Table 5c. Interleukin-6 Inhibitors: Selected Clinical Trial Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Adults With COVID-19 in the United Kingdom[1]		

Key Inclusion Criteria
• Evidence of COVID-19 progression ≤21 days after initial randomization to an intervention within the RECOVERY protocol, defined as:
  • SpO_2 <92% on room air or receipt of supplemental oxygen; *and*
  • CRP ≥75 mg/L
Key Exclusion Criterion
• Presence of non-SARS-CoV-2 infection
Interventions
• 1 weight-based dose of tocilizumab (maximum 800 mg) with possible second dose (n = 2,022)
• Usual care (n = 2,094)
Primary Endpoint
• 28-day all-cause mortality
Key Secondary Endpoints
• Time to hospital discharge within 28 days
• Among those not on MV at baseline, death or receipt of MV (including ECMO) within 28 days
	Participant Characteristics
	• Mean age 64 years; 67% men; 76% White
	• 95% with PCR-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 45% on conventional oxygen
	  • 41% on HFNC oxygen or NIV
	  • 14% on MV
	  • 82% receiving corticosteroids
	Primary Outcomes
	• 28-day all-cause mortality: 31% in tocilizumab arm vs. 35% in usual care arm (rate ratio 0.85; 95% CI, 0.76–0.94; $P = 0.003$)
	• 28-day all-cause mortality among those who required MV at baseline: 49% in tocilizumab arm vs. 51% in usual care arm (risk ratio 0.93; 95% CI, 0.74–1.18)
	Secondary Outcomes
	• Proportion discharged from hospital within 28 days: 57% in tocilizumab arm vs. 50% in usual care arm (rate ratio 1.22; 95% CI, 1.12–1.33; $P < 0.0001$)
	• Median time to hospital discharge: 19 days in tocilizumab arm vs. 28 days in usual care arm
	• Proportion not on MV at baseline who died or required MV within 28 days: 35% in tocilizumab arm vs. 42% in usual care arm (rate ratio 0.84; 95% CI, 0.77–0.92; $P < 0.0001$)
		Key Limitations
		• Arbitrary CRP ≥75 mg/L cutoff for enrollment
		• Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial
		Interpretation
		• Among hospitalized patients with COVID-19, hypoxemia, and elevated CRP levels, the use of tocilizumab was associated with a reduction in all-cause mortality and a shorter time to hospital discharge.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Adults With COVID-19 in 21 Countries in Europe and North America[2,4]		

Key Inclusion Criteria
• ICU admission
• Suspected or laboratory-confirmed SARS-CoV-2 infection
• Receipt of MV, NIV, or cardiovascular support
Key Exclusion Criteria
• >24 hours after ICU admission
• Death imminent
• Immunosuppression
• ALT >5 times ULN
Interventions
• SOC plus 1 of the following (drug selection based on provider preference, availability, or adaptive probability):
  • 1 dose of tocilizumab 8 mg/kg IV with possible second dose in 12–24 hours (n = 952)
  • Single dose of sarilumab 400 mg IV (n = 485)
• SOC alone (n = 406)
Primary Endpoint
• Composite of in-hospital mortality or number of organ support-free days by Day 21, as measured by an OS
Key Secondary Endpoints
• In-hospital survival
• All-cause mortality at 180 days
	Participant Characteristics
	• Mean age 60 years; 69% men; 75% White
	• 86% with PCR-confirmed SARS-CoV-2 infection
	• Median of 14 hours between ICU admission and enrollment
	• At baseline:
	  • 68% on HFNC oxygen or NIV
	  • 32% on MV
	  • Receiving corticosteroids: 67% in SOC arm, 82% in tocilizumab arm, 89% in sarilumab arm
	Primary Outcomes
	Tocilizumab vs. SOC
	• Median number of organ support-free days: 7 in tocilizumab arm vs. 0 in SOC arm
	• Improvement in OS score by Day 21 for composite outcome was more likely in tocilizumab arm (median aOR 1.46; 95% CrI, 1.13–1.87).
	  • Highest CRP tercile: aOR 1.87 (95% CrI, 1.35–2.59)
	• Outcomes were consistent across subgroups according to oxygen requirement at baseline.
	Sarilumab vs. SOC
	• Median number of organ support-free days: 9 in sarilumab arm vs. 0 in SOC arm
	• Improvement in OS score by Day 21 for composite outcome was more likely in sarilumab arm (median aOR 1.50; 95% CrI, 1.13–2.00).
	  • Highest CRP tercile: aOR 1.85 (95% CrI, 1.24–2.69)
	• Outcomes were consistent across subgroups according to oxygen requirement at baseline.
	Secondary Outcomes
	Tocilizumab vs. SOC
	• In-hospital survival: 66% in tocilizumab arm vs. 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93)
		Key Limitation
		• The SOC arm closed in November 2020, after which patients were randomized to active drug arms only; enrollment in the tocilizumab and sarilumab arms was partially nonconcurrent with the SOC arm. Although comparisons to the SOC arm were adjusted for this time period, there is a possibility of bias.
		Interpretation
		• Among patients with respiratory failure who were within 24 hours of ICU admission, the tocilizumab and sarilumab arms had higher rates of in-hospital survival and shorter durations of organ support than the SOC arm.
		• The use of IL-6 receptor antagonists reduced all-cause mortality at 180 days.
		• The treatment effect appeared to be strongest in the highest CRP tercile.
		• Tocilizumab and sarilumab were similarly effective in these patients.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Adults With COVID-19 in 21 Countries in Europe and North America[2,4], cont'd		
	• All-cause mortality at 180 days: 36% in tocilizumab arm vs. 40% in SOC arm (aHR 0.76; 95% CrI, 0.61–0.93) *Sarilumab vs. SOC* • In-hospital survival: 67% in sarilumab arm vs. 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20) • All-cause mortality at 180 days: 33% in sarilumab arm vs. 40% in SOC arm (aHR 0.72; 95% CrI, 0.56–0.91) *Pooled Tocilizumab and Sarilumab Arms vs. SOC Arm* • All-cause mortality at 180 days: 35% in pooled arms vs. 40% in SOC arm (aHR 0.74; 95% CrI, 0.61–0.90)	
COVACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 9 Countries in Europe and North America[5]		
Key Inclusion Criteria • PCR-confirmed SARS-CoV-2 infection • Hypoxemia • Bilateral chest infiltrates **Key Exclusion Criteria** • Death imminent • Presence of active non-SARS-CoV-2 infection **Interventions** • 1 dose of tocilizumab 8 mg/kg with possible second dose, plus SOC (n = 294) • Placebo plus SOC (n = 144) **Primary Endpoint** • Clinical status at Day 28, as measured by an OS **Key Secondary Endpoints** • Time to hospital discharge • ICU LOS • Mortality by Day 28	**Participant Characteristics** • Mean age 61 years; 70% men; 58% White • 30% on HFNC oxygen or NIV • 38% on MV • 25% with multiorgan failure • Received corticosteroids at entry or during follow-up: 36% in tocilizumab arm vs. 55% in placebo arm **Primary Outcome** • No significant difference between arms in clinical status at Day 28 (P = 0.31) **Secondary Outcomes** • Median time to hospital discharge: 20 days in tocilizumab arm vs. 28 days in placebo arm (HR 1.35; 95% CI, 1.02–1.79) • Median ICU LOS: 9.8 days in tocilizumab arm vs. 15.5 days in placebo arm (difference 5.8 days; 95% CI, -15.0 to 2.9) • Mortality by Day 28: 20% in tocilizumab arm vs. 19% in placebo arm (P = 0.94)	**Key Limitations** • Modest power to detect differences in clinical status at Day 28 • More patients received corticosteroids in placebo arm than in tocilizumab arm. **Interpretation** • There was no difference between the tocilizumab and placebo recipients in clinical status at Day 28 or survival. • The median time to hospital discharge was significantly shorter in the tocilizumab arm than in the placebo arm. • Although the result was not statistically significant, the tocilizumab arm had a shorter ICU LOS than the placebo arm.

Methods	Results	Limitations and Interpretation
EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 6 Countries in North America, South America, and Africa[6]		

Key Inclusion Criteria
• PCR-confirmed SARS-CoV-2 infection
• COVID-19 pneumonia
Key Exclusion Criteria
• Death imminent
• Receiving NIV or MV
Interventions
• 1 dose of tocilizumab 8 mg/kg with possible second dose, plus SOC (n = 249)
• Placebo plus SOC (n = 128)
Primary Endpoint
• Progression to MV, ECMO, or death by Day 28
Key Secondary Endpoints
• Time to hospital discharge or readiness for discharge, as measured by an OS
• All-cause mortality by Day 28
	Participant Characteristics
	• Mean age 56 years; 59% men; 56% Hispanic/Latinx, 15% Black/African American, 13% American Indian/Alaska Native
	• 84% with elevated CRP
	• Concomitant medications:
	  • Corticosteroids: 80% in tocilizumab arm vs. 88% in placebo arm
	  • RDV: 53% in tocilizumab arm vs. 59% in placebo arm
	Primary Outcome
	• Proportion who progressed to MV, ECMO, or death by Day 28: 12% in tocilizumab arm vs. 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; $P = 0.04$)
	Secondary Outcomes
	• Median time to hospital discharge or readiness for discharge: 6.0 days in tocilizumab arm vs. 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48)
	• All-cause mortality by Day 28: 10.4% in tocilizumab arm vs. 8.6% in placebo arm (95% CI, -5.2 to 7.8)
		Key Limitation
		• Moderate sample size
		Interpretation
		• In patients with COVID-19 pneumonia, tocilizumab reduced the likelihood of progression to MV, ECMO, or death by Day 28 but did not reduce all-cause mortality by Day 28.

Methods	Results	Limitations and Interpretation
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in the United States[7]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• ≥2 of the following conditions:
  • Fever >38°C
  • Pulmonary infiltrates
  • Need for supplemental oxygen
• ≥1 of the following laboratory criteria:
  • CRP ≥50 mg/L
  • D-dimer >1,000 ng/mL
  • LDH ≥250 U/L
  • Ferritin >500 ng/mL
Key Exclusion Criteria
• Receipt of supplemental oxygen at rate >10 L/min
• Recent use of biologic agents or small-molecule immunosuppressive therapy
• Receipt of immunosuppressive therapy that increased risk for infection
Interventions
• Tocilizumab 8 mg/kg plus usual care (n = 161)
• Placebo plus usual care (n = 81)
Primary Endpoint
• Progression to MV or death by Day 28
Key Secondary Endpoints
• Clinical worsening of disease by Day 28, as measured by an OS
• Discontinuation of supplemental oxygen among patients receiving it at baseline
	Participant Characteristics
	• Median age 60 years; 58% men; 45% Hispanic/Latinx, 43% White
	• 50% with BMI ≥30; 49% with HTN; 31% with DM
	• 80% receiving oxygen ≤6 L/min; 4% on HFNC oxygen; 16% receiving no supplemental oxygen
	• Concomitant medications:
	  • Corticosteroids: 11% in tocilizumab arm vs. 6% in placebo arm
	  • RDV: 33% in tocilizumab arm vs. 29% in placebo arm
	Primary Outcome
	• Progression to MV or death by Day 28: 11% in tocilizumab arm vs. 12% in placebo arm (HR 0.83; 95% CI, 0.38–1.81; $P = 0.64$)
	Secondary Outcomes
	• Proportion with clinical worsening of disease by Day 28: 19% in tocilizumab arm vs. 17% in placebo arm (HR 1.11; 95% CI, 0.59–2.10; $P = 0.73$)
	• Median time to discontinuation of supplemental oxygen: 5.0 days in tocilizumab arm vs. 4.9 days in placebo arm ($P = 0.69$)
		Key Limitations
		• Wide confidence intervals due to small sample size and low event rates
		• Few patients received RDV or corticosteroids.
		Interpretation
		• The use of tocilizumab did not prevent MV or death, reduce the risk of clinical worsening, or reduce the time to discontinuation of oxygen. This could be due to the low rate of concomitant corticosteroid use among the study participants.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Sarilumab in Hospitalized Adults With Severe to Critical COVID-19 in 11 Countries in Europe, North America, South America, and Asia[8]		

Key Inclusion Criteria
• COVID-19 pneumonia
• Need for supplemental oxygen or intensive care
Key Exclusion Criteria
• Low probability of surviving or remaining at study site
• Dysfunction of ≥2 organ systems and need for ECMO or renal replacement therapy
Interventions
• Sarilumab 200 mg IV (n = 159)
• Sarilumab 400 mg IV (n = 173)
• Placebo (n = 84)
Primary Endpoint
• Time to clinical improvement of ≥2 points on a 7-point OS
Key Secondary Endpoint
• Survival to Day 29
	Participant Characteristics
	• Median age 59 years; 63% men; 77% White, 36% Hispanic/Latinx
	• 39% on HFNC oxygen, MV, or NIV
	• 42% with BMI ≥30; 43% with HTN; 26% with type 2 DM
	• 20% received systemic corticosteroids before receiving intervention; 63% received ≥1 doses of corticosteroids during the study.
	Primary Outcomes
	• Median time to clinical improvement: 10 days in sarilumab 200 mg arm vs. 10 days in sarilumab 400 mg arm vs. 12 days in placebo arm
	  • Sarilumab 200 mg arm vs. placebo arm: HR 1.03; 95% CI, 0.75–1.40; $P = 0.96$
	  • Sarilumab 400 mg arm vs. placebo arm: HR 1.14; 95% CI, 0.84–1.54; $P = 0.34$
	Secondary Outcome
	• Survival to Day 29: 92% in placebo arm; 90% in sarilumab 200 mg arm ($P = 0.63$ vs. placebo); 92% in sarilumab 400 mg arm ($P = 0.85$ vs. placebo)
		Key Limitation
		• Moderate sample size
		Interpretation
		• The use of sarilumab did not reduce mortality or time to clinical improvement in hospitalized adults with COVID-19.

Methods	Results	Limitations and Interpretation
REMDACTA: Double-Blind RCT of Tocilizumab and Remdesivir in Hospitalized Patients With Severe COVID-19 Pneumonia in Brazil, Russia, Spain, and the United States[9]		

Key Inclusion Criteria
• Aged ≥12 years
• PCR-confirmed SARS-CoV-2 infection
• Hospitalized with pneumonia confirmed by CXR or CT scan
• Required supplemental oxygen >6 L/min
Key Exclusion Criteria
• eGFR <30 mL/min
• ALT or AST >5 times ULN
• Presence of non-SARS-CoV-2 infection
• Treatment with antivirals, CCP, CQ, HCQ, or JAK inhibitors
Interventions
• Up to 10 days of RDV plus:
  • Tocilizumab 8 mg/kg IV with possible second dose in 8–24 hours (n = 434)
  • Placebo (n = 215)
Primary Endpoint
• Time to hospital discharge or readiness for discharge by Day 28
Key Secondary Endpoints
• Time to MV or death by Day 28
• Clinical status at Day 14, as measured by an OS
• Time to death by Day 28
	Participant Characteristics
	• Mean age 59 years; 40% in tocilizumab arm and 34% in placebo arm aged ≥65 years; 63% men; 67% White
	• Respiratory support:
	  • HFNC oxygen or NIV: 78% in tocilizumab arm vs. 83% in placebo arm
	  • MV or ECMO: 15% in tocilizumab arm vs. 11% in placebo arm
	• Corticosteroid use:
	  • At baseline: 83% in tocilizumab arm vs. 86% in placebo arm
	  • During trial: 88% in each arm
	Primary Outcome
	• Median time to hospital discharge or readiness for discharge by Day 28: 14 days in each arm (HR 0.97; 95% CI, 0.78–1.19; $P = 0.74$)
	Secondary Outcomes
	• No difference between arms in:
	  • Proportion who required MV or died by Day 28: 29% in each arm; time to death was not evaluable (HR 0.98; 95% CI, 0.72–1.34; $P = 0.90$).
	  • Mean OS score for clinical status at Day 14: 2.8 in tocilizumab arm vs. 2.9 in placebo arm ($P = 0.72$)
	  • Proportion who died by Day 28: 18% in tocilizumab arm vs. 20% in placebo arm; time to death was not evaluable (HR 0.95; 95% CI, 0.65–1.39; $P = 0.79$).
		Key Limitations
		• During the trial, primary outcome changed from clinical status at Day 28 to time to hospital discharge or readiness for discharge by Day 28.
		• Imbalances in patient characteristics at baseline between arms
		• Possible underrepresentation of patients with rapidly progressive disease
		Interpretation
		• Compared with placebo plus RDV, tocilizumab plus RDV did not shorten the time to discharge or readiness for discharge in patients with severe COVID-19 pneumonia.
		• In these patients, the use of tocilizumab plus RDV did not reduce mortality when compared with RDV alone.

Key: ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; CCP = COVID-19 convalescent plasma; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LDH = lactate dehydrogenase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal

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