

MIT Open Access Articles

Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19

The MIT Faculty has made this article openly available. **Please share** how this access benefits you. Your story matters.

Citation: Ascierto, Paolo Antonio, et al., "Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19." *Journal for Immunotherapy of Cancer* 8, 1 (Jan. 2020): no. e000878 doi 10.1136/jitc-2020-000878 ©2020 Author(s)

As Published: 10.1136/jitc-2020-000878

Publisher: BMJ








Persistent URL: <https://hdl.handle.net/1721.1/124891>

Version: Final published version: final published article, as it appeared in a journal, conference proceedings, or other formally published context

Terms of use: Creative Commons Attribution NonCommercial License 4.0



Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19

Paolo Antonio Ascierto ¹, Bernard A Fox,² Walter J Urba,² Ana Carrizosa Anderson ³, Michael B Atkins ⁴, Ernest C Borden,⁵ Julie R Brahmer,⁶ Lisa H Butterfield ⁷, Alessandra Cesano,⁸ Daniel S Chen ⁹, Tanja D de Gruijl,¹⁰ Robert O Dillman,¹¹ Charles G Drake,¹² Leisha A Emens,¹³ Thomas F Gajewski,¹⁴ James L Gulley ¹⁵, F Stephen Hodi Jr,¹⁶ Patrick Hwu,¹⁷ David Kaufman,¹⁸ Howard L Kaufman,¹⁹ Michael T Lotze,²⁰ Douglas G McNeel,²¹ Kim A Margolin,²² Francesco M Marincola,²³ Michael J Mastrangelo,²⁴ Marcela V Maus,²⁵ David R Parkinson,²⁶ Pedro J Romero,²⁷ Paul M Sondel ²⁸, Stefani Spranger,²⁹ Mario Sznol,³⁰ George J Weiner,³¹ Jon M Wigginton,³² Jeffrey S Weber³³

To cite: Ascierto PA, Fox BA, Urba WJ, *et al.* Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19. *Journal for ImmunoTherapy of Cancer* 2020;**8**:e000878. doi:10.1136/jitc-2020-000878

Accepted 01 April 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Jeffrey S Weber;
Jeffrey.Weber@nyulangone.org

The hypoxia and profound inflammatory response associated with the pneumonitis observed with the SARS-CoV-2 virus responsible for the recent COVID-19 pandemic has overwhelmed intensive care facilities in the epicenters of infection including Wuhan, China, Northern Italy and in the USA, the Seattle and New York City areas. The Society for Immunotherapy of Cancer (SITC) stands along with and supports our colleagues in emergency departments, intensive care units (ICUs) and inpatient wards in the global effort to overcome this unprecedented pandemic. It is becoming apparent that the ‘ground glass’ infiltrative appearance seen on CT scans from patients with COVID-19 with pneumonitis is reminiscent of imaging from patients with immune checkpoint inhibitor (ICI)-induced pneumonitis.^{1 2} Additionally, elevated interleukin-6 (IL-6) is a hallmark inflammatory signature seen in serum of patients with severe COVID-19 acute respiratory distress.³ Many of us have experience with the administration of immune-modulatory agents, which is why the cancer immunotherapy community is poised to contribute to the current fight against COVID-19.

One possibility is to encourage the use of IL-6 or IL-6-receptor (IL-6R) blocking antibodies like tocilizumab (ActemraTM, Roche-Genentech), sarilumab (KevzaraTM, Regeneron) and siltuximab (SylvantTM, EUSA Pharma) that are Food

and Drug Administration (FDA) approved for various conditions, including rheumatological disease and the lymphoproliferative disorder Castleman’s syndrome. These agents could be used on easily and immediately available compassionate use protocols that could be approved on an emergency basis by all institutional review boards (IRBs) around the world for critically ill patients with COVID-19-induced hypoxia. Tocilizumab also is already FDA approved to manage cytokine release syndrome (CRS) in patients receiving chimeric antigen receptor T cell therapy.^{4 5} In addition, tocilizumab has been shown to reduce toxicity in patients treated with ICIs who were steroid refractory,⁶ and has been added to the ICI agents ipilimumab and nivolumab in an ongoing US phase II study (NCT03999749) to ameliorate immune-related toxicity. In Castleman’s disease, a lymphoproliferative disorder caused by Kaposi’s Sarcoma Herpesvirus, a pathogen that produces viral IL-6, tocilizumab has been shown to reduce viral loads.⁷ Tocilizumab is also being explored as a potential supportive care measure for the management of CRS in patients with cancer treated with a number of CD3-based bispecific molecules. Now, data from the frontlines of the pandemic indicates that the agent may offer lifesaving benefit for COVID-19 patients with respiratory distress.

Emerging evidence suggests that high levels of C reactive protein (CRP) and IL-6 are observed in patients infected with COVID-19.^{1,8} Anecdotal experience on the use of tocilizumab at doses comparable to those used for the management of CRS from investigators in Italy⁹ and from China¹⁰ has reported rapid improvement in both intubated and non-intubated patients. In these reports, expeditious administration of anti-IL-6R therapy for patients in acute respiratory distress has been critical. A recent study protocol to evaluate the efficacy of tocilizumab in COVID-19-induced pneumonitis accrued over 300 patients worldwide in less than 24 hours. Additionally, Genentech will also provide 10000 vials of tocilizumab to the US Strategic National Stockpile.¹¹ Tocilizumab was also approved in China in March 2020, for the treatment of patients with COVID-19 with serious lung damage and elevated IL-6. Sponsors, investigators and regulators have moved with unprecedented speed and collaboration to initiate protocols to formally study the safety and efficacy of antiviral agents and vaccines, as well as various anti-IL-6 antibodies in patients with COVID-19. In the USA, a trial of sarilumab in the COVID-19 setting is ongoing.¹²

Although randomized data definitively showing that IL-6R blockade benefits patients with COVID-19-induced pneumonitis are currently lacking, we propose that an effort should be made to maximize the availability of anti-IL-6 agents, including tocilizumab and sarilumab for use on a compassionate basis to critically ill hospitalized SARS-CoV-2-infected patients during this extraordinary situation. In addition, consideration should be given to focus efforts on rapidly expanding the ability of clinicians and clinical investigators to access investigational anti-IL-6 agents, in particular for those agents where phase 1 and/or phase 2 studies have been completed, and acceptable safety has been demonstrated. Even if the primary impact of a single dose of these drugs is to accelerate recovery and get patients off ventilator support and out of the ICU more rapidly, this could significantly decompress our severely overburdened healthcare systems. We suggest that straightforward parameters including complete blood counts and differentials, serum lactate dehydrogenase (LDH), ferritin, CRP and IL-6 be recorded in treated patients, that serum be retained for future analyses, and simple clinical parameters be assessed including time in ICU, days of hospitalization and pulmonary parameters, including forced expiratory volume in 1 s (for non-intubated patients), fractional inspired oxygen (FiO₂), arterial oxygen tension/FiO₂ ratio and type of oxygen supplementation need be recorded pre-anti-IL-6R and post-anti-IL-6R therapy. A simple compassionate use protocol could be assembled from existing templates, and all efforts should be made for emergency approval of the use of IL-6R blocking antibodies by local IRBs within 24 hours of the request being made. Additionally, consideration should be given by pharma and biotech to redirect the use of facilities and increase personnel involved in drug manufacturing and those serving as liaisons to the frontlines to facilitate drug availability. Extraordinary times call for extraordinary measures, and SITC calls on all involved,

including pharmaceutical sponsors, health authorities and IRBs, to continue to move swiftly and creatively to remove barriers and increase access to agents like anti-IL-6R drugs that may improve our care for COVID-19 pneumonitis.

Author affiliations

- ¹Istituto Nazionale Tumori IRCCS Fondazione 'G. Pascale', Naples, Italy
- ²Earle A. Childs Research Institute, Providence Cancer Institute, Portland, Oregon, USA
- ³Harvard Medical School, Boston, Massachusetts, USA
- ⁴Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA
- ⁵University of Wisconsin Clinical Cancer Center, Madison, Wisconsin, USA
- ⁶Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, USA
- ⁷Research, Parker Institute for Cancer Immunotherapy, San Francisco, California, USA
- ⁸ESSA Pharma Inc, Redwood City, California, USA
- ⁹IGM Biosciences Inc, Mountain View, California, USA
- ¹⁰Medical Oncology - Amsterdam University Medical Centers, Vrije Universiteit-Cancer Center Amsterdam, Amsterdam, The Netherlands
- ¹¹AIVITA Biomedical, Inc, Irvine, California, USA
- ¹²Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, New York, USA
- ¹³UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA
- ¹⁴Pathology and Medicine, Immunology and Cancer Program, University of Chicago, Chicago, Illinois, USA
- ¹⁵National Cancer Institute, Bethesda, Maryland, USA
- ¹⁶Dana Farber Cancer Institute, Boston, Massachusetts, USA
- ¹⁷University of Texas MD Anderson Cancer Center, Houston, Texas, USA
- ¹⁸Bill & Melinda Gates Medical Research Institute, Cambridge, Massachusetts, USA
- ¹⁹Immuneering Corp New York, New York, New York, USA
- ²⁰University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
- ²¹Carbone Cancer Center, University of Wisconsin-Madison, Madison, Wisconsin, USA
- ²²Medical Oncology, City of Hope National Medical Center, Duarte, California, USA
- ²³Refuge Biotechnologies, Menlo Park, California, USA
- ²⁴Thomas Jefferson Medical College, Philadelphia, Pennsylvania, USA
- ²⁵Massachusetts General Hospital Cancer Center, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA
- ²⁶ESSA Pharma Inc, Palo Alto, California, USA
- ²⁷Oncology, University of Lausanne, Lausanne, VD, Switzerland
- ²⁸Pediatrics, University of Wisconsin Madison, Madison, Wisconsin, USA
- ²⁹Massachusetts Institute of Technology Koch Institute for Integrative Cancer Research, Cambridge, Massachusetts, USA
- ³⁰Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, USA
- ³¹Holden Comprehensive Cancer Center, The University of Iowa, Iowa City, Iowa, USA
- ³²MacroGenics Inc, Rockville, Maryland, USA
- ³³Laura and Isaac Perlmutter Comprehensive Cancer Center, NYU Langone Medical Center, New York, New York, USA

Correction notice Since the online publication of this article, the authors have noticed errors in author names, affiliations, the competing interests section and also the main text.

Twitter Leisha A Emens @EmensLeisha, James L Gulley @gulleyj1, Kim A Margolin @kmargolin and Pedro J Romero @JITCancer

Acknowledgements The authors thank the clinicians working tirelessly on the frontlines of the COVID-19 pandemic. The authors also acknowledge SITC staff for their contributions including Sam Million Weaver, PhD for medical writing and editorial support and Angela Kilbert for project management and assistance. Additionally, the authors wish to thank the society for supporting the manuscript development.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests PAA: Consultant/Advisory Role: Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, AstraZeneca, Syndax, SunPharma,

Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar; Research Funds: Bristol-Myers Squibb, Roche-Genentech, Array; Travel support: MSD; BAF: Cofounder/Stock: UbiVac; Consulting/Research Support: Macrogenics, OncoSec, Shimadzu, Viralytics (Merck); Consulting (I-ON)/Research Support: Bristol-Myers Squibb; Consulting/Stock: PrimeVax; Research Support: NanoString, Quanterix; SAB: Argos, Bayer, CellDex, UltiVue; SAB/Institutional Research Support: AstraZeneca (MedImmune); SAB/Research Support: Akoya BioScience (Perkin Elmer), Definiens; WJU: Advisory Board: MedImmune, Bristol-Myers Squibb; Research Support/Contracted Work: Bristol-Myers Squibb; Research Support: MedImmune; ACA: Consulting Fees: Tizona Therapeutics, Compass Therapeutics, Zumutor Biologics; Ownership Interest: VBI vaccines; Scientific Advisory Board: Compass Therapeutics, Zumutor Biologics Inc, Tizona Therapeutics; MBA: Advisory Board: Bristol-Myers Squibb, Merck, Novartis, Arrowhead, Pfizer, Galactone, Werewolf, Fathom; Consultant: Bristol-Myers Squibb, Novartis, Genetech-Roche, Exelixis, Eisai, Aveo, Array, AstraZeneca, Idera, Aduro, ImmunoCore, Boehringer-Ingelheim, Lion, Newlink, Surface, Alexion, Acceleron, Lynx, Cote; Research Support: Bristol-Myers Squibb; Stock Options: Werewolf; JRB: Advisory Board: Amgen, BMS Celgene, Eli Lilly; Genentech, Merck, Syndax; Consulting: BMS, Genentech, Eli Lilly, Merck; Research/Grant Funding: MedImmune/AstraZeneca, Merck; LHB: Consulting Fees: StemImmune/Calidi Scientific and Medical Advisory Board, NextCure; Scientific Advisory Board: Replimmune, Western Oncolytics, Torque Therapeutics, Khloris, Pyxis, Cytomix, Roche-Genentech Biomarkers Roundtable; AC: Consulting Fees: Refuge Bio, Arch Oncology, Qognit, Nanostring; Salary: ESSA Pharma; DSC: Ownership Interest: IGM Biosciences; Salary: IGM Biosciences; CGD: Consultant Fees: Agenus, AstraZeneca, Dendreon, Eli Lilly, Janssen, Merck, Pierre Fabre, Roche/Genetech; Ownership Interests: Compugen, Harpoon, Kleo; Patents/Royalties: AstraZeneca, Bristol-Myers Squibb, Janssen; Research Funding: Aduro Biotech, Bristol-Myers Squibb, Janssen; LAE: Contracted Research: Aduro Biotech, AstraZeneca, Bristol-Myers Squibb, Corvus, EMD Serono, Genentech, F Hoffman La Roche, Maxcyte, Merck, Tempest; Consulting Fees: Genentech, F Hoffman La Roche, Syndax, Eli Lilly, AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Chugai, Genentech, F Hoffman La Roche, Gritstone, MedImmune, MacroGenics, Novartis, Peregrine, Replimmune, Silverback, Vaccinex; IP Rights: Aduro Biotech; Royalty: Elsevier; Salary: University of Pittsburgh, UPMC UPP; Grants from non-industry entities: HeriTX Incorporated, NSABP Foundation, Translational Breast Cancer Research Consortium, Breast Cancer Research Foundation, National Cancer Institute, Department of Defense, Johns Hopkins University, University of California San Francisco; TDG: Consulting Fees: DCPrime BV, Macrophage Pharma, Partner Therapeutics; Contracted Research: Idera Pharmaceuticals, Macrophage Parma; IP Rights/Patents: The use of cytostatics for the accelerated differentiation of DC W02009019320-A2; W02009019320-A3; AU2008285598-A1; EP2281030-A2; CA2724018-A1; US201117051-A1. US8,470,789B2 of DC prime BV, Immunoglobulins binding human V α 9V β 2 T cell receptors, CD1d domain antibodies targeting CD1d P32016NL00 EP16715360.0-1412, LAVA Tx BV; Ownership Interest: LAVA Therapeutics BV (stocks), Salary: Vrije Universiteit Medical Center Amsterdam; TFG: Consultant/Advisory Board: Roche-Genentech, Merck, Abbvie, Bayer, Jounce, Aduro, Fog Pharma, Adaptimmune, FivePrime, Sanofi; Research Support: Roche-Genentech, Bristol-Myers Squibb, Merck, Incyte, Seattle Genetics, CellDex, Ono, Evelo, Bayer, Adure; IP/Licensing: Aduro, Evelo; Cofounder/shareholder: Jounce; FSH: Advisory Board: Aduro, Amgen, 7 Hills Pharma, Compass Therapeutics, Takeda, Rheos, Surface, Verastem; Advisory Board/Equity: Poinyr; Consulting Fees: Genetech/Roche, Bayer, Bristol-Myers Squibb, EMD Serono, Kairos, Merck, Partners Therapeutics, Sanofi, Pfizer, Pieris Pharmaceutical; Scientific Advisory Board/Equity: Apricity, Torque, Bicara; Grant/Royalties to Institution: Bristol-Myers Squibb, Novartis; PH: Consulting Fees: Immatics, Sanofi, Dragonfly, GlaxoSmithKline; DK: Scientific Advisory Board, Celsius Therapeutics, Hookipa Pharma; HLK: Salary: Immuneering Corporation; MTL: Consulting Fees: Torque, Repertone, Checkmate, Salary: Iovance; FMM: Consulting Fees: Calidi Biotechnologies, Salary: Refuge Biotechnologies; KAM: Consulting Fees: ImaginAb SAB, Iovance DMC, Neoleukin ad board (Non CME Services, <10k/year from each entity); MVM: Consulting/Advising: Adaptimmune Therapeutics, Agentus, Agenus inc, Allogene, Arcellx, Bluebird Bio, GSK, Incysus, Kite Pharma, Novartis; Scientific Advisory Boards: Century Therapeutics, CRISPR Therapeutics, TCR2, WindMIL Therapeutics; DGM: Clinical Trial Contracts (Served as PI): Merck, Bristol-Myers Squibb, Janssen, Pfizer, Novartis; Consulting Fees: Madison Vaccines; Contracted Research: Madison Vaccines, Merck; Ownership Interest: Madison Vaccines; DRP: President & CEO: ESSA Pharma; Board of Directors: CTI BioPharma, Tocagen, 3SBI; Scientific Advisory Board: Caris Life Science; PJR: Scientific advisory board: Immatics Biotechnologies, NexImmune, Life Science Partners, Speaker Fees: Bristol-Myers Squibb, Roche Pars, Astra Zeneca; SS: Consulting Fees: Arcus,

Dragonfly, Merck, Ribon, Replimmune, Takeda, Tango; Partner Salary: Nanoview Biosciences; Salary: MIT; MS: Consulting fees: Abbvie, Allakos, Anaeropharma, Almac, Array, AstraZeneca, Biodesix, Bristol-Myers Squibb, Chugai-Roche, Genentech-Roche, Genmab, Genocera, GI Innovation, Hinge, Immunocore, Innate pharma, Lilly, Modulate Therapeutics, Molecular Partner, Nektar, Newlink Genetics, Novartis, Seattle Genetics, Zelluna; Scientific Advisory Boards: Adaptimmune, Lycera (no longer active), Nanobot, Omnio, Pieris, Symphogen, Torque; Ownership Interest (Stock Options): Nanobot, Torque; GJW: Consulting Fees: Cancer Centers at the Universities of Colorado, Hawaii, Kansas, Kentucky, Ohio State, Virginia, Wake Forest, Oregon Health Sciences, University of Illinois Chicago, Memorial Sloan Kettering; Contracted Research: Checkmate Pharmaceuticals; JMW: Consulting Fees: Western Oncolytics; Employee and Shareholder: MacroGenics; JSW: Consulting: Merck, Genentech, Astra Zeneca, GSK, Novartis, Nektar, Medivation, Celldex, Incyte and EMD Serono; Advisory Board: BMS, CellDex, CytoMx, Incyte, Biond, Protean, CV6 and Sellas; Equity: CytoMx, Biond and Altor; Patent/IP: Moffitt Cancer Center IPIILIMUMAB biomarker, BioDesix PD-1 biomarker

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Paolo Antonio Ascierto <http://orcid.org/0000-0002-8322-475X>
 Ana Carrizosa Anderson <http://orcid.org/0000-0002-0877-2932>
 Michael B Atkins <http://orcid.org/0000-0003-3901-9924>
 Lisa H Butterfield <http://orcid.org/0000-0002-3439-9844>
 Daniel S Chen <http://orcid.org/0000-0001-5085-3579>
 James L Gulley <http://orcid.org/0000-0002-6569-2912>
 Paul M Sondel <http://orcid.org/0000-0002-0981-8875>

REFERENCES

- Ye Z, Zhang Y, Wang Y, *et al*. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* 2020. doi:10.1007/s00330-020-06801-0. [Epub ahead of print: 19 Mar 2020].
- Puzanov I, Diab A, Abdallah K, *et al*. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for immunotherapy of cancer (SITC) toxicity management Working group. *J Immunother Cancer* 2017;5.
- Wang Z, Yang B, Li Q, *et al*. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*.
- Teachey DT, Lacey SF, Shaw P, *et al*. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Cancer Discov* 2016;6:664–79.
- Maude SL, Barrett D, Teachey DT, *et al*. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J* 2014;20:119–22.
- Stroud CR, Hegde A, Cherry C, *et al*. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract* 2019;25:551–7.
- Ramaswami R, Lurain K, Widell A, *et al*. Pilot Study of Tocilizumab in Patients with HIV and Symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-Associated Multicentric Castlemans Disease. *Blood* 2018;132:2894.
- Mehta P, McAuley DF, Brown M, *et al*. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
- Ascierto PA. Personal communication.
- Xiaoling X, Mingfeng H, Tiantian L, *et al*. Effective treatment of severe COVID-19 patients with tocilizumab.
- Genentech. Genentech Announces FDA approval of clinical trial for Actemra to treat hospitalized patients with severe COVID-19 pneumonia. Available: <https://www.gene.com/media/press-releases/14843/2020-03-23/genentech-announces-fda-approval-of-clin>
- SANOFI. Sanofi and Regeneron begin global Kevzara® (sarilumab) clinical trial program in patients with severe COVID-19. Available: <http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19>