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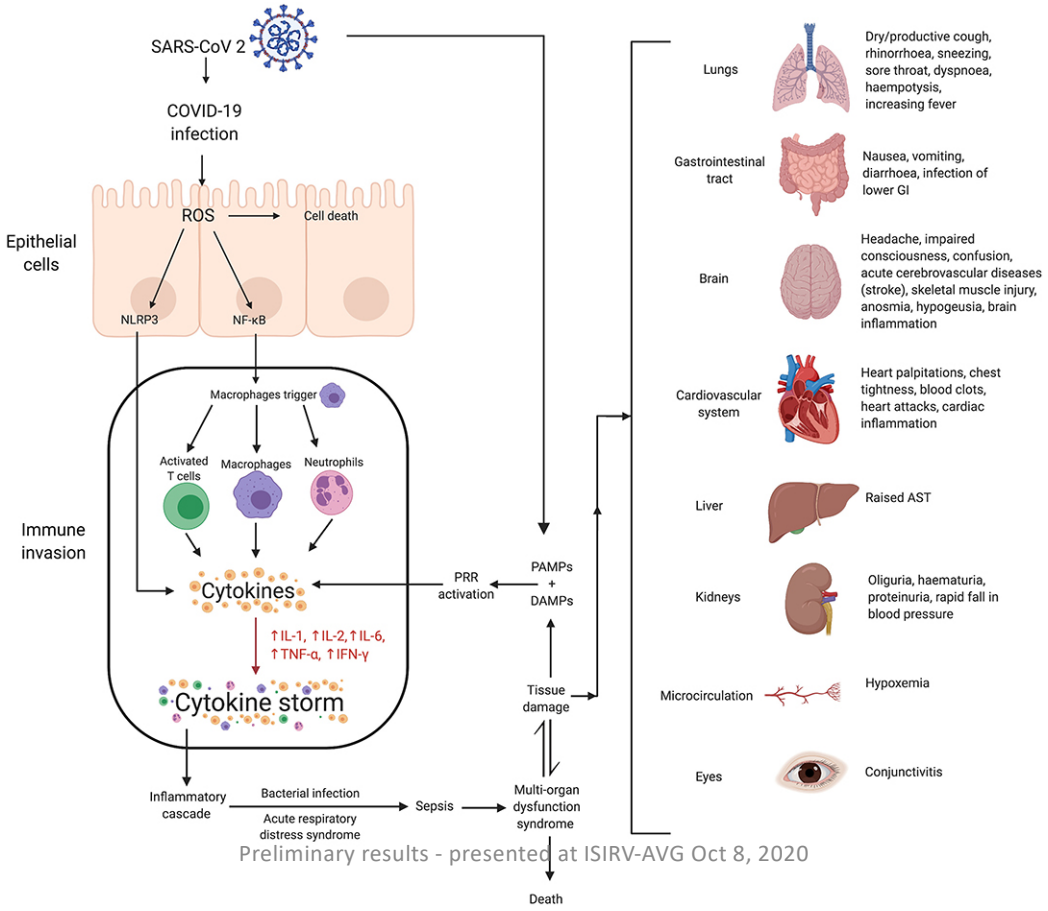
CLINICAL TRIAL UPDATE: JAK inhibitors in COVID-19

isirv
Antiviral Group

THERAPEUTICS FOR COVID-19
6-8 OCTOBER 2020

Preliminary results - presented at ISIRV-AVG Oct 8, 2020

Cytokine Storm in COVID-19



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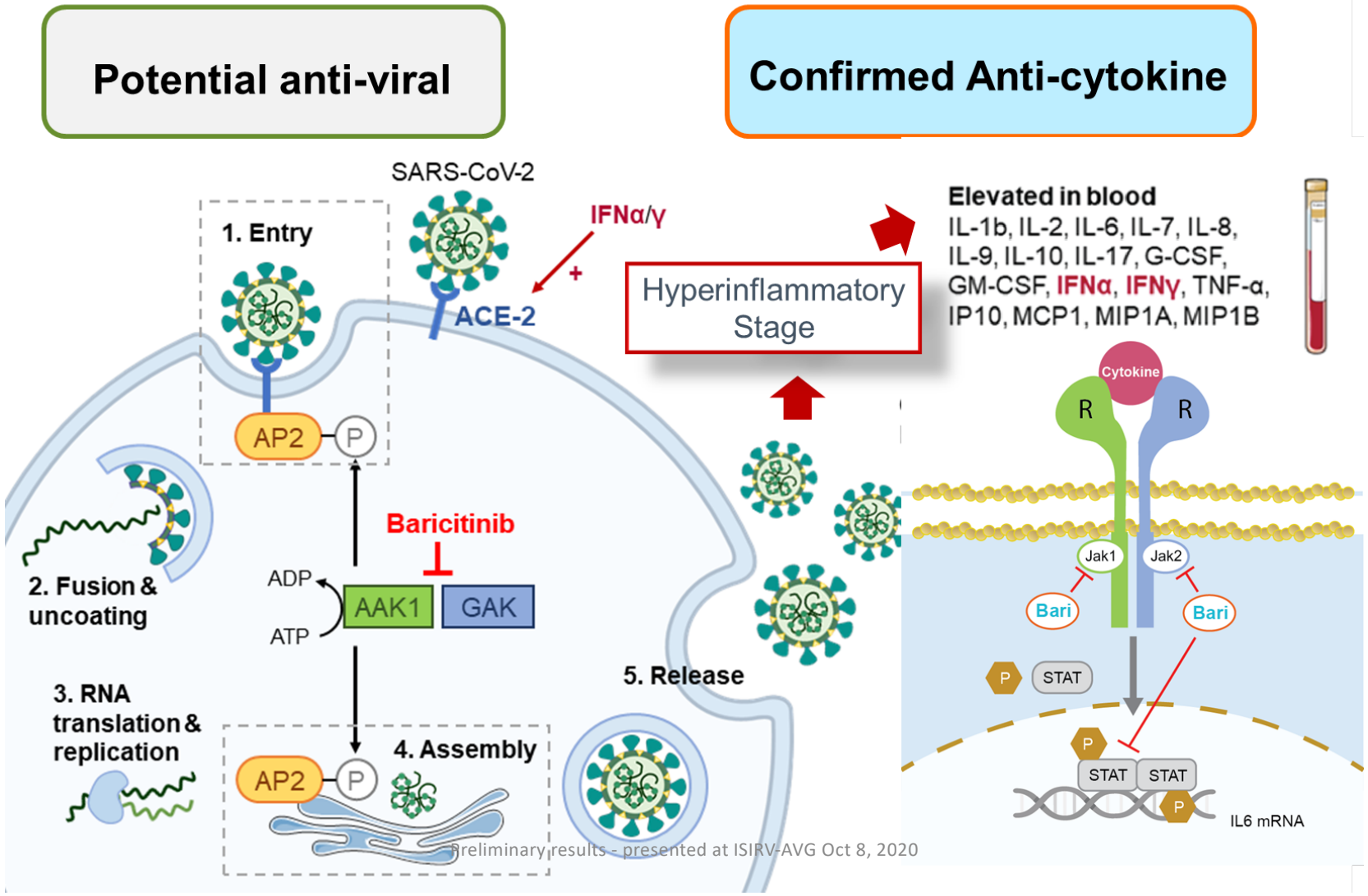

Potential anti-viral
Confirmed Anti-cytokine
SARS-CoV-2
1. Entry
IFNα/γ
+
ACE-2
Hyperinflammatory Stage
Elevated in blood
IL-1b, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFNα, IFNγ, TNF-α, IP10, MCP1, MIP1A, MIP1B
AP2
P
Baricitinib
ADP
ATP
AAK1
GAK
2. Fusion & uncoating
3. RNA translation & replication
4. Assembly
5. Release
Cytokine
R
R
Jak1
Jak2
Bari
Bari
P
STAT
STAT
STAT
IL6 mRNA
Preliminary results - presented at ISIRV-AVG Oct 8, 2020

ACTT-2 Design

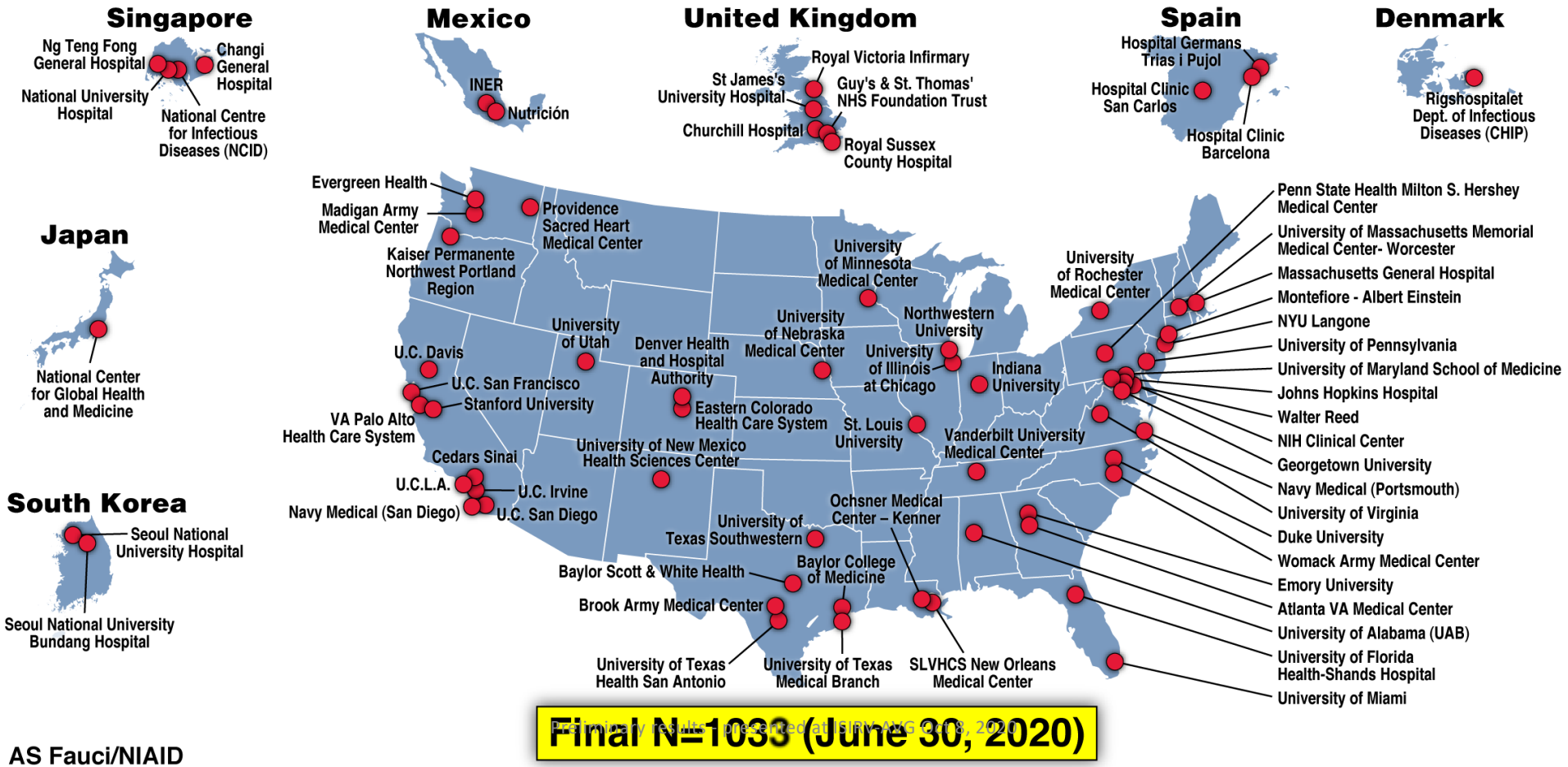
- Design is similar to ACTT-1 (remdesivir vs placebo)

- Hospitalized adults with SARS-CoV-2 by PCR or other clinical assay
- Evidence of lower respiratory tract disease
  - Radiographic infiltrates, hypoxia, need for oxygen/mechanical ventilation
- Randomized to
  - Remdesivir up to 10 days + placebo for up to 14 days
  - Remdesivir up to 10 days + baricitinib for up to 14 days
  - Remdesivir and baricitinib stop on discharge

Why Baricitinib?

- Short half-life
  - About 10 hours
- Established safety profile
  - Approved for RA in since 2017
  - Licensed in > 70 countries
  - Rapidly scalable intervention
- Inhibits signaling of cytokines implicated in COVID-19
- Potential antiviral activities
  - Inhibitor of AP2-associated protein kinase 1

ACTT 2: Randomized Controlled Trial of Baricitinib + Remdesivir vs. Remdesivir Alone



AS Fauci/NIAID

Caveats

- Topline data only
  - Still awaiting full analysis

Ordinal Scale used in ACTT studies

	1	Not hospitalized, no limitations on activities
	2	Not hospitalized, limitation on activities and/or requiring home oxygen
	3	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
	4	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care
	5	Hospitalized, requiring supplemental oxygen
	6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
	7	Hospitalized, on mechanical ventilation or ECMO
	8	Death

Primary Endpoint
time to recovery on ordinal score

Recovered	1	Not hospitalized, no limitations on activities
	2	Not hospitalized, limitation on activities and/or requiring home oxygen
	3	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
Population Enrolled	4	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care
	5	Hospitalized, requiring supplemental oxygen
	6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
	7	Hospitalized, on mechanical ventilation or ECMO
	8	Death

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Baseline characteristics

Characteristic	All Subjects (N=1033)	Baricitinib + RDV (N=515)	Placebo + RDV (N=518)
Age — mean ± standard deviation, yr	55.4 ±15.7	55.0 ± 15.4	55.8 ± 16.0
Male sex - no.(%)	652 (63%)	319 (62%)	333 (64%)
Coexisting conditions – no./total no. (%)			
Diabetes II, no.(%)	370 (37%)	195 (39%)	175 (35%)
Hypertension, no.(%)	522 (52%)	258 (51%)	264 (52%)
Obesity, no.(%)	567 (56%)	295 (58%)	272 (53%)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	142 (14%)	70 (14%)	72 (14%)
5. Hospitalized, requiring supplemental oxygen	564 (55%)	288 (56%)	276 (53%)
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices	216 (21%)	103 (20%)	113 (22%)
7. Hospitalized, on invasive mechanical ventilation or ECMO	111(11%)	54 (10%)	57 (11%)

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Primary Endpoint

	Overall	
	Baricitinib + RDV (n=515)	Placebo + RDV (n=518)
Recovery		
No. of recoveries	433	406
Median time to recovery (95% CI) - days	7 (6, 8)	8 (7, 9)
Rate ratio (95% CI)	1.16 (1.01, 1.32); p=0.04	

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Primary Endpoint by Ordinal Scale

Ordinal Score at Baseline										
	Overall		4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
	Bari + RDV (n=515)	Placebo + RDV (n=518)	Bari + RDV (n=70)	Placebo + RDV (n=72)	Bari + RDV (n=287)	Placebo + RDV (n=276)	Bari + RDV (n=104)	Placebo + RDV (n=113)	Bari + RDV (n=54)	Placebo + RDV (n=57)
Recovery										
No. of recoveries	433	406	67	69	261	243	83	73	22	21
Median time to recovery (95% CI) - days	7 (6, 8)	8 (7, 9)	5 (4, 6)	4 (4, 6)	5 (5, 6)	6 (5, 6)	10 (9, 13)	18 (13, 21)	NE (25, NE)	NE (26, NE)
Rate ratio (95% CI)	1.16 (1.01, 1.32); p=0.04		0.88 (0.63, 1.23)		1.17 (0.98, 1.39)		1.51 (1.10, 2.08)		1.08 (0.59, 1.97)	

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Key Secondary Endpoint
Ordinal Status on Day 15

Ordinal Score at Baseline										
	Overall		4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
	Baricitinib + RDV (n=515)	Placebo + RDV (n=518)	Baricitinib + RDV (n=70)	Placebo + RDV (n=72)	Baricitinib + RDV (n=287)	Placebo + RDV (n=276)	Baricitinib + RDV (n=104)	Placebo + RDV (n=113)	Baricitinib + RDV (n=54)	Placebo + RDV (n=57)
Ordinal Scale at day 15 (±2 days) – no. (%)**										
1	177 (34.4)	165 (31.9)	33 (47.1)	44 (61.1)	114 (39.7)	101 (36.6)	27 (26.0)	17 (15.0)	3 (5.6)	3 (5.3)
2	177 (34.4)	163 (31.5)	25 (35.7)	20 (27.8)	120 (41.7	115 (41.7)	30 (29.1)	24 (21.2)	2 (3.7)	4 (7.0)
3	8 (1.6)	3 (0.6)	5 (7.1)	2 (2.8)	2 (0.7)	1 (0.4)	0 (0)	0 (0)	1 (1.9)	0 (0)
4	31 (6.0)	18 (3.5)	7 (10.0)	6 (8.3)	14 (4.9)	7 (2.5)	7 (6.8)	3 (2.7)	3 (5.6)	2 (3.5)
5	43 (8.3)	50 (9.7)	0 (0)	0 (0)	18 (6.2)	27 (9.8)	15 (14.6)	20 (17.7)	10 (18.5)	3 (5.3)
6	20 (3.9)	19 (3.7)	0 (0)	0 (0)	9 (3.1)	1 (0.4)	7 (6.8)	16 (14.2)	4 (7.4)	2 (3.5)
7	48 (9.3)	83 (16.0)	0 (0)	0 (0)	8 (2.8)	19 (6.9)	15 (14.6)	28 (24.8)	25 (46.3)	36 (63.2)
8	11 (2.1)	17 (3.3)	0 (0)	0 (0)	3 (1.0)	5 (1.8)	2 (1.9)	5 (4.4)	6 (11.1)	7 (12.3)
Odds ratio (95% CI)	1.3 (1.0, 1.6); p=0.04		0.6 (0.3,1.1)		1.2 (0.9, 1.6)		2.2 (1.4, 3.6)		1.7 (0.8, 3.4)	

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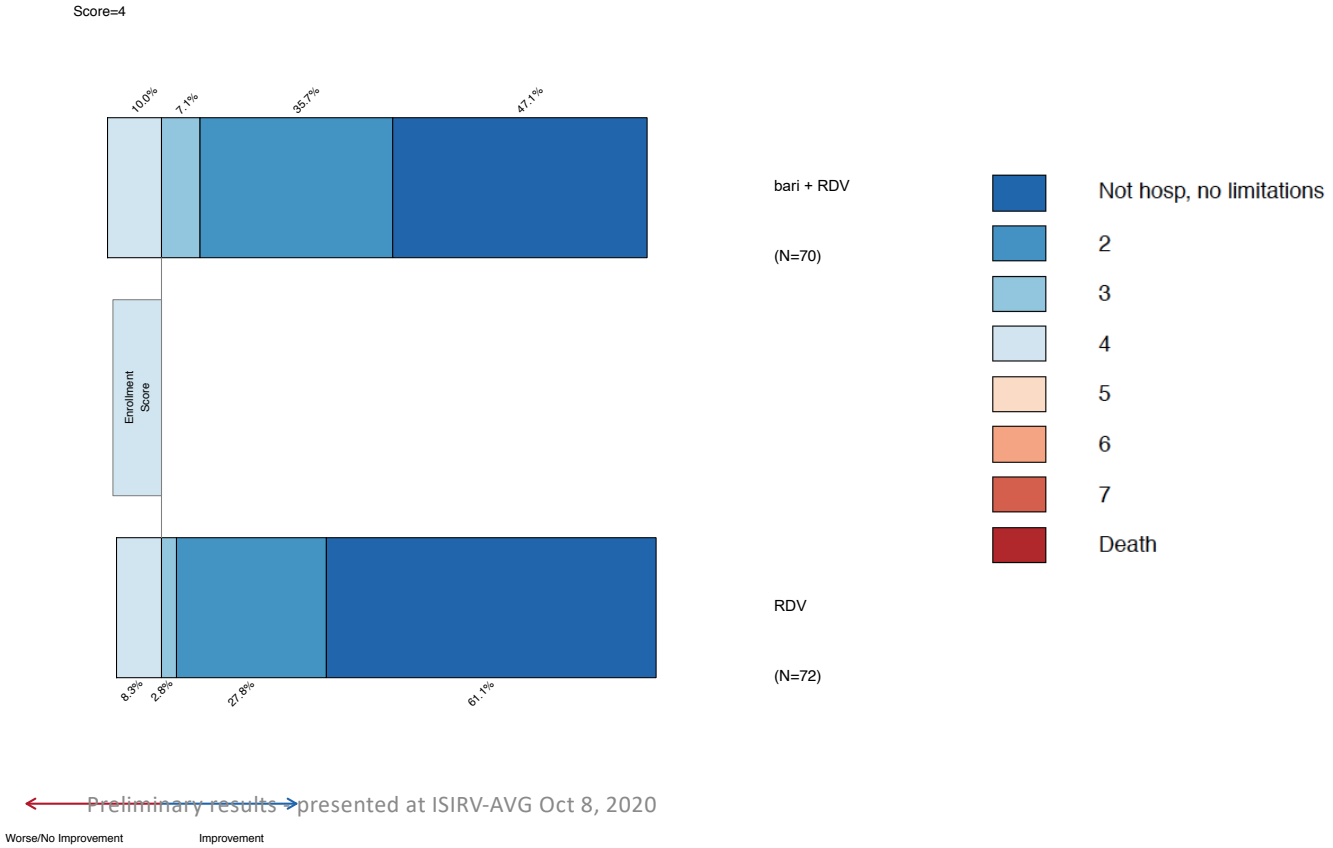
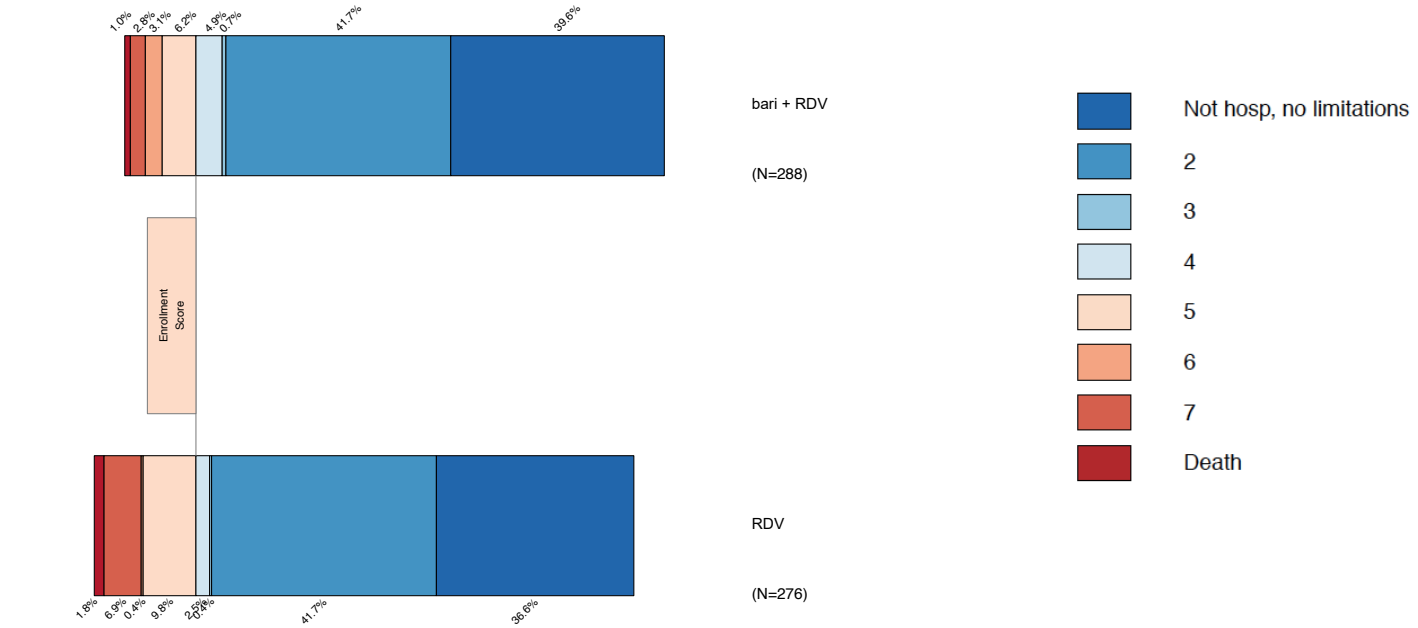
Shifted Bar Plots
Ordinal Status on Day 15

Ordinal 4 - no oxygen



Shifted Bar Plots
Ordinal Status on Day 15

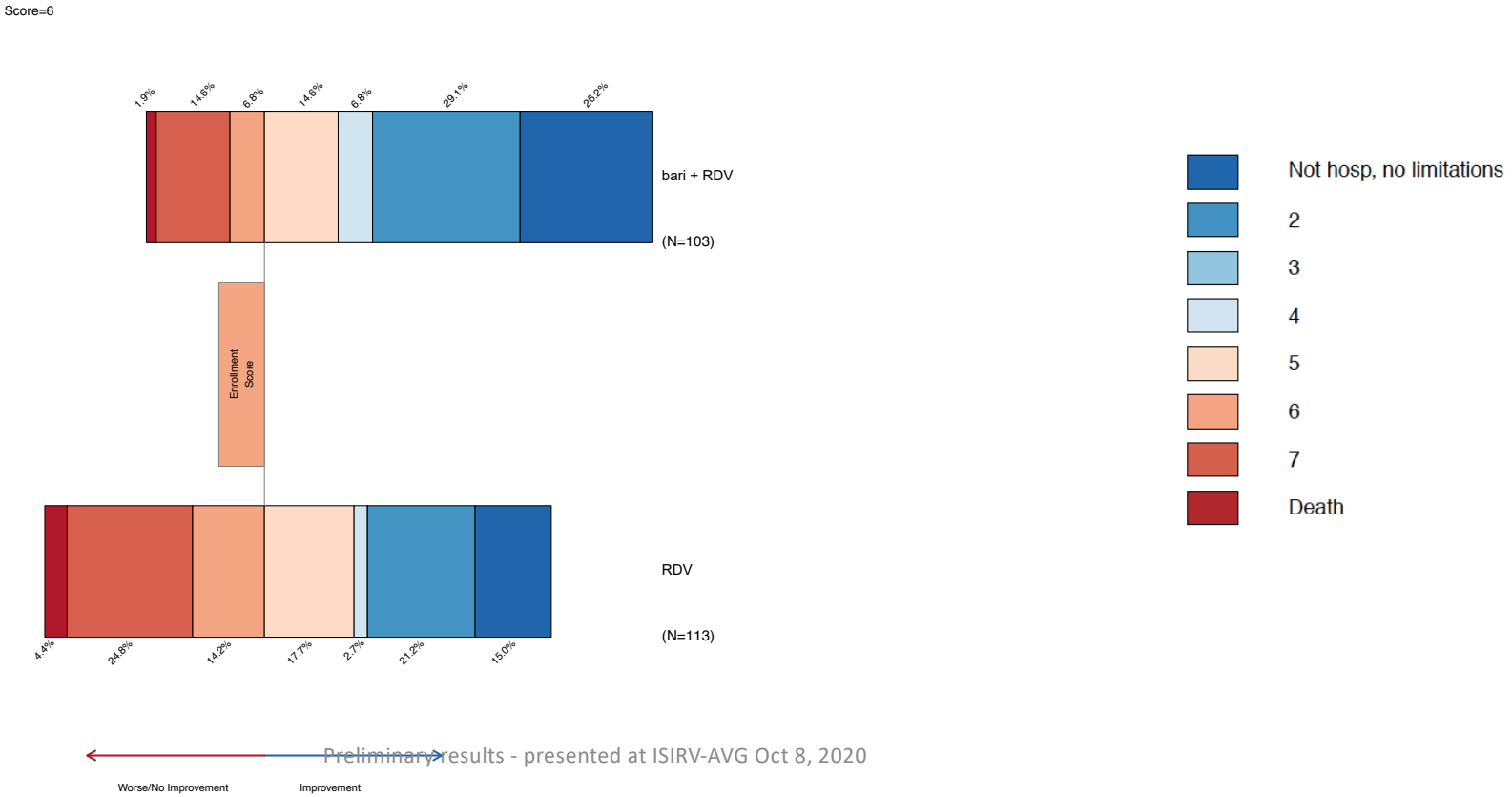
Ordinal 5 - low flow oxygen
Score=5



Worse/No Improvement Improvement

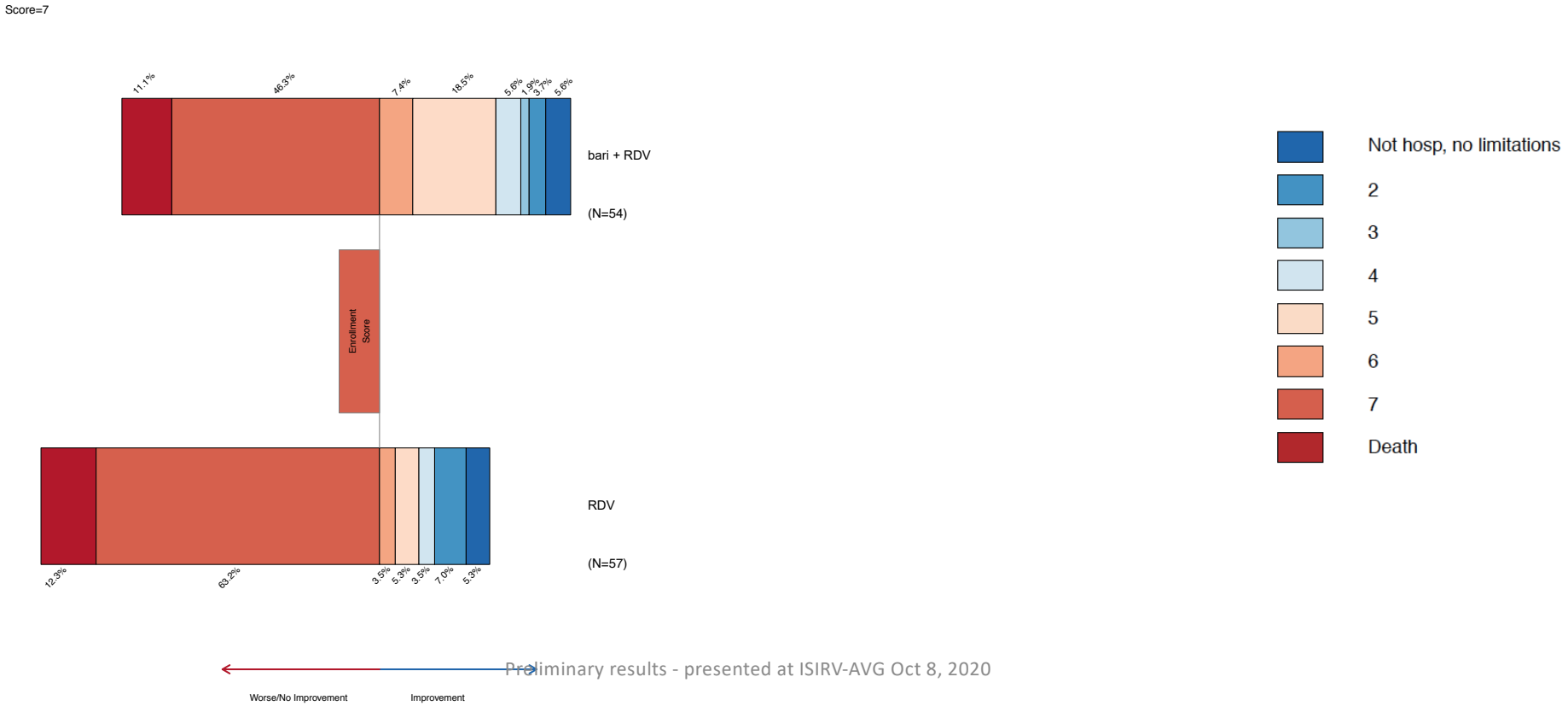
Shifted Bar Plots
Ordinal Status on Day 15

Ordinal 6 - high flow oxygen / non-invasive mechanical ventilation



Shifted Bar Plots
Ordinal Status on Day 15

Ordinal 7 - Invasive mechanical ventilation / ECMO



Mortality

	Overall		Ordinal Score at Baseline							
			4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
	Baricitinib + RDV (n=515)	Placebo + RDV (n=518)	Baricitinib + RDV (n=70)	Placebo + RDV (n=72)	Baricitinib + RDV (n=287)	Placebo + RDV (n=276)	Baricitinib + RDV (n=104)	Placebo + RDV (n=113)	Baricitinib + RDV (n=54)	Placebo + RDV (n=57)
Mortality over entire study period										
Hazard ratio (95% CI) over entire study period	0.65 (0.39, 1.08); p=0.09		NE		0.4 (0.14, 1.14)		0.55 (0.22, 1.37)		1.00 (0.45, 2.22)	
Number of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan-Meier estimate of mortality by day 28 – % (95% CI)	5.1 (3.5, 7.6)	7.8 (5.7, 10.6)	0 (NE, NE)	0 (NE, NE)	1.9 (0.8, 4.4)	4.7 (2.7, 8.1)	7.4 (3.6, 15.0)	12.9 (7.7, 21.3)	23.1 (13.8, 37.1)	22.6 (13.5, 36.4)

ACTT-2 vs RECOVERY

			Ordinal Score at Baseline							
	Overall		4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
Mortality– ACTT-2										
	Bari + RDV (n=515)	Placebo + RDV (n=518)	Bari + RDV (n=70)	Placebo + RDV (n=72)	Bari + RDV (n=287)	Placebo + RDV (n=276)	Bari + RDV (n=104)	Placebo + RDV (n=113)	Bari + RDV (n=54)	Placebo + RDV (n=57)
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Mortality – RECOVERY Trial										
	Overall		No oxygen		Oxygen only		Mechanical ventilation			
	Dex (n=2104)	Usual Care (n=4321)	Dex (n=501)	Usual Care (n=1034)	Dex (n=1279)	Usual Care (n=2604)	Dex (n=324)	Usual Care (n=683)		
Rate ratio	0.83 p<0.001		1.19		0.82		0.64			
28 Day mortality %	22.9	25.7	17.8	14.0	23.3	26.2	29.3	41.4		

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ACTT-2 vs RECOVERY

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ACTT-2 vs RECOVERY

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28 Day mortality %	22.9	25.7	17.8	14.0	23.3	26.2	29.3	41.4		

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Safety
(as treated population)

Subjects with at least 1	Bari + RDV, N=507, n (%)	Pbo + RDV, N=509, n (%)
SAEs	77(15.2%)	103 (20.2%)
Serious infections	12 (2.3%)	20 (3.9%)
Renal	6 (1.2%)	16 (3.1%)
AE	210 (41%)	242 (48%)
AE leading to study drug discontinuation	34 (7%)	59 (12%)
Infections	32 (6%)	50 (10%)
VTE	21 (4%)	16 (3%)
Pulmonary Embolism	5 (1.0%)	2 (0.4%)

Recovery with and without concomitant steroids

- Fewer patients in the Bari + RDV group used steroids compared to the PBD + RDV group
- More patients receiving steroids recovered in the Bari + RDV group compared to the PBO + RDV group
- Use of systemic corticosteroids in ACTT-2 was a non-randomized and non-standardized intervention utilized by approximately 20% of patients

	Steroid use			Time to recovery			
Randomized arms		**Number of patients (n)**	**Proportion of patients (%)**	**Number of recovered patients (n)**	**Proportion of recovered patients (%)**	**Median time to recovery (days)**	**95% CI**
Bari + RDV N=515	Yes	106	20.6	66	62.3	13	10.0, 23.0
	No	409	79.4	367	89.7	6	6.0, 7.0
PBO + RDV N=518	Yes	118	22.8	69	58.5	22	15.0, 27.0
	No	400	77.2	337	84.3	6	6.0, 7.0

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Data not yet available

- Multiple secondary analyses
- Additional corticosteroid analysis

ACTT-2 Conclusion

- Baricitinib in addition to remdesivir improves outcomes in COVID-19
  - Time to recovery (primary) and ordinal score at Day 15 (key secondary)
  - Those hospitalized with COVID-19 requiring oxygen (high flow and low flow) appear to have the largest benefit
- It is unknown if it is better or worse than dexamethasone
  - Studies are not comparable in design
  - Populations are not comparable
  - Based on hazard ratio – each may have optimal populations
    - Baricitinib – low or high flow oxygen
    - Dexamethasone – mechanical ventilation
- We are working to have full analysis completed and the manuscript available soon

Preliminary results - presented at ISIRV-AVG Oct 8, 2020

ACTT-2 Study Team

Networks / Partners

IDCRC
NETEC
DOD / IDCRP
INSIGHT
BARDA
CDC
Gilead
Eli Lilly

US Sites:

Baylor College of Medicine
Baylor Scott & White Health
Brooke Army Medical Center
Cedars-Sinai
Denver Health
Duke University
Eastern Colorado Health
Emory University
Evergreen Healthcare
Georgetown University
Indiana University
Johns Hopkins Hospital
Kaiser Permanente Northwest Portland
Madigan Army Medical Center
Massachusetts General Hospital
Montefiore/Albert Einstein
Navy Medical Center Portsmouth
Navy Medical Center San Diego
NIH Clinical Center
Northwestern University
NYU Langone
Ochsner Medical Center Kenner
Penn State Medical Center
Providence Sacred Heart
Saint Louis University
Southeast Louisiana Veterans
Stanford University
University of California Davis
University of California Irvine
University of California Los Angeles
University of California San Diego
University of California San Francisco
University of Alabama
University of Florida Health
University of Illinois at Chicago
University of Maryland
University of Massachusetts
University of Miami
University of Minnesota
University of Nebraska
University of New Mexico
University of Pennsylvania
University of Rochester
University of Texas San Antonio
University of Texas Medical Branch
University of Texas Southwestern
University of Utah
University of Virginia
VAMC Atlanta
VAMC Palo Alto
Vanderbilt University
Walter Reed National Medical Center
Womack Army Medical Center

International

Denmark

Rigshospitalet Dept of Infectious Diseases (CHIP)
Aalborg University Hospital
Aarhus University Hospital
Hvidovre Hospital
Nordsjællands Hospital
Odense University Hospital
Rigshospitalet Infectious Medicine Clinic
Sjaellands University Hospital
Kolding Sygehus

Japan

National Center for Global Health and Medicine

Korea

Seoul National University Hospital
Seoul National University Bundang Hospital

Mexico

INER
Nutricion

International

Singapore

National Centre for Infectious Diseases
Changi General Hospital
Ng Teng Fong General Hospital
National University Hospital

Spain

Hospital Germans Trias i Pujol
Hospital Clinic Barcelona
Hospital Clinic San Carlos

United Kingdom

John Radcliffe/Churchill Hospital
Guy's & St. Thomas' NHS Foundation Trust
Royal Sussex County Hospital
Royal Victoria Infirmary
St James's University Hospital