CAR-TALKING

News dal mondo CAR-T

Milano, Starhotels E.c.ho.
4 aprile 2023

CAR-T nel DLBCL dalla terza linea

Caso Clinico 1

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Ematologia
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Disclosures, Annalisa Chiappella

Company name	Advisory board	Educational activities/Lecture fees
Astrazeneca		x
Celgene-BMS	x	x
Gilead-Sciences	x	x
Ideogen	x	
Incyte		x
Janssen-Cilag	x	x
Novartis		x
Roche	x	x
SecuraBIO	x	
Takeda	x	x

Maschio, 62 anni

APR:
2019: adenoCa polmone sottoposto a lobectomia polmonare superiore dx + chemoterapia neoadiuvante.
2019 → 2021: controlli negativi per recidiva della neoplasia polmonare.

Novembre 2021
- ✓ Comparsa di adenopatie laterocervicali e sovraclaveari bilaterali; rinolalia
- ✓ Sintomi sistemici B
- ✓ LDH 428 (max 220)
- ✓ ECOG PS 2
- ✓ TAC/PET total body: ipercaptazione della parete posteriore del rinofaringe, regione tonsillare; plurime e confluenti adenopatie in quasi tutte le stazioni linfonodali sovra e sottodiaframmatiche; captazione splenica; captazioni sottocutanee; captazione ossea diffusa
- ✓ RMN encefalo: infiltrazione ORL e parotidea; ipertrofia ghiandole lacrimali e muscoli retti inferiori, palpebre, nervi infraorbitari

Maschio, 62 anni

Novembre 2021

- ✓ Biopsia linfonodale: **DLBCL non-GCB sec. Hans, Ki-67 95%, BCL2 (100%)** e c-MYC (20%) in immunoistochimica, FISH negativa per traslocazioni BCL2, BCL6 e C-MYC
- ✓ MYD88 positivo
- ✓ Biopsia osteomidollare e aspirato midollare: infiltrato da parte di linfoma a grandi cellule B del 55%
- ✓ Rachicentesi diagnostica: citoflussimetria compatibile con meningosi linfomatosa

DLBCL non-GCB sec. Hans, Ki-67 95%, BCL2 (100%), IPI 4, CNS-IPI 4, stadio IV B
R-CODOX-M/R-IVAC

Terapia di induzione complicata da: insufficienza renale acuta durante Mtx e infezione Sars-Cov2 sintomatica.

Maschio, 62 anni

DLBCL non-GCB sec. Hans, Ki-67 95%, BCL2 (100%), IPI 4, CNS-IPI 4, stadio IV B
R-CODOX-M/R-IVAC

Terapia di induzione complicata da: insufficienza renale acuta durante Mtx e infezione Sars-Cov2 sintomatica, risolte senza sequele.

Rivalutazione di malattia:
- Aspirato midollare e biopsia osteomidollare negativi
- Rachicentesi: citoflussimetria negativa
- RMN encefalo: regredita l'ipertrofia dei nervi infraorbitari
- PET: Persistenza di malattia linfonodale e ORL; Deauville Score 5.

Eseguita linfocitoaferesi per CAR-T
Eseguita II linea: R-Gemox, con progressione dopo un ciclo di terapia.

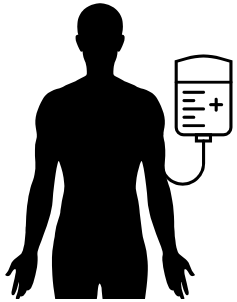
Patient selection is primarily guided by the AIFA approved indications

- Age 18-75 (axi-cel and tisa-cel); ≥ 18 (brexu-cel)
- Histotypes according to product specification
- Active uncontrolled infections → no use
- ECOG > 1 → no use
- HBV/HCV/HIV active infection → no use
- Venous thrombosis in the last six months → no use
- Active CNS disorder or primary CNS lymphoma → selected cases
- Previous allo-SCT → selected cases
- Adequate renal (eGFR > 60 ml/min), hepatic, pulmonary or cardiac function (LVEF >50%)
- Prior anti-CD19 therapy → repeat biopsy to prove the presence of CD19
- ANC > 1000, Hb > 8, PLTS > 75.000, ALC >100

CAR T-Cell Therapy: more than one step

Leukapheresis

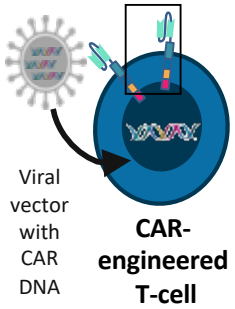
Collect patient's white blood cells

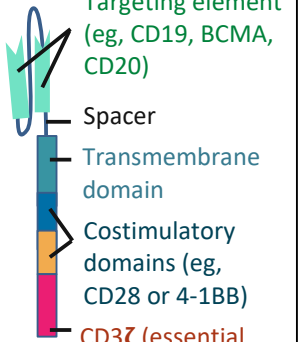


Manufacturing

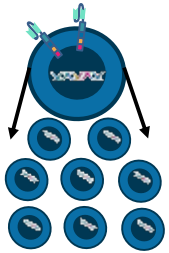
Isolate and activate T-cells

Engineer T-cells with CAR gene





Expand CAR T-cells

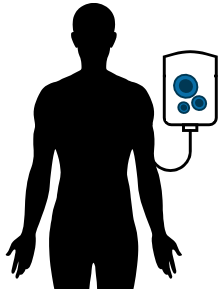


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Infusion

Infuse same patient with CAR T-cells



Activity

Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

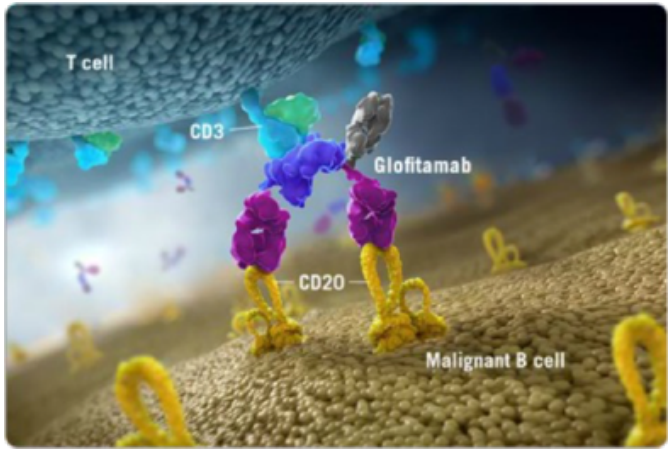
Bridging therapy?

The NEW ENGLAND JOURNAL of MEDICINE N ENGL J MED 387;24 NEJM.ORG DECEMBER 15, 2022

ORIGINAL ARTICLE

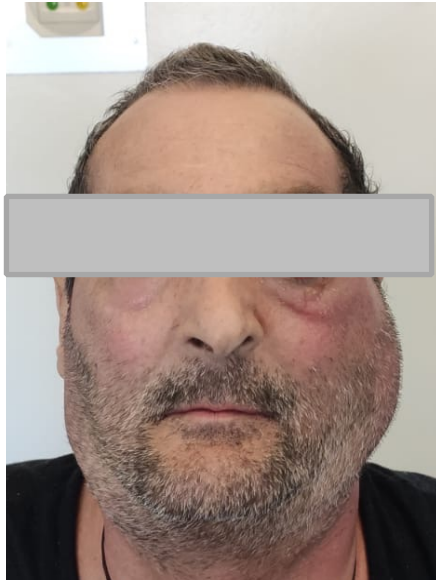
Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Michael J. Dickinson, Carmelo Carlo-Stella, Franck Morschhauser, Emmanuel Bachy, Paolo Corradini, Gloria Iacoboni, Cyrus Khan, Tomasz Wrobel, Fritz Offner, Marek Trněny, Shang-Ju Wu, Guillaume Cartron, Mark Hertzberg, Anna Sureda, David Perez-Callejo, Linda Lundberg, James Relf, Mark Dixon, Emma Clark, Kathryn Humphrey, and Martin Hutchings



Male, 62 years, DLBCL non-GCB sec. Hans, Ki-67 95%, BCL2 (100%), IPI 4, CNS-IPI 4, stage IV B
Primary refractory to R-CODOX-M/R-IVAC; R-Gemox.
Bridging therapy: Glofitamab.

23/JUN/2022



25/JUL	I inf	2.5 mg
01/AUG	II inf	10 mg
08/AUG	III inf	30 mg
31/AUG	IV inf	30 mg
21/SEP	V inf	30 mg

20/SEP/2022

Male, 62 years, DLBCL non-GCB sec. Hans, Ki-67 95%, BCL2 (100%), IPI 4, CNS-IPI 4, stage IV B
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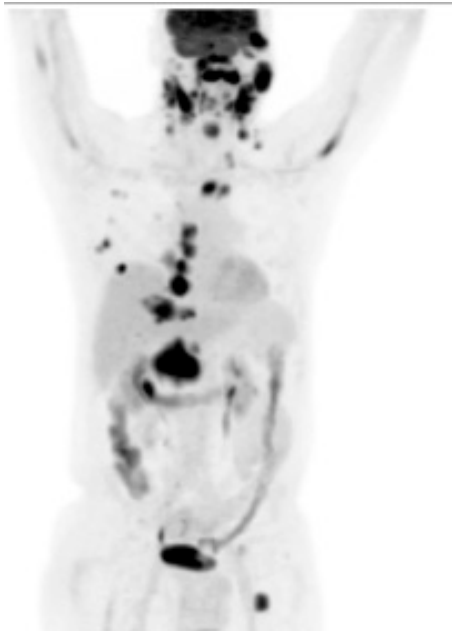

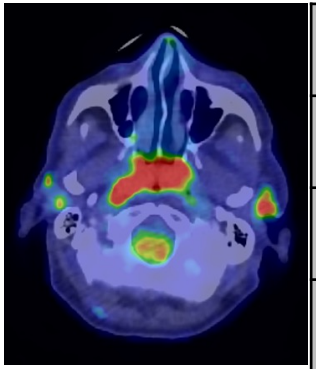

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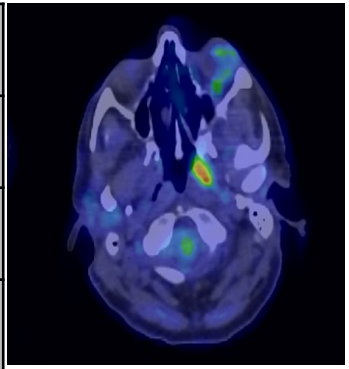

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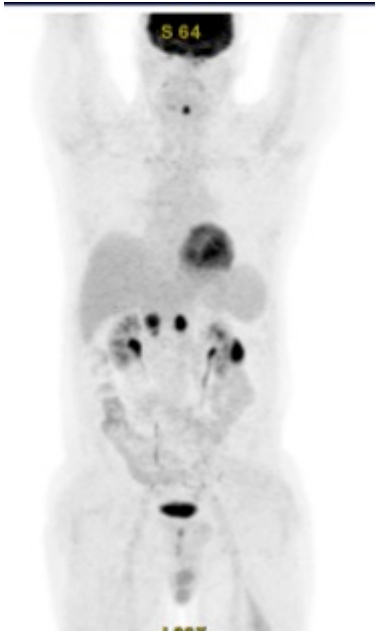

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Primary refractory to R-CODOX-M/R-IVAC; R-Gemox.
Bridging therapy: Glofitamab.

The patient achieved a clinical condition in terms of control disease (PR) and ECOG PS (0) that allowed the use of CAR-T cells.

Lymphodepleting chemotherapy: Bendamustine 90 mg/mq

09/NOV/2022: CAR-T Tisa-cel infusion

- ✓ CRS grade 1
- ✓ ICANS 0
- ✓ Grade 4 neutropenia

Tixagevimab+Cilgavimab as SarsCov2 prophylaxis

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

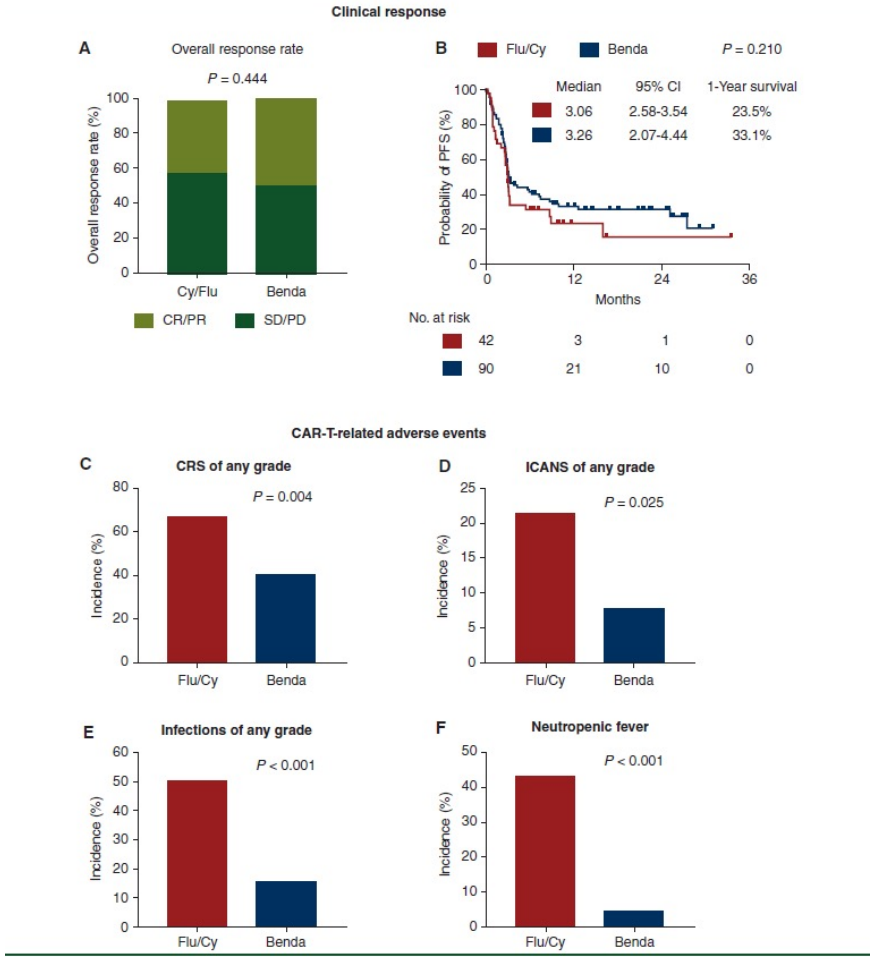
Volume 33 ■ Issue 9 ■ 2022

ANNALS OF ONCOLOGY driving innovation in oncology

Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas

G. Ghilardi[1,2,3†], E. A. Chong[1,2,3†], J. Svoboda[1,2,3], P. Wohlfarth[4], S. D. Nasta[1,3], S. Williamson[5], J. D. Landsburg[1,3], J. N. Gerson[1,3], S. K. Barta[1,2,3], R. Pajarillo[1,2,3], J. Myers[5], A. I. Chen[5], L. Schachter[5], R. Yelton[1,2], H. J. Ballard[1,3], A. Hodges Dwinal[5], S. Gier[2,3], D. Victoriano[2,3], E. Weber[1,3], E. Napier[1,3], A. Garfall[2,3], D. L. Porter[1,3], U. Jäger[4], R. T. Maziarz[5], M. Ruella[1,2,3†] & S. J. Schuster[1,2,3*†]

Characteristics	Total population $N = 132$ (100%)	Flu/Cy $N = 42$ (31.8%)	Benda $N = 90$ (68.2%)	P
Sex, *n* (%)				
Female	50 (37.9)	16 (38.1)	34 (37.8)	0.972
Male	82 (62.1)	26 (61.9)	56 (62.2)	
Age at infusion (median [IQR])	65 [56-70]	67 [56-73]	65 [56-70]	0.222
Diagnosis, *n* (%)				
DLBCL NOS	66 (50.0)	27 (64.3)	39 (43.3)	0.128
HGBCL NOS	5 (3.8)	1 (2.4)	4 (4.4)	
tFL	47 (35.6)	12 (28.6)	35 (38.9)	
HGBCL with MYC and BCL2 and/ or BCL6 rearrangements	14 (10.6)	2 (4.8)	12 (13.3)	
Center, *n* (%)				
University of Pennsylvania	90 (68.2)	5 (11.9)	85 (94.4)	<0.001
Oregon Health & Science University	35 (26.5)	35 (83.3)	0 (0.0)	
University of Vienna	7 (5.3)	2 (4.8)	5 (5.6)	
ECOG PS, *n* (%)				
0-1	124 (93.9)	39 (92.9)	85 (94.4)	0.722
≥2	8 (6.1)	3 (7.1)	5 (5.6)	
Renal function, *n* (%)				
Normal	108 (81.8)	32 (76.2)	76 (84.4)	0.252
Reduced	24 (18.2)	10 (23.8)	14 (15.6)	
Previous ASCT, *n* (%)				
No	104 (78.8)	31 (63.8)	73 (81.1)	0.339
Yes	28 (21.2)	11 (26.2)	17 (18.9)	
N of previous lines of therapy (median [IQR])	3 [3-4]	3 [2-4]	3 [3-4]	0.569
Serum LDH ($N = 131$)				
Normal, *n* (%)	68 (51.9)	20 (47.6)	48 (53.9)	0.500
Elevated, *n* (%)	63 (48.1)	22 (52.4)	41 (46.1)	
Pre-LD CRP ($N = 54$)				
Normal, *n* (%)	34 (63.0)	13 (65.0)	21 (61.8)	0.812
Elevated, *n* (%)	20 (37.0)	7 (35.0)	13 (38.2)	
Pre-LD ferritin ($N = 52$)				
Normal, *n* (%)	28 (53.8)	11 (55.0)	17 (53.1)	0.895
Elevated, *n* (%)	24 (46.2)	9 (45.0)	15 (46.9)	
Bulky disease (>10 cm), *n* (%)				
No	119 (90.2)	36 (85.7)	84 (92.2)	0.242
Yes	13 (9.8)	6 (14.3)	7 (7.8)	
Bridging therapy, *n* (%)				
No	27 (20.5)	11 (26.2)	16 (17.8)	0.264
Yes	105 (79.5)	31 (73.4)	74 (82.2)	



CLINICAL CANCER RESEARCH

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS

In vivo expansion is associated with response and survival

Article Contents

Abstract

Supplementary data

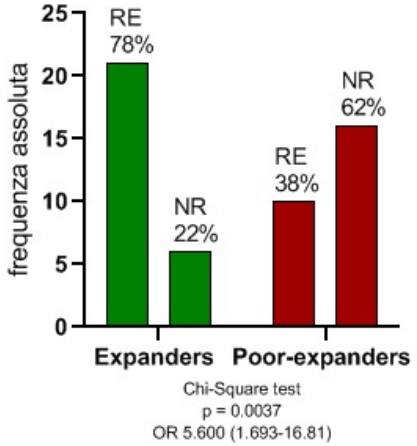
RESEARCH ARTICLE | MAY 18 2022

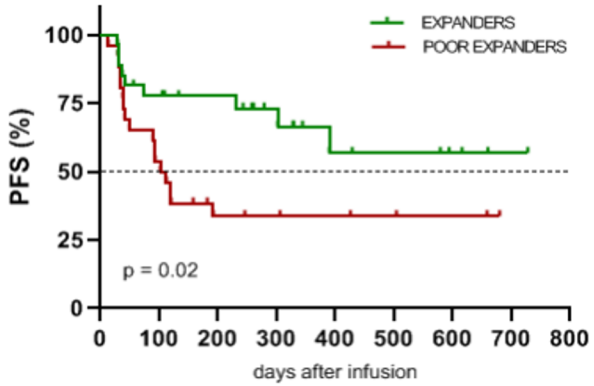
Phenotypic composition of commercial anti-CD19 CAR-T cells affects *in vivo* expansion and disease response in large B-cell lymphoma patients

Chiara Monfrini; Federico Stella; Vanessa Aragona; Martina Magni; Silva Ljevar; Cristina Vella; Eugenio Fardella; Annalisa Chiappella; Francesca Nanetti; Martina Pennisi; Anna Dodero; Anna Guidetti; Paolo Corradini; Cristiana Carniti

median C_{10}: it was selected to dichotomize the population into **Expanders** & **Poor-Expanders**

Response → CR + PR by day 90 after CAR T





C_{10} could represent an early biomarker to predict response and survival in vivo on an individual patient level, regardless of the IP used

Male, 62 years, DLBCL non-GCB sec. Hans, Ki-67 95%, BCL2 (100%), IPI 4, CNS-IPI 4, stage IV B
Primary refractory to R-CODOX-M/R-IVAC; R-Gemox.
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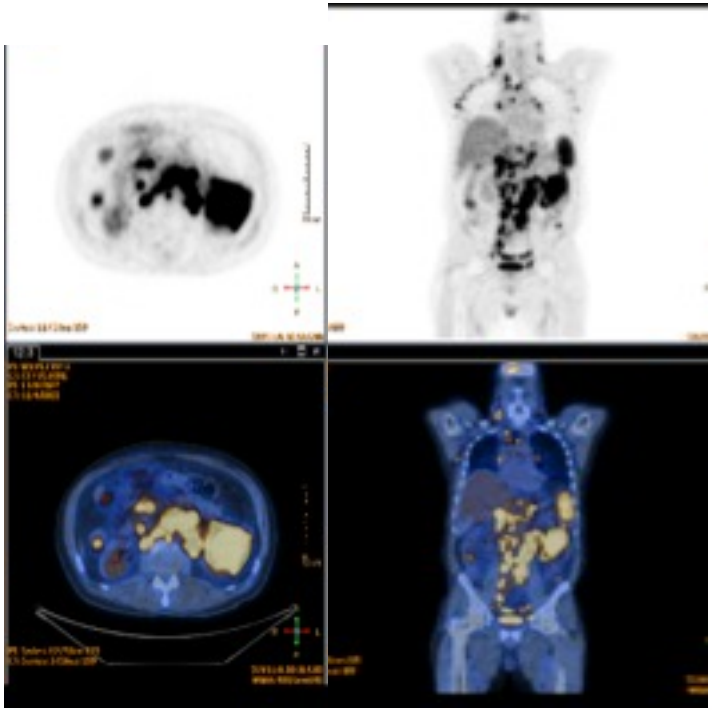
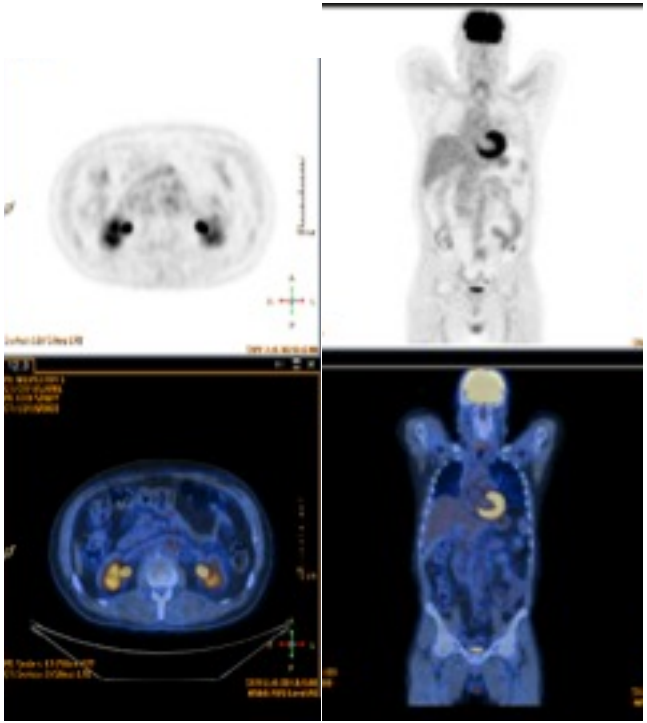
Before CAR-T infusion



Day + 30 CR → Day +90 CR



Acknowledgments

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI
Sistema Sanitario Regione Lombardia

CAR-T Team @INT

Hematology	**Paolo Corradini** Annalisa Chiappella, Anna Dodero Anna Guidetti, Martina Pennisi
Hematology Lab	Cristiana Carniti, Martina Magni
Apheresis Unit	Flavio Arienti, Paola Coluccia
Tissue Establishment	Michele Magni, Paolo Longoni
Neurology	Fabio Simonetti, Davide Rossi
Intensive Care Unit	Franco Valenza, Luca Fumagalli
Pharmacy	Vito Ladisa, Barbara Re, Erika Cataldo
Study coordinator	Anisa Bermema
Study nurses	Ilaria Lo Russo, Chiara Ghidoli
Head Nurses	Giorgia Gobbi, Lucia Saracino
Nuclear Medicine	Alessandra Alessi
Radiotherapy	Sabina Vennarini, Filippo Patti, Emilia Pecori
Radiology	Rodolfo Lanocita, Davide Scaramuzza
Cardiology	Fabio Turazza, Irina Arendar
Biostatistics Unit	Rosalba Miceli, Silva Ljevar

All the Referral centers, patients, families and nurses
All the CAR-T teams: