# Eppur si muove...

## La terapia nel MONDO LINFOMI

## *Gestione del paziente refrattario in era Covid*

*Guido Gini*

BOLOGNA, 11 MARZO 2022

# Dati del paziente e anamnesi

- P. R., uomo, 61 anni
- Epatite B nell'infanzia
- IPB, vescica neurologica
- Nel 2015 linfoma marginale della ghiandola salivare
  → follow up
- Piastrinopenico da 20 anni (100.000/mmc)

# Diagnosi

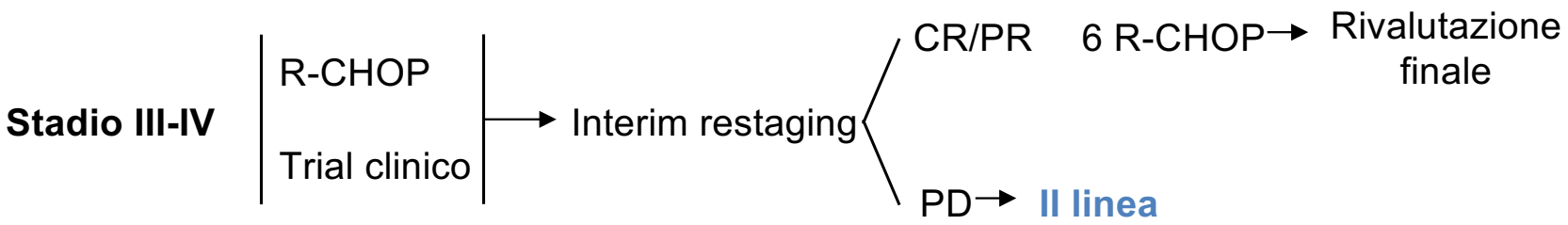
TC c/t/a gennaio 2019 → negativa

<u>Agosto 2019:</u>
Dolore al rachide dorsale con irradiazione intercostale ed anteriore
RMN lombo sacrale con MDC → neoformazione paravertebrale sx D12-L2

Biopsia ossea (fine agosto 2019)
TC c/t/a (settembre 2019) Interessamento sovra-sottodiaframmatico e paravertebrale
BOM (settembre 2019) negativa
PET (settembre 2019) Conferma delle lesioni sopraindicate con interessamento osseo vertebrale

LINFOMA A GRANDI CELLULE B FENOTIPO NON CENTRO GERMINATIVO
stadio IV E-B

# I linea




*NCCN guidelines versione 5.2021*

# I linea

Programma terapeutico:
6 R-CHOP + 2 RTX + 2 MTX finali.
4 Rachicentesi medicate a partire dal II ciclo

Esegue:
**5 R-CHOP**

Dicembre 2019: FA ed Emorragia cerebrale (con emiparesi sx) → STOP
Residua emianopsia sx omonima bilaterale

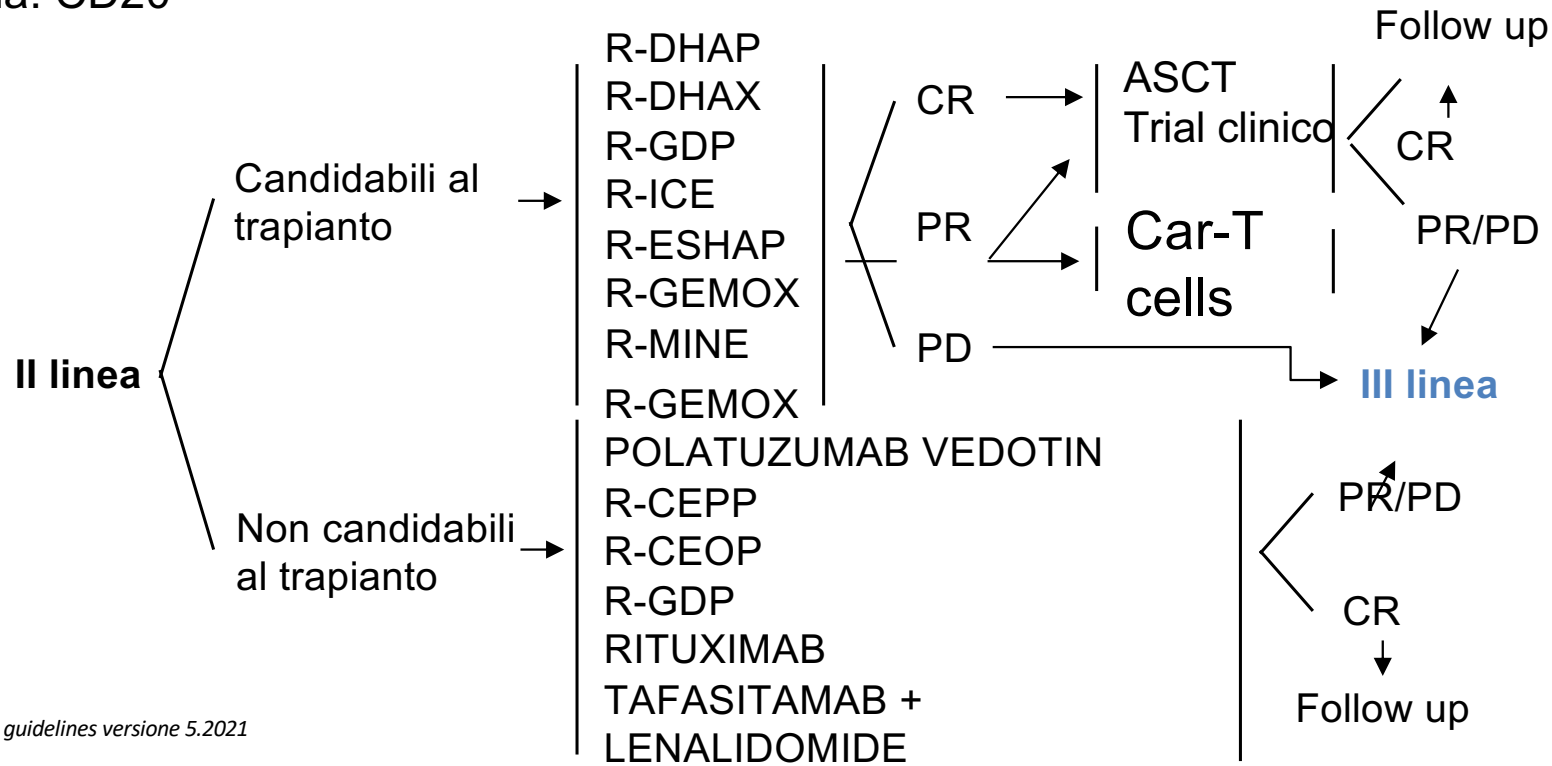
TC (gennaio 2020): RC

Infezione Sars-Cov2 con positività dal 2/4/2020 al 1/7/2020

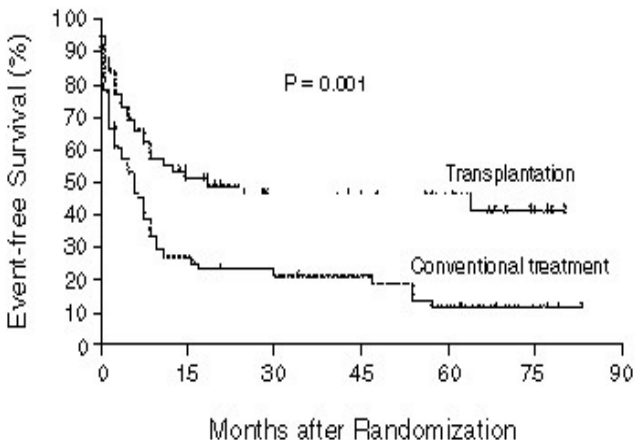
# Progressione e II linea

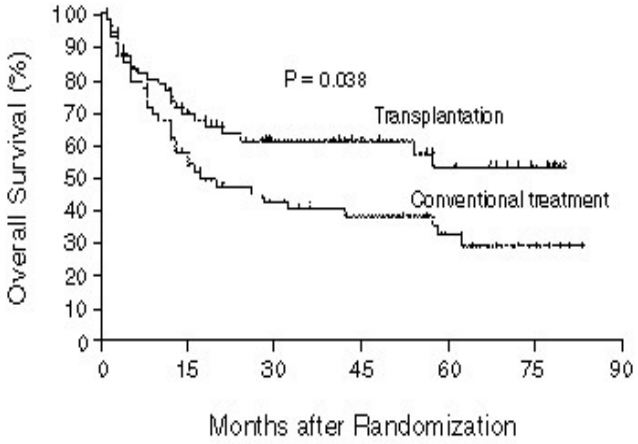
Agosto 2020

- TC: ingrandimento del tessuto patologico in sede paramediastinica destra.
- PET: accumulo patologico nelle sedi già segnalate (SUV massimo 16,5)
- Biopsia: CD20-

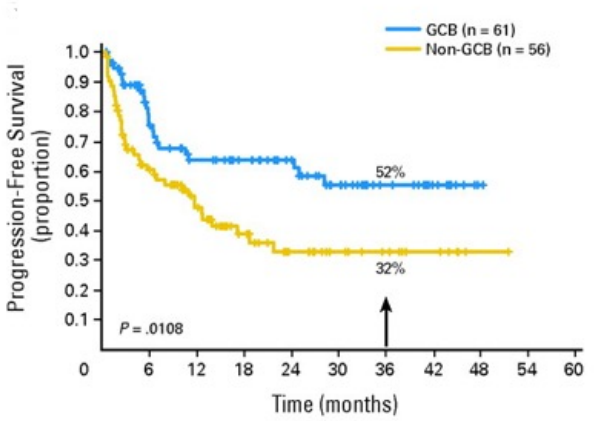


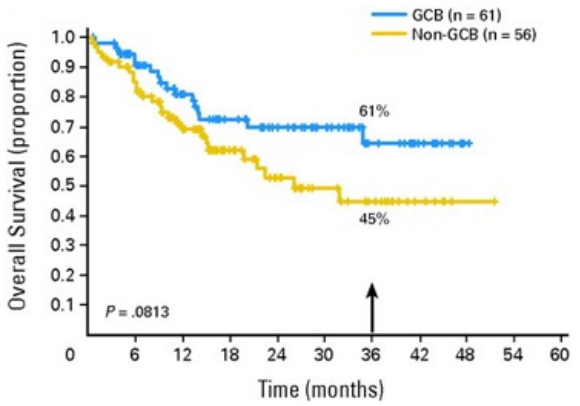

*NCCN guidelines versione 5.2021*




*Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995 Dec 7;333(23):1540-5. doi: 10.1056/NEJM199512073332305. PMID: 7477169.*




Progression-free survival (PFS) and overall survival (OS) according to the R-DHAP

*Published in: Catherine Thieblemont; et al.Journal of Clinical Oncology 2011 294079-4087.*

# II linea

Programma terapeutico:
2 cicli di R-DHAP + ASCT

Esegue:
**2 R-DHAP**

Novembre 2020: persistenza di malattia

Infezione Sars-Cov2 con positività dal 19/11/2020 al 25/02/2021

PET: aumentate per intensità metabolica glucidica (SUV MAX odierno 21.9 vs SUV MAX precedente 16.5) le note due aree tissutali in sede paramediastinica superiore destra
CITOPENIA PERSISTENTE
BOM (dicembre 2020): negativa buona cellularità

# III linea (in covid unit)

***4 cicli con Pixantrone***

Positività per Sars-Cov2 (10/3/2021) → plasma iperimmune

Rivalutazione: PR (DOPO 2 CICLI)

TC (marzo 2021): netta riduzione volumetrica del tessuto solido in sede paramediastinica sup dx, invariate le formazioni linfonodali in sede paraortica dx

Nuova positività (Aprile 2021) → anticorpo monoclonale (14/05) (Imdevimab) negativizzato il 17/5

TC (giugno 2021): torace: ulteriore lieve riduzione del tessuto solido in sede paramediastinica sup dx ); lieve riduzione volumetria e della densità della focalità al segmento dorsale del lobo polmonare sup dx; addome: tessuto solido in sede paraortica sx a livello D12-L1

# How should we use convalescent plasma therapies for the management of COVID-19?

Erica M. Wood,[1,2] Lise J. Estcourt,[3,4] and Zoe K. McQuilten[1,2]

[1]Transfusion Research Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia; [2]Department of Clinical Haematology, Monash Health, Melbourne, VIC, Australia; [3]Haematology/Transfusion Medicine, National Health Service (NHS) Blood and Transplant, Oxford, United Kingdom; and [4]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom

**Convalescent plasma (CP) from blood donors with antibodies to severe acute respiratory syndrome coronavirus 2 may benefit patients with COVID-19 by providing immediate passive immunity via transfusion or by being used to manufacture hyperimmune immunoglobulin preparations. Optimal product characteristics (including neutralizing antibody titers), transfusion volume, and administration timing remain to be determined. Preliminary COVID-19 CP safety data are encouraging, but establishing the clinical efficacy of CP requires an ongoing international collaborative effort. Preliminary results from large, high-quality randomized trials have recently started to be reported. (*Blood*. 2021;137(12):1573-1581)**

- 20000 patients
- 141 severe adverse effects and 63 deaths (<1%) within 4 hours of CP tranfusions

"CP may be of benefit for patients with COVID-19, but more information on both efficacy and safety is needed"

| Study | Country | No./ Planned | Study design | Participants* | Median time from symptom onset to randomization | Intervention† | Control | NAb assay | NAb titer in donor plasma | Primary outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Li et al[30] | China | 103/200 | Open label | Laboratory confirmed SARS-CoV-2, severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, requiring MV); excluded patients with high titer S-RBD–specific IgG (≥1:640) | 27 d in CP and 30 in control | 4-13 mL/kg of CP | Standard care | S-RBD–specific IgG antibody titer | Minimum of S-RBD–specific IgG of 1:640 (approximately equivalent to NAb of 1:40) | Time to clinical improvement (patient discharge or reduction 2 points on 6-point disease severity scale) |
| Rasheed et al[31] | Iraq | 49/not stated | Open label | Laboratory confirmed SARS-CoV-2, critically ill with $SpO_2$ ≤90%, receiving $O_2$ or MV | 21 d in CP and 28 in control | 400 mL of CP on day 1 | Standard care | SARS-CoV-2 IgG (semi-quantitative) and IgM (qualitative) | 52% "moderately" positive and 48% "strongly" positive | Time to recovery from critical illness (clinical improvement permitting discharge from respiratory care unit to ward) |
| Agarwal et al[32] | India | 464/464 | Open label | Laboratory confirmed SARS-CoV-2, moderately ill with either $SpO_2$ ≤93% and RR > 24/min or $PaO_2/FiO_2$ 200-300; excluded critically ill ($PaO_2/FiO_2$ <200 or shock requiring vasopressors) | 8 d in CP and 8 in control | Two doses 200 mL of CP, 24 h apart, preferably different donors | Standard care | Micro-neutralization test | NAb not used to select plasma, tested at end of study: 63% of donors had NAb titer ≥1:20 with median titer 1:40 | Composite all-cause mortality or progression to severe disease ($PaO_2/FiO_2$ <100) within day 28 |
| Gharbharan et al[33] | The Netherlands | 86/426 | Open label | Laboratory confirmed SARS-CoV-2 within 96 h; excluded patients on MV >96 h | 9 d in CP and 11 in control | 300 mL of CP on day 1 | Standard care | SARS-CoV-2 PRNT | Minimum of PRNT50 titer of ≥1:80 | Mortality until discharge or maximum of 60 d |
| Avendano-Sola[34] | Spain | 81/278 | Open label | Laboratory confirmed SARS-CoV-2, radiological changes or clinical features plus $SpO_2$ <94%, <12 d onset<br>Excluded: MV, high flow $O_2$ | 8 d in CP and control | 250-300 mL of CP on day 1 | Standard care | VMNT pseudovirus neutralizing ID50 assay | NAb not available to select plasma, all donation on subsequent testing had VMNT:ID50 >1:80 | Proportion of patients in category 5, 6, 7 of 7-category COVID-19 ordinal scale at day 15 |
| Libster et al, NEJM[35] | Argentina | 160/210 | Double-blind | Laboratory confirmed SARS-CoV-2, mild illness, not requiring hospitalization, age >74 or 65 to 74 and comorbidity, ≤48 h from symptom onset | <3 d | 250 mL CP on day 1 | Saline | anti–S IgG SARS-CoV-2 (COVIDAR IgG) | Minimum titer 1:1000 | Development of severe disease—defined as RR ≥ 30 breaths/min or oxygen saturations <93% on air |
| Simonovich et al, NEJM[36] | Simonovich et al, NEJM | 333/333 | Double-blind | Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥18, pneumonia, plus $SpO_2$ <93% or or $PaO2/FiO_2$ <300<br>Excluded: MV or NIV | 8 d in CP and control | 10 to 15 mL/kg mini-pools (5 to 10 donors) | Saline | anti–S IgG SARS-CoV-2 (COVIDAR IgG) | IgG median titer of 1: 3200 (IQR 1:800 to 1:3200 | Clinical status at day 30 ordinal categories<br>1- death<br>2- invasive ventilatory support<br>3- hospitalized with supplemental oxygen requirements<br>4- hospitalized without supplemental oxygen requirements<br>5- discharged without full return of baseline physical function<br>6- discharged with full return of baseline physical function |
| Al Ghatani et al, preprint[37] | Bahrain | 40/40 | Open-label | Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥21, pneumonia, plus $SpO_2$ <92% or $PaO2/FiO_2$ <300<br>Excluded: MV or MOF | Not reported | Two doses 200 mL CP, 24 h apart | Standard care | Lansionbio COVID-19 IgM/IgG | Not reported | Requirement for ventilation |
| Bajpai et al, preprint[38] | India | 29/20 | Open-label | Laboratory confirmed SARS-CoV-2, requiring hospitalization, age 18 to 65, pneumonia, plus $SpO_2$ <93% or $PaO2/FiO_2$ <300<br>Excluded: comorbidities (kidney, heart or liver disease, COPD) | Not reported | Two doses 250 mL CP, 24 h apart | Nonimmune plasma | SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (Genscript, USA) | Variable | Proportion of patients remaining free of mechanical ventilation day 7 |
| Balcells et al, preprint[39] | Chile | 58/58 | Open-label | Suspected or confirmed SARS-CoV-2, requiring hospitalization, age ≥18, ≤7 d from symptom onset, CALL score ≥9 points at enrollment<br>Excluded: $PaO_2/FiO_2$ <200, pregnant | 5 d in CP and 6 days in control | Two doses 200 mL CP, 24 h apart | Delayed CP if clinical deterioration ($PaO2/FiO_2$ <200 OR hospitalized on day 7) | anti-SARS-CoV-2 (S1) IgG titers | IgG ≥ 1:400 | Composite of mechanical ventilation, hospitalization for >14 d or death during hospitalization |
| Hamdy Salman et al, EJA[40] | Egypt | 30/30 | Double-blind | Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥18, 2 or more of RR ≥ 24, $SpO_2$ ≤93%, $PaO_2/FiO_2$ <300, pulmonary infiltrates<br>Excluded: MOF, septic shock | 30 d in CP and control | 250 mL CP on day 1 | Saline | Neutralizing antibody, Cusabio, ELISA Kit catalog number CSB-E23253HU | NAb not used to select plasma | At least 50% improvement of the severity of illness at any time during 5 d study period |
| Ray et al, preprint[41] | India | 80/80 | Open label | Laboratory confirmed SARS-CoV-2, requiring hospitalization, age ≥18, RR > 30, $SpO_2$ <90%, $PaO_2/FiO_2$ <300<br>Excluded: pregnant, MV | Not reported | Two doses 200 mL CP, 24 h apart | Standard care | anti-SARS-CoV2 spike IgG (Euroimmun) | Euroimmun ≥1.5 | All-cause mortality at 30 d |

Cochrane Library

Cochrane Database of Systematic Reviews

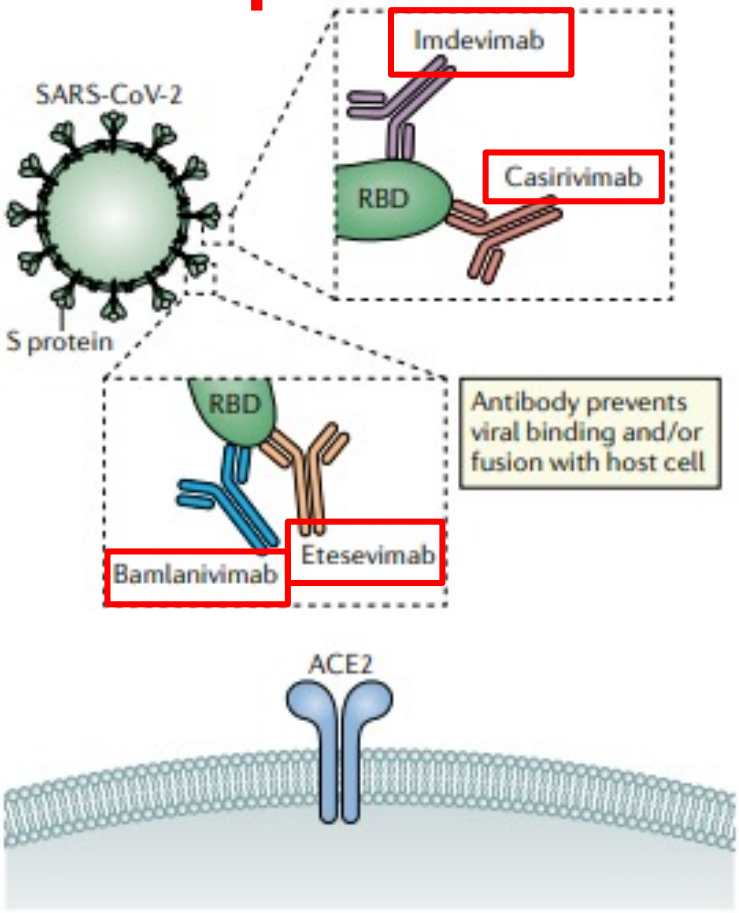
## Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review)

Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N

"We are very uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19. For safety outcomes we also included non-controlled NRSIs. There was limited information regarding adverse events. Of the controlled studies, none reported on this outcome in the control group. There is only very low-certainty evidence for safety of convalescent plasma for COVID-19."

Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N.
Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review.
*Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No.: CD013600.
DOI: 10.1002/14651858.CD013600.pub2.

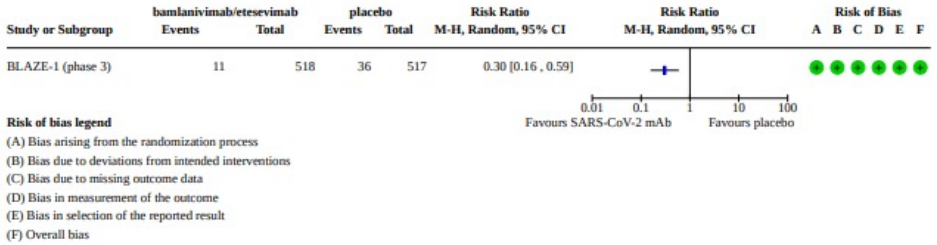
# Anticorpi monoclonali



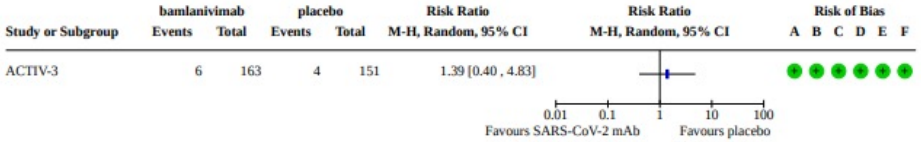

Legandosi alla proteina S, ne impediscono l'interazione con il recettore ACE2 cellulare

*Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol. 2021 Jun;21(6):382-393. doi: 10.1038/s41577-021-00542-x. Epub 2021 Apr 19. PMID: 33875867; PMCID: PMC8054133*

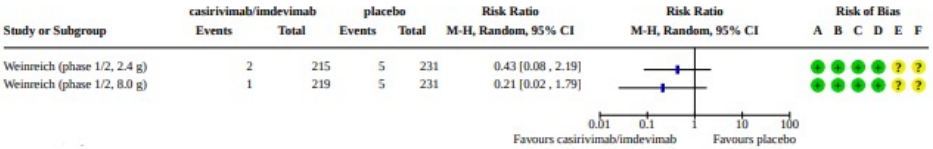
**Analysis 2.2. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 2: Admission to hospital or death**



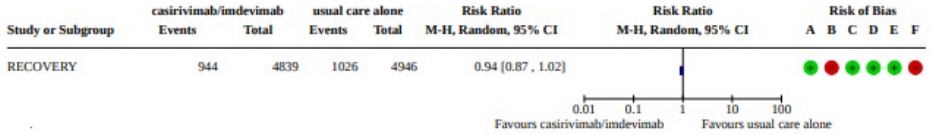

**Analysis 6.1. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 1: Mortality by day 30**




**Analysis 3.1. Comparison 3: Casirivimab/imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 1: Admission to hospital or death**

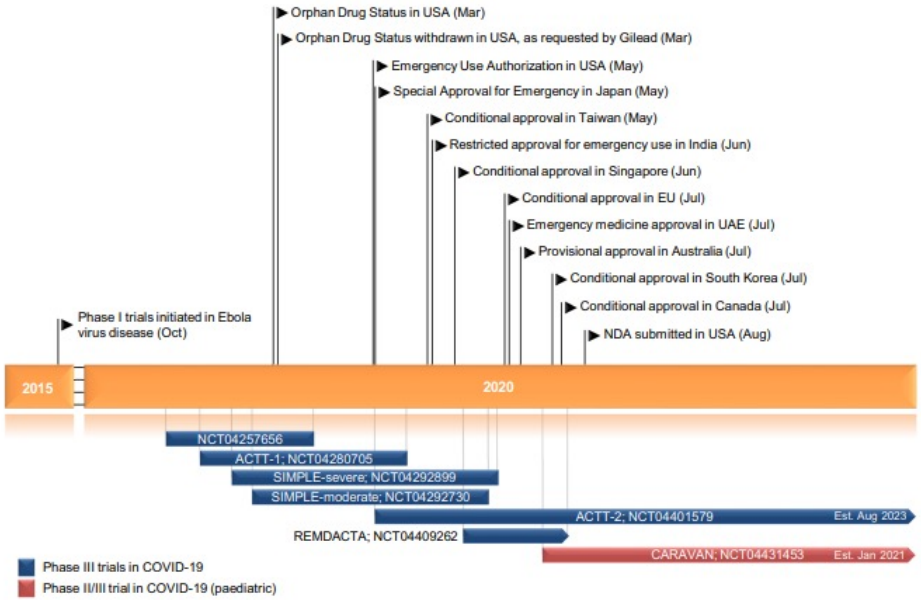


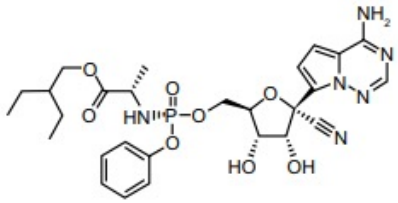

**Analysis 7.1. Comparison 7: Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 1: Mortality by day 30**




*Kreuzberger N, Hirsch C, Chai KL, Tomlinson E, Khosravi Z, Popp M, Neidhardt M, Piechotta V, Salomon S, Valk SJ, Monsef I, Schmaderer C, Wood EM, So-Osman C, Roberts DJ, McQuilten Z, Estcourt LJ, Skoetz N. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. Cochrane Database Syst Rev. 2021 Sep 2;9(9):CD013825. doi: 10.1002/14651858.CD013825.pub2. PMID: 34473343; PMCID: PMC8411904.*

# Antivirali: Remdesivir



Analogo ATP, compete per siti di binding con RNA, bloccando la trascrizione.

*Lamb YN. Remdesivir: First Approval. Drugs. 2020 Sep;80(13):1355-1363. doi: 10.1007/s40265-020-01378-w. PMID: 32870481; PMCID: PMC7459246.*

## Forme lievi-moderate:

**Gilead Announces Results From Phase 3 Trial of Remdesivir in Patients With Moderate COVID-19**

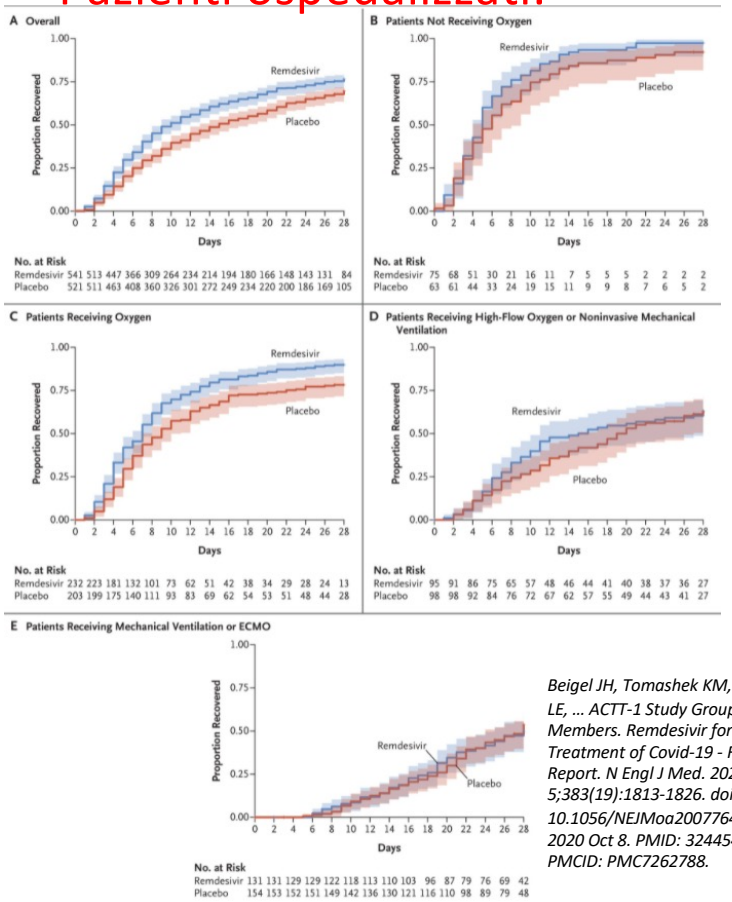
*-- Study Demonstrates 5-Day Treatment Course of Remdesivir Resulted in Significantly Greater Clinical Improvement Versus Treatment with Standard of Care Alone --*

| | 5-Day RDV n=191 | 10-Day RDV n=193 | SOC n=200 |
|---|---|---|---|
| **Clinical Efficacy Outcomes at Day 11** | | | |
| ≥ 2-point improvement in ordinal scale | 134 (70) | 126 (65) | 121 (61) |
| ≥ 1-point improvement in ordinal scale | 146 (76) | 135 (70) | 132 (66) |
| Requiring any oxygen support | 12 (6) | 13 (7) | 22 (11) |
| ≥ 1-point worsening in ordinal scale | 6 (3) | 12 (6) | 22 (11) |
| Death | 0 | 2 (1) | 4 (2) |
| **Safety** | | | |
| Any adverse event (AE) | 97 (51) | 106 (55) | 90 (45) |
| Grade ≥3 AE | 20 (10) | 21 (11) | 24 (12) |
| Any serious adverse event (SAE) | 8 (4) | 7 (4) | 18 (9) |

OR 1.65; 95% CI 1.09–2.48; p = 0.017

*Gilead Sciences. Gilead announces results from phase 3 trial of remdesivir in patients with moderate COVID-19 [media release]. 1 Jun 2020. http://www.gilead.com.*

## Pazienti ospedalizzati:




*Beigel JH, Tomashek KM, Dodd LE, ... ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813-1826. doi: 10.1056/NEJMoa2007764. Epub 2020 Oct 8. PMID: 32445440; PMCID: PMC7262788.*

reduced time to recovery relative to placebo
(median 11 vs 15 days; OR 1.32; 95% CI 1.12–1.55; p < 0.001)

# IV linea

26/07/2021

**Car-T cells *(*Axicabtagene Ciloleucel)**

*Condizionamento FLUBY*

**CRS grado II** (ipotensione, desaturazione con necessità di supporto fino a 6 l/min O2→ Tocilizumab 8 mg/kg

**Ricovero in terapia intensiva** dal 29/07 al 6/08 → Tocilizumab 8 mg/kg x 2

Sindrome da inappropriata secrezione di ADH

Neurotossicità di grado I

GUIDELINE | VOLUME 25, ISSUE 4, P625-638, APRIL 01, 2019

# ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee # • Bianca D. Santomasso # • Frederick L. Locke • Armin Ghobadi • Cameron J. Turtle • Jennifer N. Brudno • Marcela V. Maus • Jae H. Park • Elena Mead • Steven Pavletic • William Y. Go • Lamis Eldjerou • Rebecca A. Gardner • Noelle Frey • Kevin J. Curran • Karl Peggs • Marcelo Pasquini • John F. DiPersio • Marcel R.M. van den Brink • Krishna V. Komanduri • Stephan A. Grupp • Sattva S. Neelapu • Show less • Show footnotes

Open Access • Published: December 25, 2018 • DOI: https://doi.org/10.1016/j.bbmt.2018.12.758 •

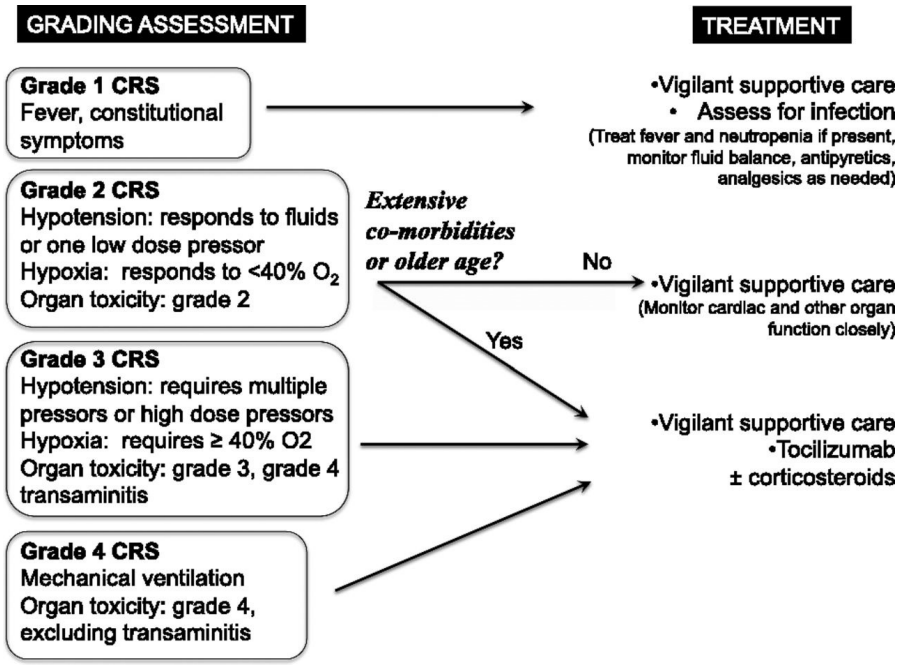
ASTCT CRS Consensus Grading

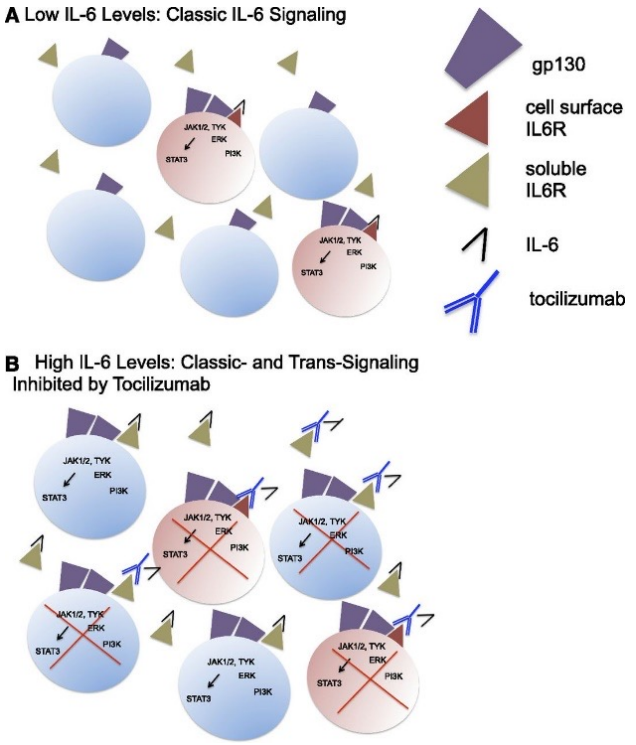
| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Fever*** | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C |
| | | With | | |
| **Hypotension** | None | Not requiring vasopressors | Requiring a vasopressor with or without vasopressin | Requiring multiple vasopressors (excluding vasopressin) |
| | | And/or† | | |
| **Hypoxia** | None | Requiring low-flow nasal cannula‡ or blow-by | Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask | Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation) |

ASTCT ICANS Consensus Grading for Adults

| Neurotoxicity Domain | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **ICE score*** | 7-9 | 3-6 | 0-2 | 0 (patient is unarousable and unable to perform ICE) |
| **Depressed level of consciousness†** | Awakens spontaneously | Awakens to voice | Awakens only to tactile stimulus | Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma |
| **Seizure** | N/A | N/A | Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention | Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between |
| **Motor findings‡** | N/A | N/A | N/A | Deep focal motor weakness such as hemiparesis or paraparesis |
| **Elevated ICP/ cerebral edema** | N/A | N/A | Focal/local edema on neuroimaging§ | Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad |

# CRS management



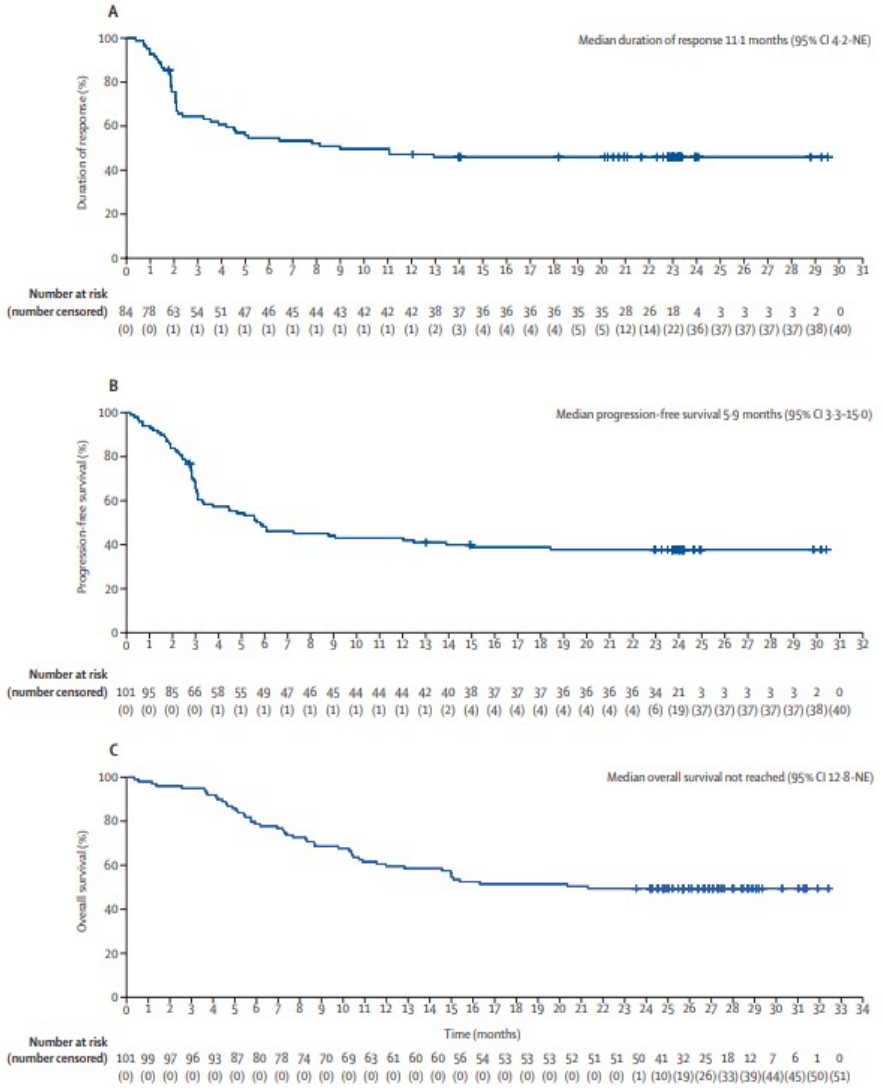

*Daniel W. Lee,Rebecca Gardner,David L. Porter,Chrystal U. Louis,Nabil Ahmed,Michael Jensen,Stephan A. Grupp,Crystal L. Mackall, Current concepts in the diagnosis and management of cytokine release syndrome, Blood, 2014, Figure 1,2*

ARTICLES | VOLUME 20, ISSUE 1, P31-42, JANUARY 01, 2019

# Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

Frederick L Locke, MD • Armin Ghobadi, MD • Caron A Jacobson, MD • David B Miklos, MD • Lazaros J Lekakis, MD • Olalekan O Oluwole, MBBS • Yi Lin, MD • Ira Braunschweig, MD • Brian T Hill, MD • Prof John M Timmerman, MD • Abhinav Deol, MD • Patrick M Reagan, MD • Prof Patrick Stiff, MD • Ian W Flinn, MD • Umar Farooq, MD • Andre Goy, MD • Peter A McSweeney, MBChB • Javier Munoz, MD • Tanya Siddiqi, MD • Julio C Chavez, MD • Alex F Herrera, MD • Prof Nancy L Bartlett, MD • Jeffrey S Wiezorek, MD • Lynn Navale, MS • Allen Xue, PhD • Yizhou Jiang, PhD • Adrian Bot, MD • John M Rossi, MS • Jenny J Kim, MD • William Y Go, MD • Prof Sattva S Neelapu, MD † • Show less • Show footnotes

Published: December 02, 2018 • DOI: https://doi.org/10.1016/S1470-2045(18)30864-7 • Check for updates

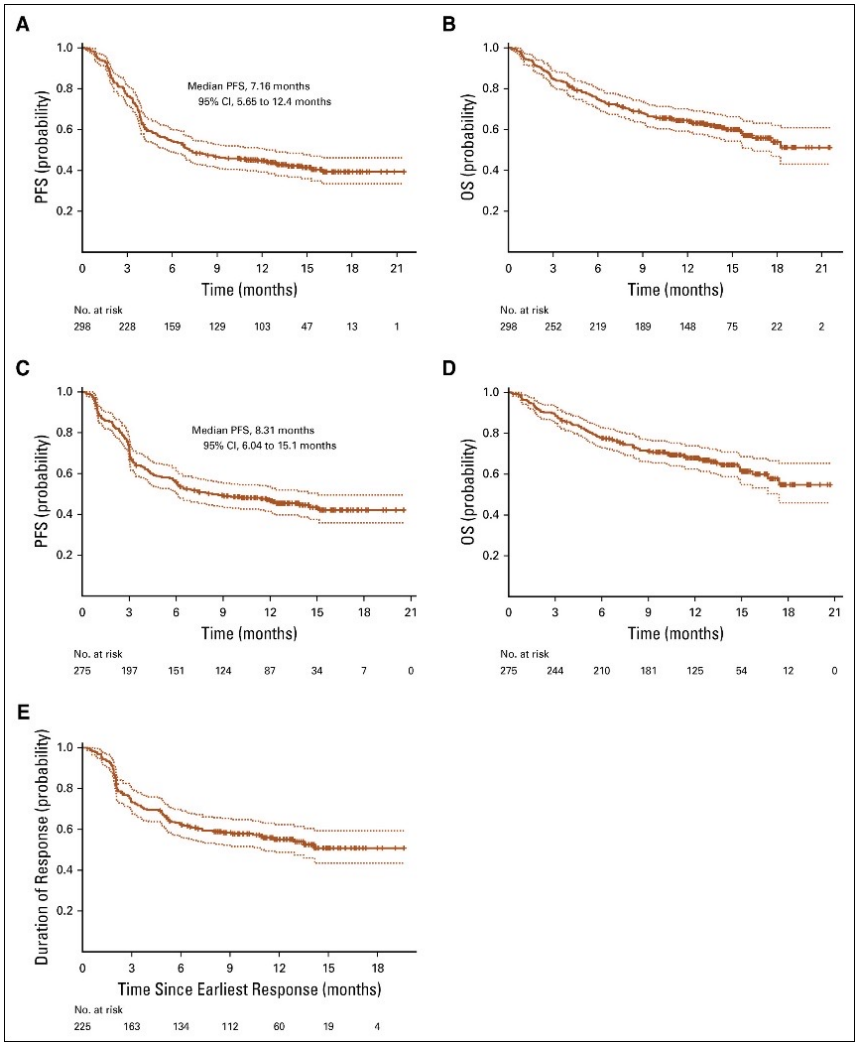


# Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium



Loretta J. Nastoupil, MD[1]; Michael D. Jain, MD, PhD[2]; Lei Feng, MD[1]; Jay Y. Spiegel, MD[3]; Armin Ghobadi, MD[4]; Yi Lin, MD, PhD[5]; Saurabh Dahiya, MD[6]; Matthew Lunning, DO[7]; Lazaros Lekakis, MD[8]; Patrick Reagan, MD[9]; Olalekan Oluwole, MBBS[10]; Joseph McGuirk, DO[11]; Abhinav Deol, MD[12]; Alison R. Sehgal, MD[13]; Andre Goy, MD[14]; Brian T. Hill, MD, PhD[15]; Khoan Vu, MD[16]; Charalambos Andreadis, MD, MSCE[16]; Javier Munoz, MD, MS[17]; Jason Westin, MD[1]; Julio C. Chavez, MD, MS[2]; Amanda Cashen, MD[4]; N. Nora Bennani, MD[5]; Aaron P. Rapoport, MD[6]; Julie M. Vose, MD[7]; David B. Miklos, MD, PhD[3]; Sattva S. Neelapu, MD[1]; and Frederick L. Locke, MD[2]

Journal of Clinical Oncology ,Volume 38, Issue 27



# Oggi…

RC PET negativo (28/2/2022) G+210 in follow-up

Residua modesta pancitopenia e ipogammaglobulinemia

Vaccinato per COVID-19: 17/11/2021-06/12/2021

Colite acuta erosiva (novembre 2021-gennaio 2022)

Nuova positività a Sars-Cov2 il 03/02/2022 risolta il 16/02/2022