Eppur si muove...

La terapia nel MONDO LINFOMI

Caso clinico 1

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ROMA, 26 MAGGIO 2022

Comorbidità: Cardi olica globale, iperte

Raccordo anamnestico:

→ 2017 LNH Follicolare G1-

→ 2021 versamento pleuric odale che interessa l'atrio dx

→ DLBCL GC "double expres matose

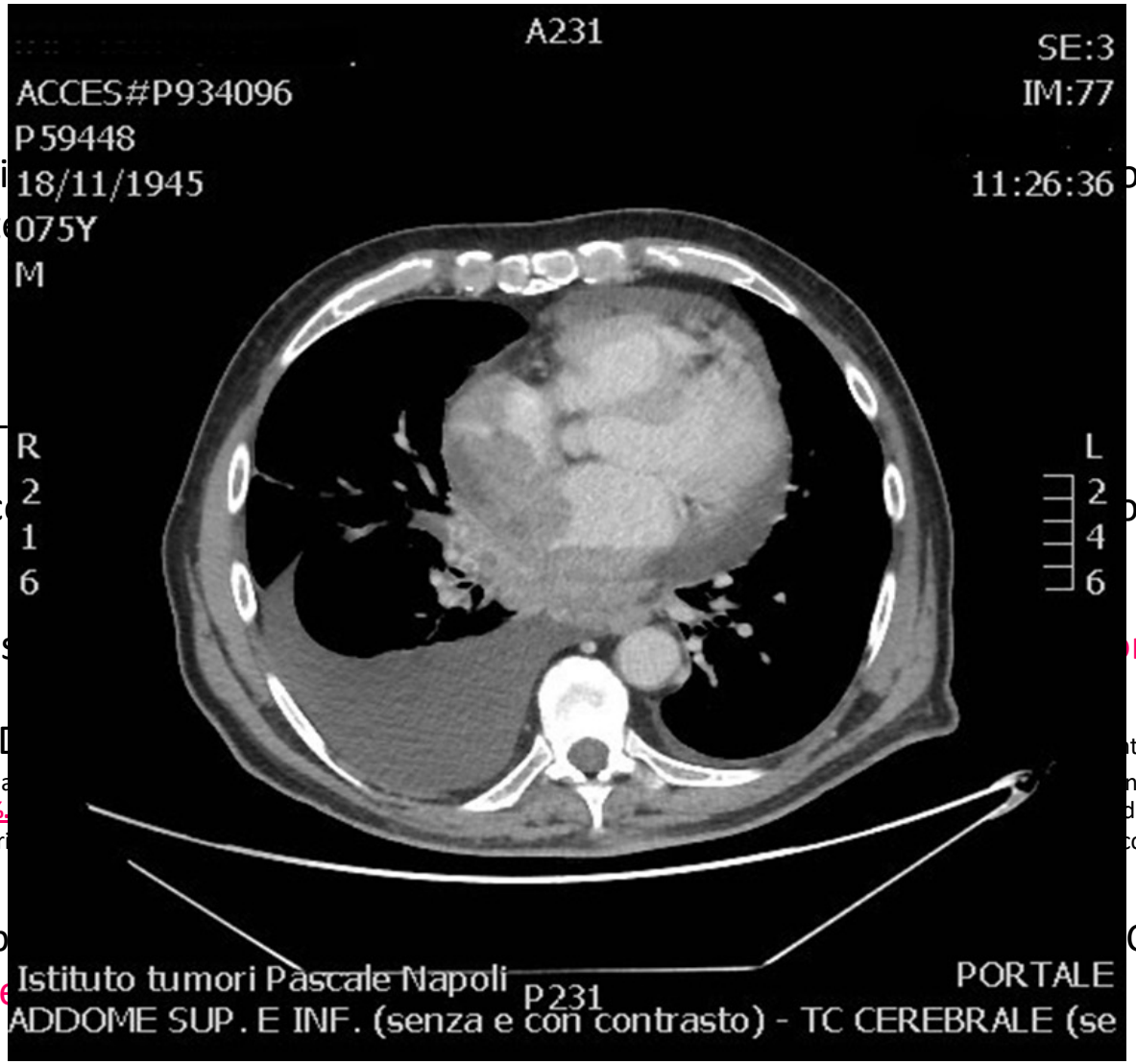
ECG/ECOCARDIOCOLORD

completo. Anomalie secondarie della ripola globale moderatamente **depressa FE 48%** ingrandito. Sezioni destre nei limiti, ventri compromissione emodinamica

tricolare. Blocco di branca destro normali, ipertrofia del setto, cinesi diastolica di I grado. Atrio sinistro ccato senza segni, al momento, di

firma consenso informato per p C7 (POLAR BEAR)

→ Braccio A: R-mini-CHOP pe



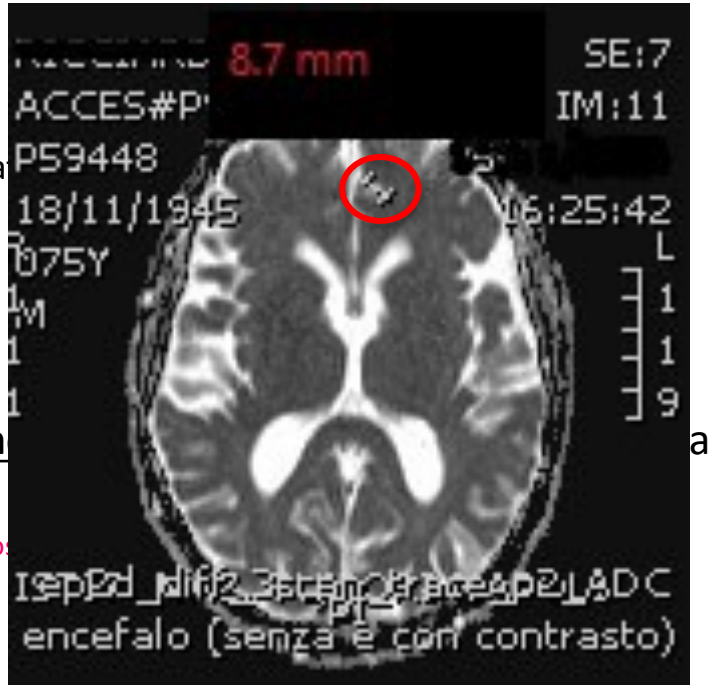
→ C1  g +20 Fibrillazione Atriale → UTIC digossina

→ dopo nulla osta cardiologico pratica II e III ciclo (ripetuti accessi per aritmie e toracentesi)

→ rivalutazione

→ Paziente in SD, prosegue tra

21.07.21: 4° R-miniCHOP
11.08.21: 5° R-miniCHOP
01.09.21: 6° R-miniCHOP



→ rivalutazione

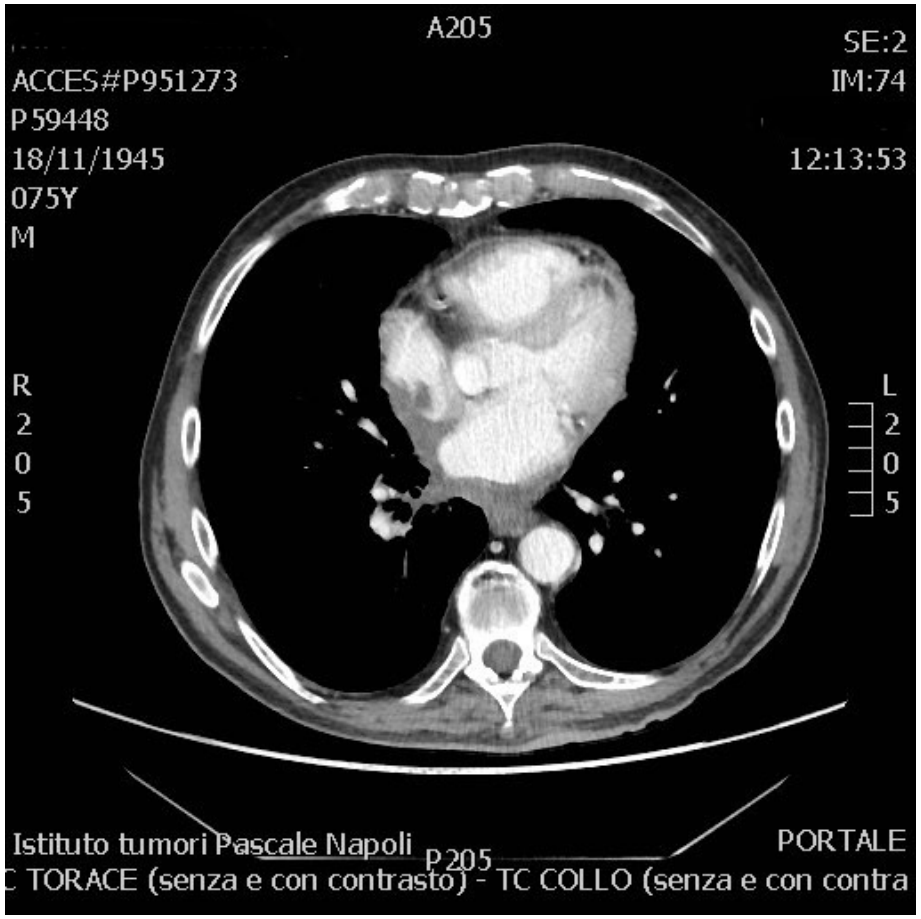
Programma terapeutico di II lin alla tollerabilità) e successiva rivalutazione.

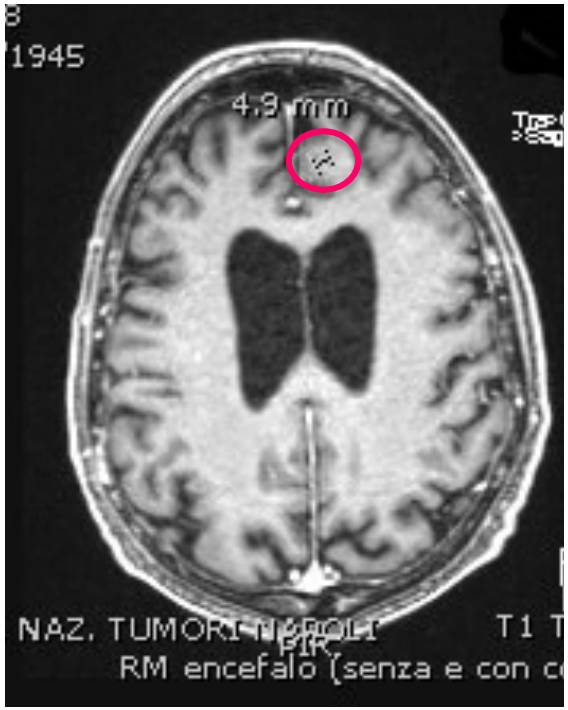
→ pratica 2 cicli ..... To

→ rivalutazione

→ inizia III linea: lenalidomide 15 mg /die 21 gg

→ rivalutazione post 4 ciclo PR... ?





Considerazioni:

1) In corso 5° ciclo … pz as … npletare il ciclo

2) Risposta parziale…. Co…

- Farmaco ben tollerato
- Non gravato da importante tossicità ematologica
- Miglior controllo della malattia sistemica
- Ma…. il passaggio attraverso la barriera ematoencefalica….

BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Biologics License Application (BLA)
Application Number(s)	761163
Priority or Standard	Priority
Submit Date(s)	December 28, 2019
Received Date(s)	December 30, 2019
PDUFA Goal Date	August 30, 2020
Division/Office	Division of Hematologic Malignancies II/Office of Oncologic Diseases
Review Completion Date	07/30/2020
Established Name	tafasitamab-cxix
(Proposed) Trade Name	Monjuvi
Pharmacologic Class	CD-19 directed cytolytic antibody
Code name	MOR208
Applicant	MorphoSys US Inc.
Formulation(s)	Injection
Dosing Regimen	The recommended dose of tafasitamab is 12 mg/kg as an intravenous infusion given according to the following schedule: • Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle • Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle • Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle
Applicant Proposed Indication(s)/Population(s)	In combination with lenalidomide (b) (4) (b) (4) for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for (b) (4) ASCT
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT)

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	There were no unscheduled deaths during the study.
Clinical Signs	Whole body (WB) tremors were observed at low-dose, high-dose and control animals during the dosing period. The number of animals effected and the number of incidences of tremors were higher at the high-dose. The slight whole body tremors occurred on single occasions in low-dose and control males, while the high-dose animals experienced tremors on 2-5 occasions during dosing. In addition, one female at the high-dose experienced severe whole body tremors during the first dose on Day 1 of dosing.
Neurobehavioral Observations	Statistically significant differences in body temperature (100-102°F) were observed in males at 100 mg/kg and females at 30 and 100 mg/kg during dosing that recovered in the recovery period.
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Blood Pressure	Unremarkable
Respiratory Rate	Unremarkable

Summary of whole body tremors observed during dosing

Group/sex	Dose/ mg/kg	Animal #	Tremors	Period	Days
1/M	0	18902M	slight WB	Dosing	43
1/M	0	18907M	slight WB	Dosing	36
2/M	10	18880M	slight WB	Dosing	57
2/M	10	18889M	slight WB	Dosing	43
4M	100	18705M	slight WB	Dosing	15, 22, 36, 43, 64
4F	100	19051F	slight WB	Dosing	1, 8, 15
4F	100	19208F	slight WB	Dosing	8,15, 36, 78
4F	100	19230F	slight WB	Dosing	8, 15, 78
4F	100	19255F	Severe WB	Dosing	1
4F	100	19255F	slight WB	Dosing	8, 15, 78

ICH GCP > US Clinical Trials Registry > Clinical Trial Page

Tafasitamab Plus Lenalidomide in Relapsed CNS Lymphoma

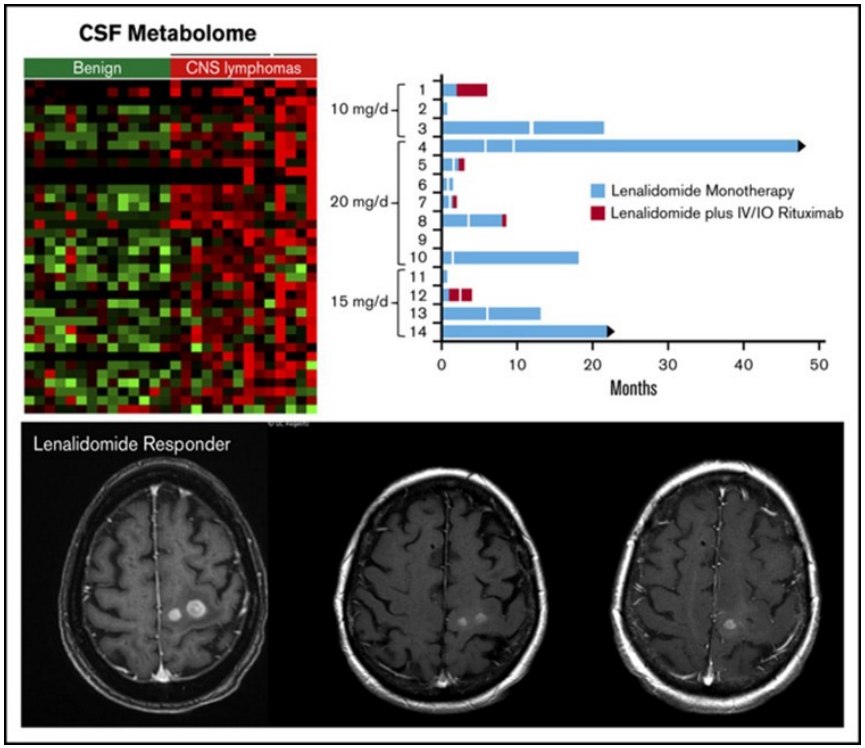
A Phase I/II Study of Tafasitamab Plus Lenalidomide in Relapsed CNS Lymphoma

Sponsors	Lead Sponsor: James Rubenstein Collaborator: Incyte Corporation
Source	University of California, San Francisco
Brief Summary	This is a single arm open-label multicenter phase I/II investigation of combination lenalidomide/Tafasitamab in patients with relapsed central nervous system (CNS) lymphoma. This is the first study to examine a naked anti-CD19 monoclonal antibody in relapsed CNS lymphoma patients as well as the combination of anti-CD19 antibody plus an Immunomodulatory imide drugs (IMiDs) in CNS lymphomas. This study will also test the novel hypothesis that Tafasitamab enhances blood-brain barrier permeability, a potential property that could have broad clinical implications.

PRIMARY OBJECTIVES: I. To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of lenalidomide in combination with Tafasitamab in patients with relapsed central nervous system (CNS) lymphoma (Phase 1). II. To evaluate the clinical benefit rate of Tafasitamab in combination with lenalidomide in relapsed CNS lymphoma (Phase 2). **SECONDARY OBJECTIVES**: I. To describe the toxicities of Tafasitamab in combination with lenalidomide in relapsed CNS lymphoma. II. To describe the efficacy of Tafasitamab in combination with lenalidomide in relapsed CNS lymphoma. **EXPLORATORY OBJECTIVES**: I. To obtain pilot information about CSF penetration of Tafasitamab as well as CSF partition coefficient of lenalidomide in combination with Tafasitamab to evaluate possibility that Tafasitamab enhances CSF penetration of lenalidomide to an extent greater than CSF/plasma partition coefficient of lenalidomide which was 20% at 15 and 20 milligram (mg) dose levels. II. To evaluate the relationship between tumor mutational profile and response to Tafasitamab plus lenalidomide, via whole exome sequencing of diagnostic specimens. II. To evaluate change in immune cell phenotypes in CSF and blood in patients via flow-cytometry of natural killer (NK) cell, T-cells and CSF monocytes/macrophages in patients treated with combination Tafasitamab plus lenalidomide. IV. To evaluate the relationship between CSF cytokine microenvironment such as Interleukin-10 (IL-10), Chemokine ligand 13 (CXCL13), etc. as well as CSF metabolites, including energy metabolites and neurotransmitters, and response to combination Tafasitamab plus lenalidomide Tafasitamab, PFS, OS, and neurocognitive endpoints. V. To test the hypothesis that Tafasitamab in combination with lenalidomide impacts blood-brain barrier permeability associated with CNS lymphoma lesions, as assessed by albumin levels and MRI vascular permeability imaging metrics. VI. To explore the correlation between immune cell subsets and response and/or resistance to lenalidomide/Tafasitamab. VII. To evaluate the relationship between Minimal Residual Disease status (MRD) and response and PFS using either circulating tumor DNA or Clonoseq technologies. STUDY DESIGN: This is a single arm open-label multicenter phase I/II investigation of combination lenalidomide/Tafasitamab in patients with relapsed CNS lymphoma.During the phase 1 portion of the study, the investigators will examine three dose levels of Lenalidomide (10mg, 15mg and 20mg) in combination with Tafasitamab at a dose of 12 mg/kg. After MTD/RP2D is determined during phase 1, the phase 2 portion of the study will begin enrollment to the established dose. Participants will be followed for AEs 90 days after last dose/decision to discontinue treatment, or new treatments are administered and followed for overall survival/disease status for up to 1 year after last dose. Participants may continue study treatment until disease progression.

Phase 1 (Tafasitamab, Lenalidomide)
Participants will be given 12mg of Tafasitamab on days 1, 4, 8, 15, and 22 of cycle 1, days 1, 8, 15, and 22 of cycles 2 & 3, and days 1 and 15 for any cycle thereafter. Participants will also be given daily Lenalidomide on days 1-21 of each cycle.

Phase 2 (Tafasitamab, Lenalidomide)
Participants will be given 12mg of Tafasitamab on days 1, 4, 8, 15, and 22 of cycle 1, days 1, 8, 15, and 22 of cycles 2 & 3, and days 1 and 15 for any cycle thereafter. Participants will also be given daily Lenalidomide on days 1-21 of each cycle at the recommended phase 2 dose.



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