Eppur si muove...

La terapia nel MONDO LINFOMI

Gli studi osservazionali retrospettivi come comparazione di confronto: la valutazione statistica

ROMA, 26 MAGGIO 2022

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Centro di Ricerche B-ASC

Disclosure

AB – Incyte

Obiettivo dell'incontro

- Supporto **metodologico** per capire come interpretare i risultati degli studi a supporto di tafasitamab

Le *3-E* a sostegno di un trattamento

Can it work? Does it work? Is it worth it?

Brian Haynes

BMJ 1999;319;652-653

Le *3-E* a sostegno di un trattamento

RCT

Efficacia Teorica

Funzionerà?

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Le *3-E* a sostegno di un trattamento

Pre Marketing

EFFICACY

+ Safety
(Small Population)

RCT
Efficacia Teorica
Funzionerà?

Tafasitamab funzionerà?

Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr, Gianluca Gaidano, Marc André, Nagesh Kalakonda, Martin Dreyling, Johannes Weirather, Maren Dirnberger-Hertweck, Sumeet Ambarkhane, Günter Fingerle-Rowson, Kami Maddocks*

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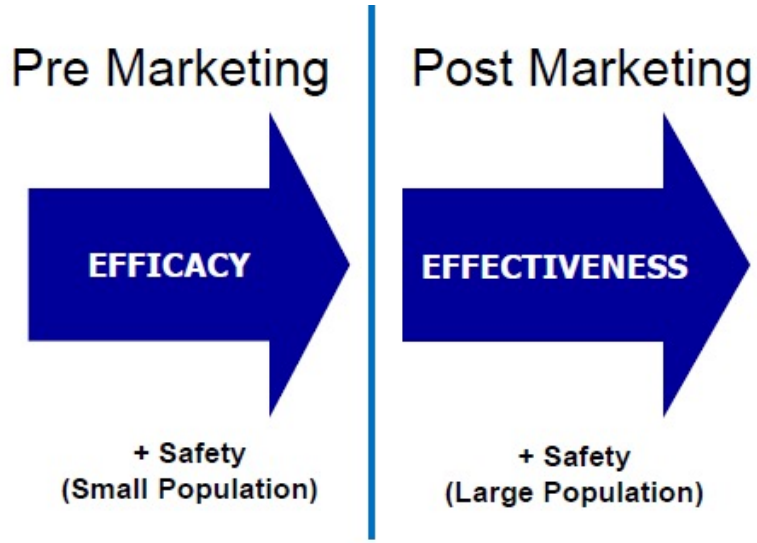

RCT
Efficacia Teorica
Funzionerà?

REAL WORLD
Efficacia pratica clinica
Funziona?

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Le *3-E* a sostegno di un trattamento

RCT
Efficacia Teorica
Funzionerà?

REAL WORLD
Efficacia pratica clinica
Funziona?

Tafasitamab funziona nella pratica clinica?

Can it work? Does it work? Is it worth it?

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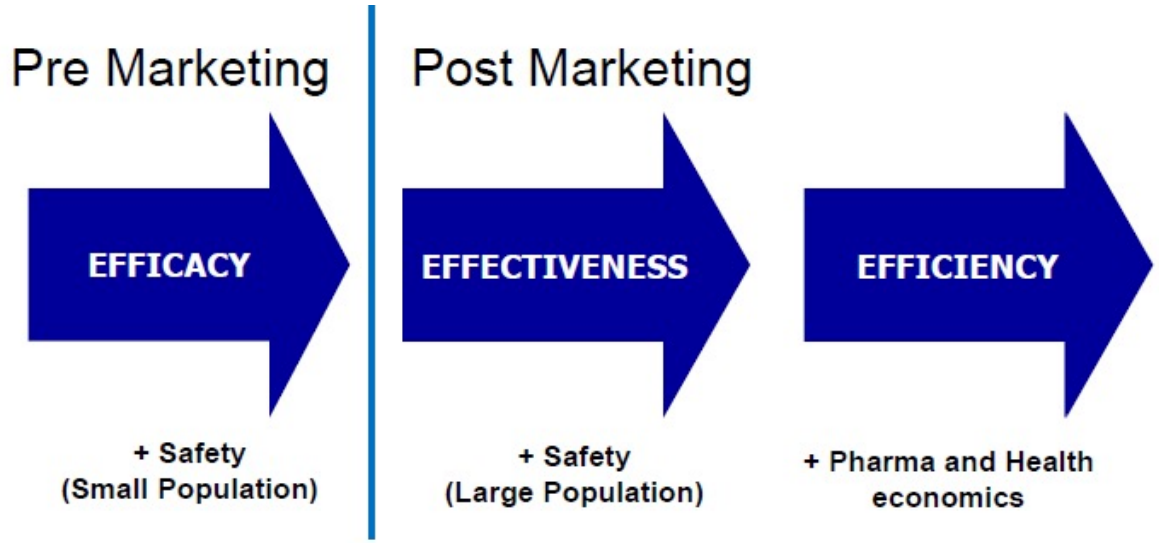
Le *3-E* a sostegno di un trattamento



RCT
Efficacia Teorica
Funzionerà?

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Efficacia pratica clinica
Funziona?

Include i COSTI
Efficienza
Conviene?

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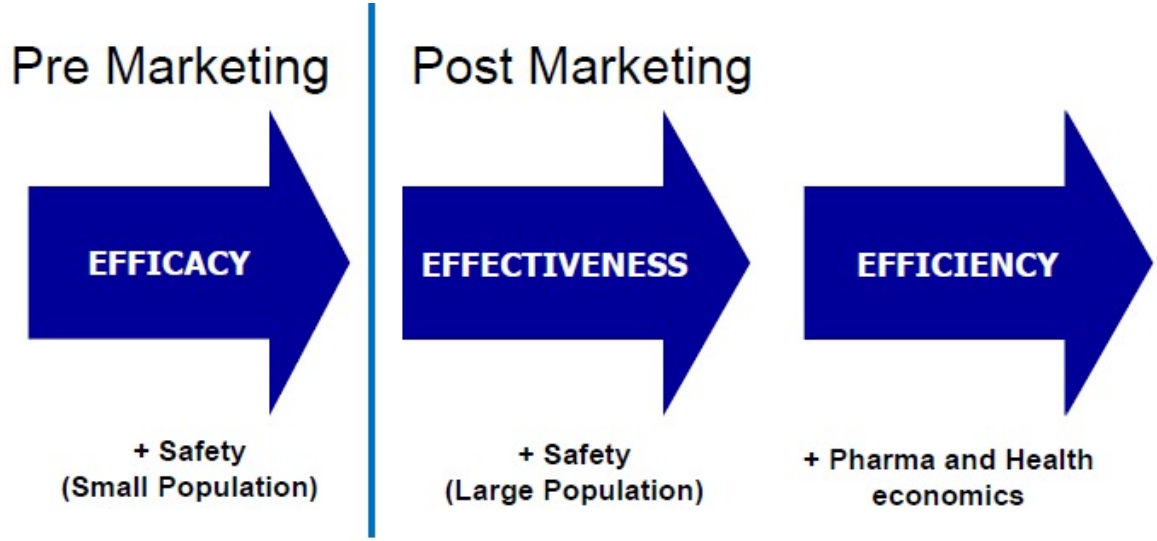
Le *3-E* a sostegno di un trattamento



RCT
Efficacia Teorica
Funzionerà?

REAL WORLD
Efficacia pratica clinica
Funziona?

Include i COS
Efficienza
Conviene?

Tafasitamab conviene?

NICE National Institute for Health and Care Excellence

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Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

In development [GID-TA10645] Expected publication date: 10 August 2022

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2021, VOL. 24, NO. S1, 14–24
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Article 0184-RT.R1/2007704

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ORIGINAL RESEARCH

OPEN ACCESS Check for updates

NEW

Economic evaluation of polatuzumab-bendamustine-rituximab *vs.* tafasitamab-lenalidomide in transplant-ineligible R/R DLBCL

Matthias Calamia[a,b], Ali McBride[b,c,d] and Ivo Abraham[b,c,d]

[a]School of Pharmacy, Utrecht University, Utrecht, Netherlands; [b]Center of Health Outcomes and PharmacoEconomic Research, Tucson, AZ, USA; [c]College of Pharmacy, University of Arizona, Tucson, AZ, USA; [d]Cancer Center, University of Arizona, Tucson, AZ, USA

ABSTRACT

Aim: Polatuzumab vedotin-bendamustin-rituximab (PBR) and tafasitamab-lenalidomide (Tafa-L) were approved recently for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) in autologous stem cell transplant (ASCT) ineligible patients. We performed an industry-independent pharmacoeconomic evaluation of both regimens over a 5-year (y) time horizon (US payer perspective; 2020 USD).

Methods: Survival curves, treatment costs, and utility values were applied in a three-state Markov model (progression-free survival (PFS), post-progression survival (PPS), death) to estimate the incremental follow-up (ICER) and cost-utility ratios (ICUR). A novel metric of the incremental cost per 1% gain in the probability of achieving objective response (OR), PFS, and OS were estimated.

Results: Five-year Tafa-L costs ($470,119) exceeded PBR's ($249,217) by $220,902 with incremental gains of 0.71 life-years (LY) and 0.32 quality-adjusted life-years (QALY); yielding ICER of $310,041/LYg and ICUR of $694,241/QALYg. Tafa-L had favorable PFS and OS rates over PBR with adjusted differences of +19.2 and +34.1%, respectively at trial follow-up (~2 years), with corresponding 5 years differences in survival of +7.8% in PFS and +21.4% in OS. The incremental cost per 1% gain in the probability of achieving OR, PFS and OS at follow-up were $8,479, $6,359, and $3,583; and $28,321 and $10,323 for PFS and OS at 5 years.

Conclusion: The sustained Tafa-L treatment demonstrated better survival outcomes than 6-cycle PBR though at a greater cost. The incremental costs to gain a 1% improvement in 2 and 5 years survival outcomes with Tafa-L over PBR were modest, underscoring the longer-term benefit of Tafa-L over PBR in patients ineligible for or opting out of ASCT.

ARTICLE HISTORY
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Accepted 4 November 2021

KEYWORDS
R/R DLBCL; lymphoma; tafasitamab; polatuzumab; cost-effectiveness

JEL CLASSIFICATION CODES
I10; I19

Transparency

Declaration of funding

This economic evaluation was performed independently without external funding.

Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr, Gianluca Gaidano, Marc André, Nagesh Kalakonda, Martin Dreyling, Johannes Weirather, Maren Dirnberger-Hertweck, Sumeet Ambarkhane, Günter Fingerle-Rowson, Kami Maddocks*

Quesito 1

L'efficacia osservata può essere dovuta solo da lena in mono?

⇩

Studio RE-MIND

Quesito 2

Tafa+lena è più efficace degli attuali trattamenti standard of care?
(Valore terapeutico aggiunto)

⇩

Studio RE-MIND 2

Published OnlineFirst August 25, 2021; DOI: 10.1158/1078-0432.CCR-21-1471

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma

Pier Luigi Zinzani[1], Thomas Rodgers[2], Dario Marino[3], Maurizio Frezzato[4], Anna Maria Barbui[5], Claudia Castellino[6], Erika Meli[7], Nathan H. Fowler[8], Gilles Salles[9], Bruce Feinberg[10], Nuwan C. Kurukulasuriya[11], Sascha Tillmanns[12], Stephan Parche[11], Debarshi Dey[11], Günter Fingerle-Rowson[11], Sumeet Ambarkhane[11], Mark Winderlich[11], and Grzegorz S. Nowakowski[12]

1. Focus disegno dello studio RE-MIND

www.clinicaltrial.gov
NCT02399085

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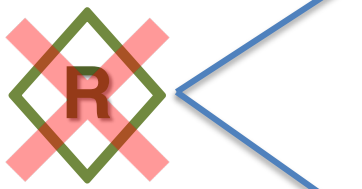
Günter Fingerle-Rowson[11], Sumeet Ambarkhane[11],

ABSTRACT

Purpose: Tafasitamab, an Fc-modified, humanized, anti-CD19 monoclonal antibody, in combination with lenalidomide, demonstrated efficacy in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), in the single-arm, phase II L-MIND study (NCT02399085). RE-MIND, a retrospective observational study, generated a historic control for L-MIND to delineate the contribution of tafasitamab to the efficacy of the combination.

Disegno dello studio comparativo – NON Randomizzato

Braccio di confronto storico

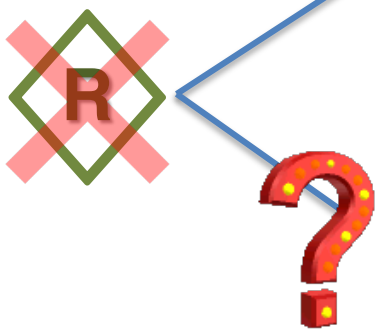


TAFA + Lena (n=**81** pazienti dello studio clinico L-Mind)

Lena in mono (n=**490** pazienti trattati nella pratica clinica con lena – coorte retrospettiva → RE-MIND)

Disegno dello studio comparativo – NON Randomizzato

Braccio di confronto storico



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Lena in mono (n=**490** pazienti trattati nella pratica clinica con lena – coorte retrospettiva → RE-MIND)

For relevant baseline patient and disease characteristics, balance between cohorts was achieved using propensity score-matching and weighting to minimize confounding effects (19). To enable adequate cohort balancing, a sample size of 500 patients was projected for the lenalidomide-monotherapy cohort. Estimated propensity score

Perché circa 500 pz?
Sample size calculation

Disegno dello studio comparativo NON Randomizzato Sui pazienti appaiati

Results: Data from 490 patients going through lenalidomide monotherapy were collected; 140 qualified for matching with the L-MIND cohort. The primary analysis included 76 patients from each cohort who received a lenalidomide starting dose of 25 mg/day.

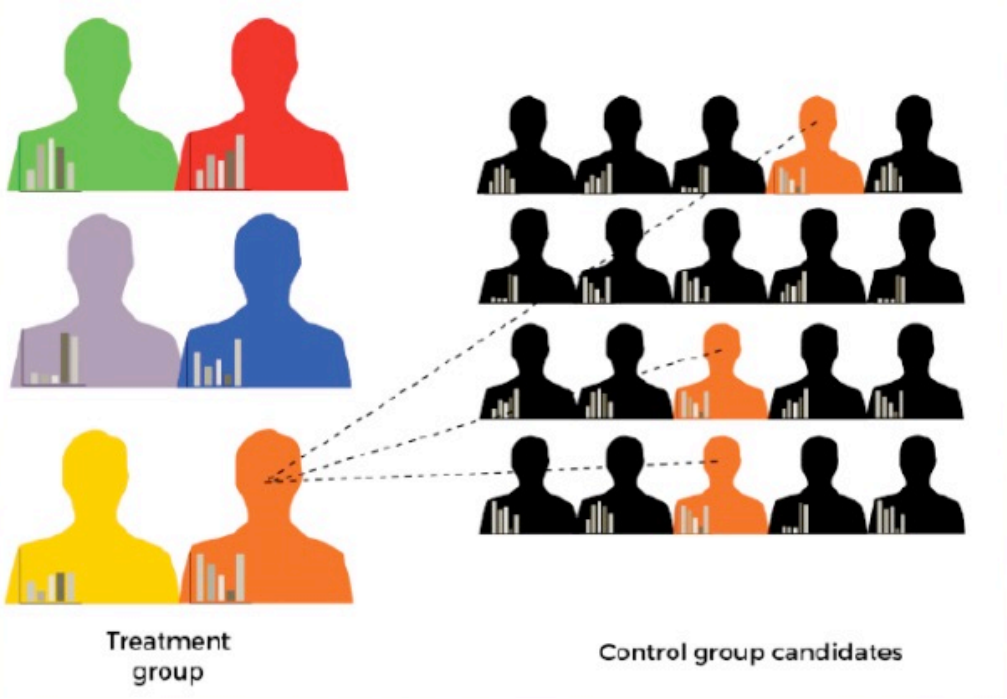
Pz appaiati

R

TAFA + Lena (n=**76** pazienti dello studio clinico L-Mind)

Lena in mono (n=**76** pazienti trattati nella pratica clinica con lena – coorte retrospettiva → RE-MIND)

Disegno dello studio comparativo NON Randomizzato
Tecnica di appaiamento dei pz: PROPENSITY SCORE MATCHING



Pz più simili possibili per le variabili cliniche prognostiche

Tafa+lena
L-MIND

Lena in mono
RE-MIND

Disegno dello studio comparativo NON Randomizzato
Tecnica di appaiamento dei pz: PROPENSITY SCORE MATCHING

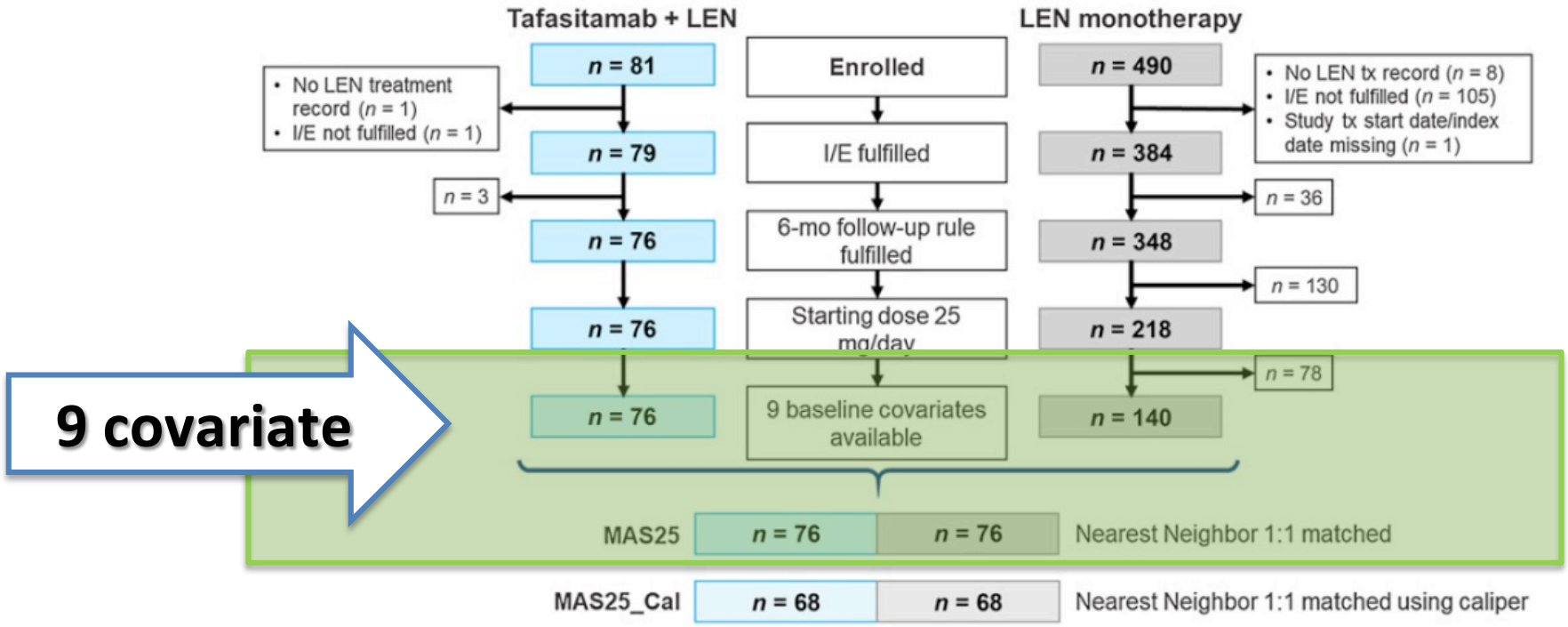


Figure 1.

RE-MIND: patient disposition. I/E, inclusion or exclusion criteria; LEN, lenalidomide; MAS25, matched analysis set 25; MAS25_Cal, matched analysis set 25 with use of caliper; mo, month; tx, treatment.

Disegno dello studio comparativo NON Randomizzato
Variabili clino prognostiche al basale di appaiamento
SONO CLINICAMENTE RILEVANTI?

9.2.2 General Aspects of Cohort Balancing

Comparable patient populations from the observational cohort and the L-MIND cohort in respect to the following baseline covariates will be created:

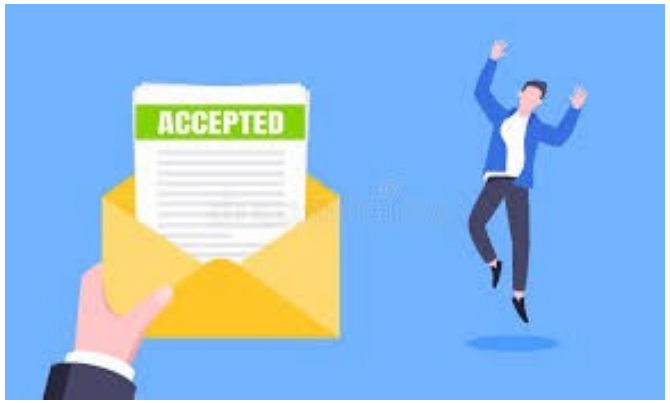
- age (as categorical variable with subgroups <70 vs. ≥70 years of age),
- Ann Arbor Stage (I/II vs. III/IV),
- refractoriness to last therapy line (Yes vs. No),
- number of previous lines of therapy (1 vs. 2/3),
- history of primary refractoriness (Yes vs. No),
- prior ASCT (Yes vs. No),
- neutropenia (cut-off <1.5 x 10^9/L) (Yes vs. No),
- anemia (cut-off <10 g/dL) (Yes vs. No) and
- elevated lactate dehydrogenase (LDH) levels (>upper limit of normal [ULN]) (Yes vs. No).

Disegno dello studio comparativo NON Randomizzato

Calcolo del sample size

Sample-size calculation

With 81 patients enrolled in L-MIND, the ePS-based 1:1 matching would result in a sample size of maximum $n = 2 \times 81$. With an assumed difference of 23% in ORR for lenalidomide monotherapy (35%) versus the tafasitamab–lenalidomide combination (58%), the achieved power was 80% and the minimal detectable statistical difference in ORR was 17% using Fisher's exact test for unpaired data. To enable adequate cohort balancing (SMD of ≤0.2 for all covariates), a sample size of 500 patients was projected for the lenalidomide-monotherapy cohort.

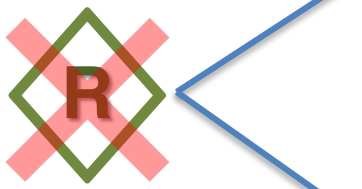


2. Focus disegno dello studio RE-MIND 2

Tutto pre-specificato nel protocollo
NCT04697160

Disegno dello studio comparativo – NON Randomizzato

Braccio di confronto storico

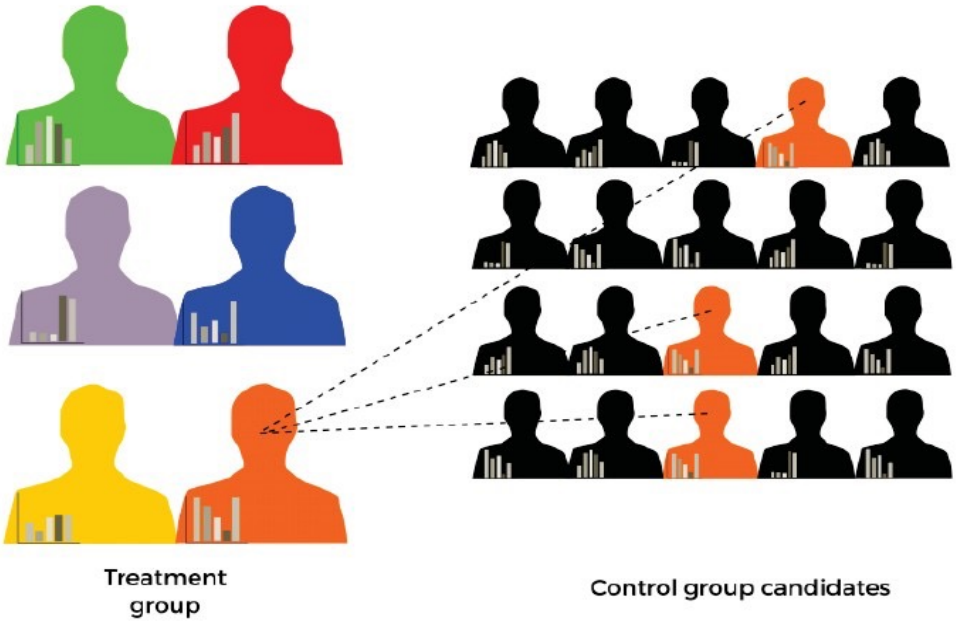


TAFA + Lena (n=**81** pazienti dello studio clinico L-Mind)

SoC (n=**3454** pazienti trattati nella pratica clinica con SoC – coorte retrospettiva→ RE-MIND2)

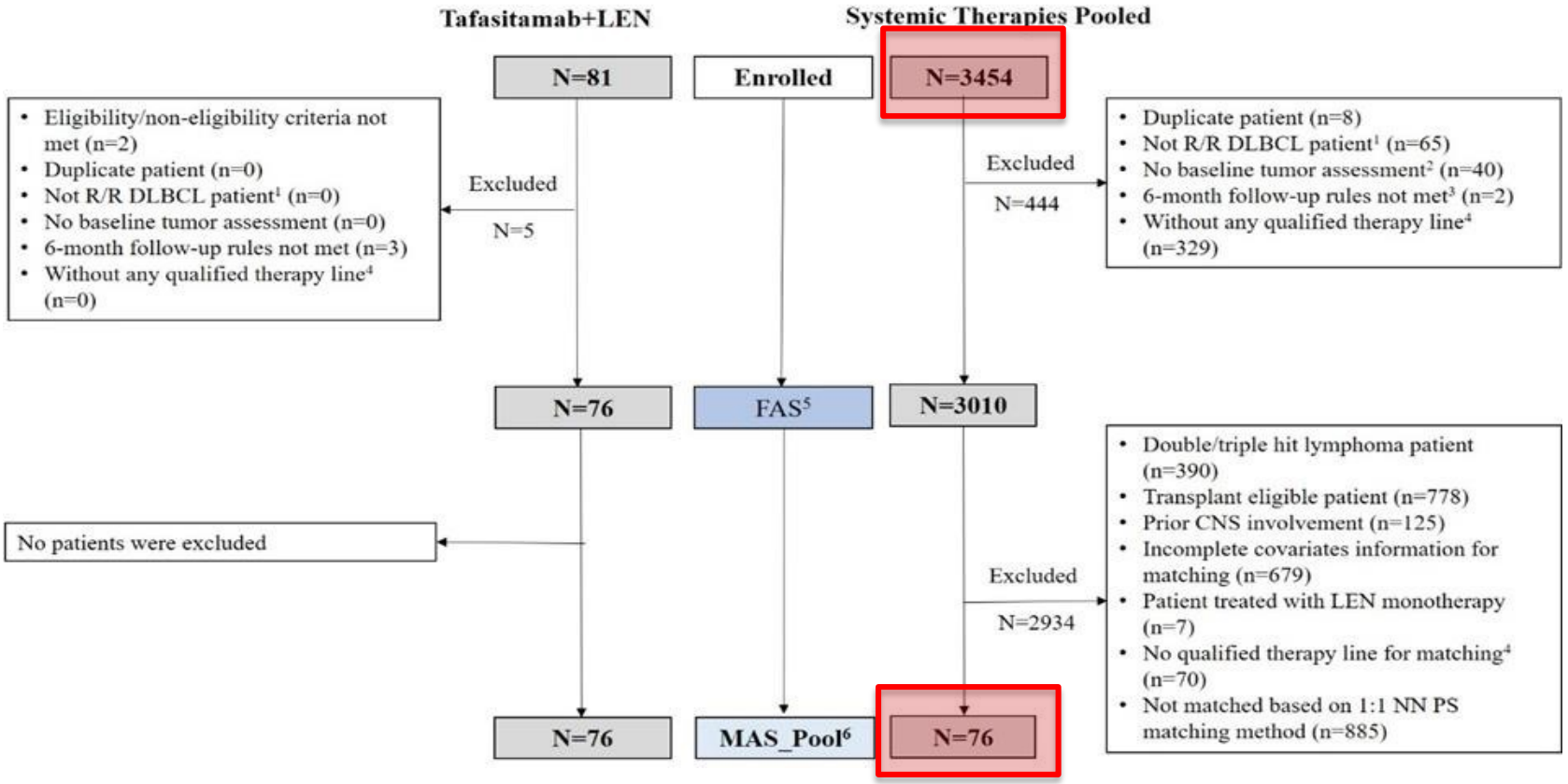
Disegno dello studio comparativo – NON Randomizzato

Tecnica di appaiamento dei pz: PROPENSITY SCORE MATCHING

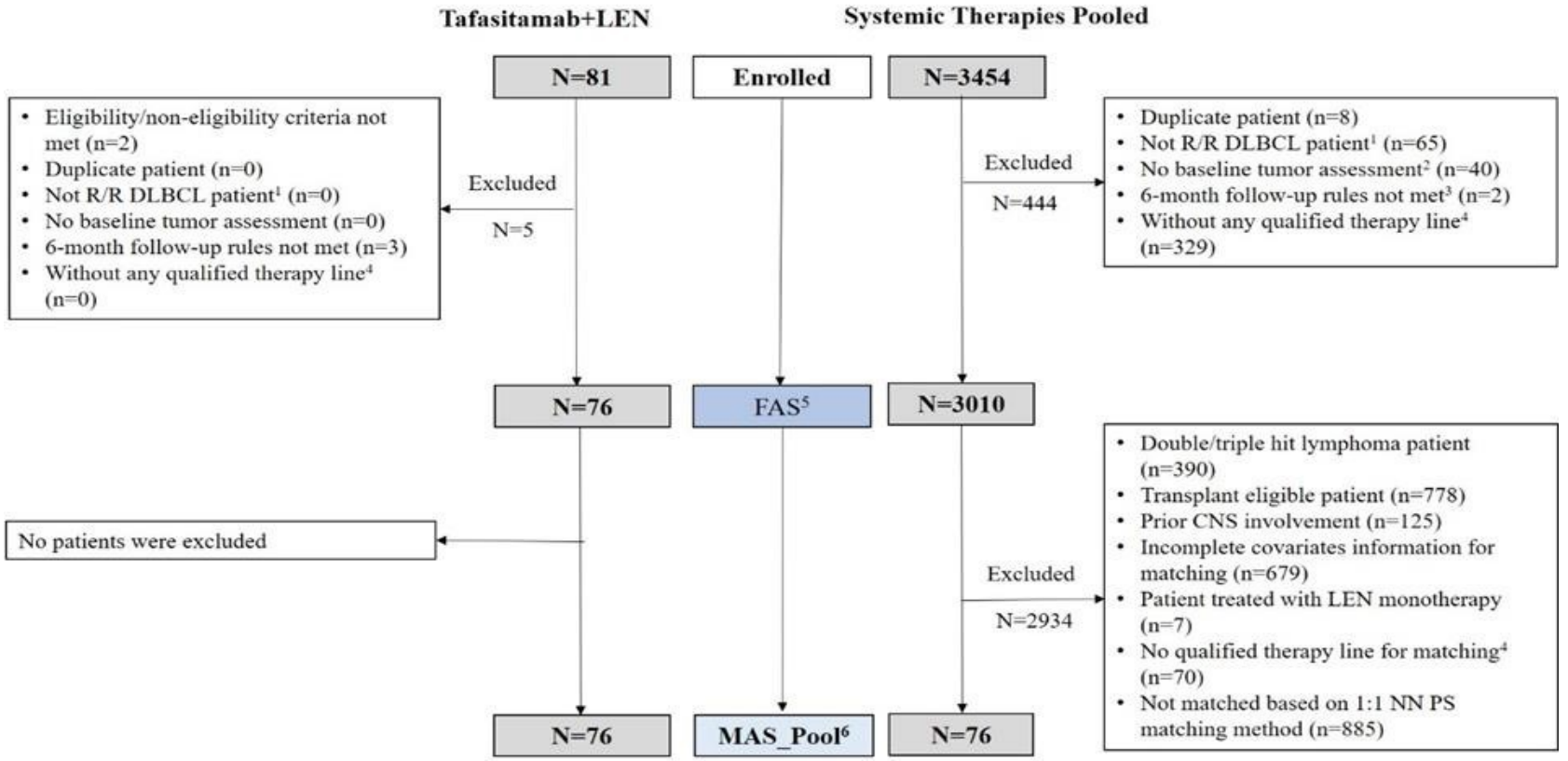


9 Baseline covariates:

- Age group,
- Ann Arbor Stage
- Number of prior lines of therapy
- History of primary refractoriness
- Refractoriness to last therapy line
- Prior ASCT
- Elevated LDH
- Neutropenia
- Anemia



Da 3454 pz arruolati … 76 pz usati per le analisi ?!?!



NON è un aspetto negativo:

Per fare confronti fra trattamenti in assenza di randomizzazione è auspicabile utilizzare un propensity score matching con molte variabili (→ perdita di molti pz nel braccio di confronto storico)

Conclusioni (1)

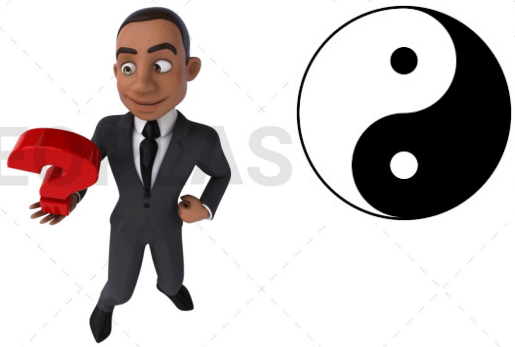
Conclusioni (2)

- Gli studi RE-MIND e RE-MIND 2 sono studi ibridi per il confronto indiretto fra tafa + lena e altri trattamenti
- Sono studi di nuova concezione (poco conosciuti ma sempre più utilizzati)
- Molto utili in assenza di altre evidenze dirette
- Sono metodologicamente solidi e ben disegnati (**protocollo prespecificato**)
- La grande perdita di pz nei bracci di confronto artificiali non è una debolezza ma una forza: sono state usate MOLTE covariate per il matching

Conclusioni (3)

Da un punto di vista **METODOLOGICO**:

Re-MIND e Re-MIND2 sono stati condotti in modo corretto



Da un punto di vista **CLINICO**:

Le 9 covariate cliniche prognostiche utilizzate hanno reso simili i pazienti?

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