEARCH

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Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial



Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang

Data Monitoring for the Chinese Clinical Trials of Remdesivir in Treating Patients with COVID-19 During the Pandemic Crisis

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