X Congresso Nazionale IG-IBD

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IG-IBD
the Italian Group for the study of Inflammatory Bowel Disease

Adalimumab biosimilar : real-life Evidence from Tuscany region

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REGIONE TOSCANA

IBD Unit, U.O. di Gastroenterologia Universitaria - Dipartimento di Chirurgia AOUP, Pisa ;

IBD Unit, CRR IBD, Dipartimento di Medicina Interna, AOU Careggi, Firenze;

U.O.di Gastroenterologia S.Giovanni di Dio – Torregalli, Firenze ;

U.O.Gastroenterologia Empoli ;

U.O.Gastroenterologia Siena ;

U.O.Gastroenterologia Grosseto;

U.O.Gastroenterologia Massa-Carrara ;

SB5 clinical studies: PK equivalence and clinical efficacy

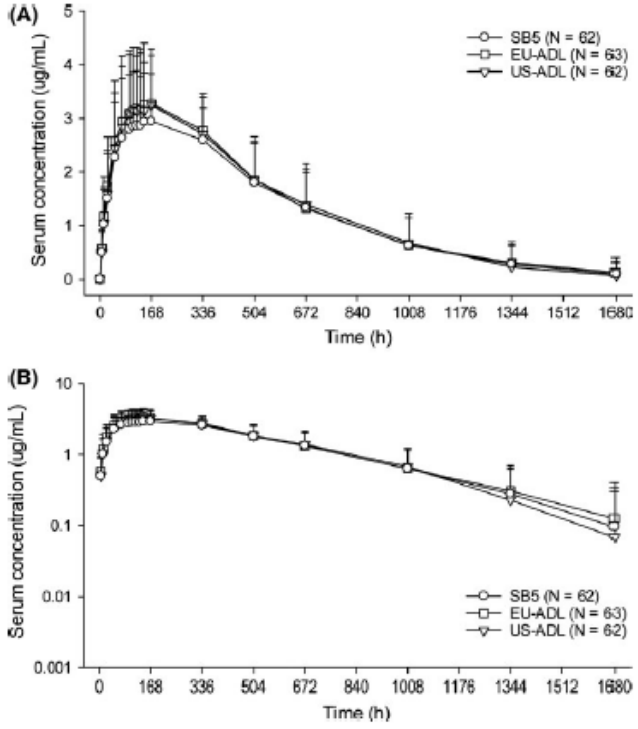
Weinblatt ME et al. Arthritis & Rheumatolog y Jan 2018; 40-48
Weinblatt ME et al. Arthritis & Rheumatolog y Jun 2018; 832-40
Shin D et al. J Clin Pharm Ther. 2017;1–7.

A randomized phase I comparative pharmacokinetic study comparing SB5 with reference adalimumab in healthy volunteers

Phase III Randomized Study of SB5, an Adalimumab Biosimilar, Versus Reference Adalimumab in Patients With Moderate-to-Severe Rheumatoid Arthritis

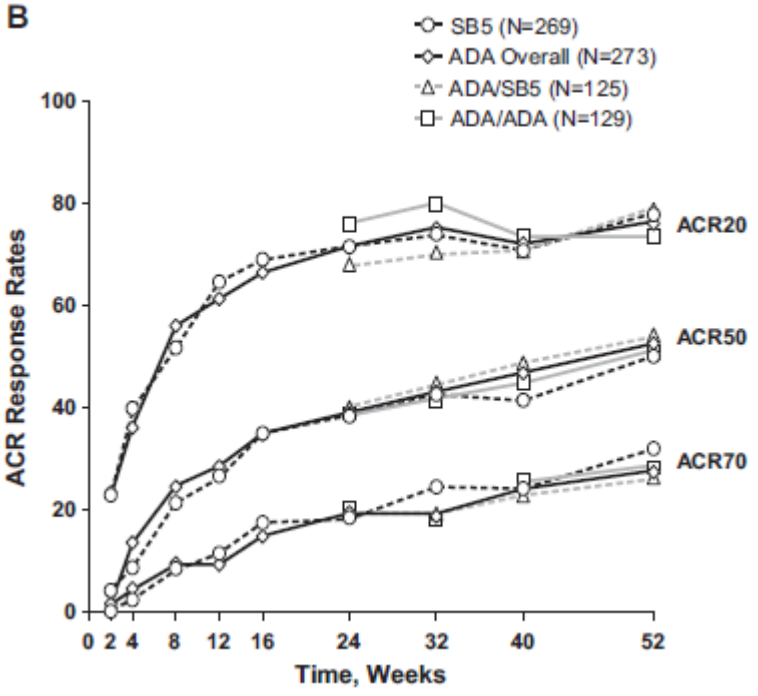
Clinical Pharmacokinetics

AS study: SB5 PK similar to ADA



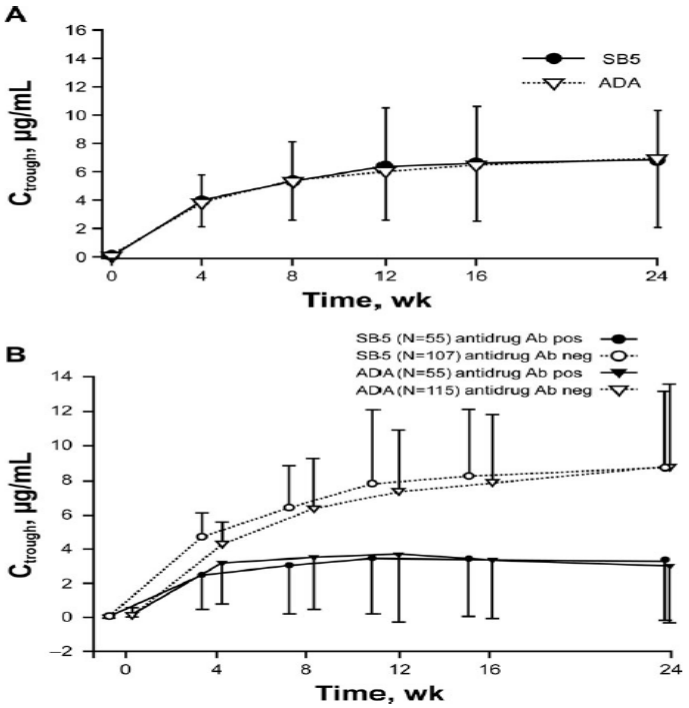
Clinical efficacy

Primary Endpoint: ACR20-50-70 at Week 54
RA study: clinical efficacy similar to ADA



Immunogenicity

Serum trough concentration of SB5 and reference adalimumab (ADA) at week 24 among patients in each treatment group among subsets of antidrug antibody–positive patients and antidrug antibody–negative patients within each treatment group.

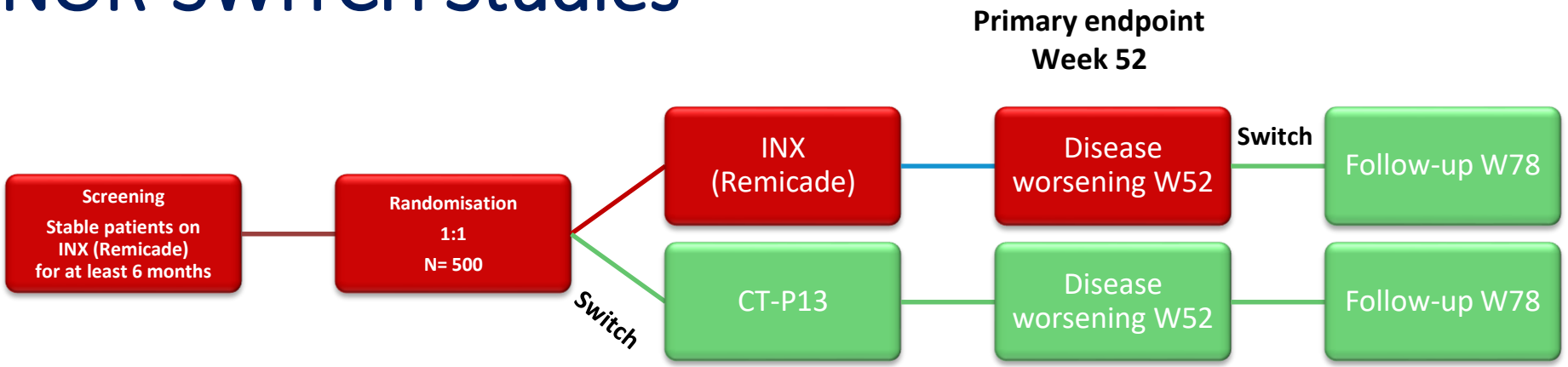


Extrapolation

-concerns-

- Different dosing (higher in IBD)
- Combo tx (Rheuma >IBD)
- Different immunogenicity and different downstream effects (soluble and/or transmembrane TNF-a)
- FcγRIIIa receptor binding (Apoptosis and Antibody-Dependent Cell-Mediated Cytotoxicity (*ADCC*) (certolizumab pegol ?)
- Safety profile of infliximab is also different (hepatosplenic T-cell lymphoma in adolescents and young adults exclusively in IBD pts)
- Fucosilation ?? Solved Problem after EMA inquiring

The NOR-SWITCH Studies



1. Jørgensen K, et al. UEGW 2016. Abstract #LB15
2. Jørgensen K, et al.Lancet 2017 Jun 10;389:2304-23

Assumption:
30% worsening in 52 weeks
Non-inferiority margin: 15%

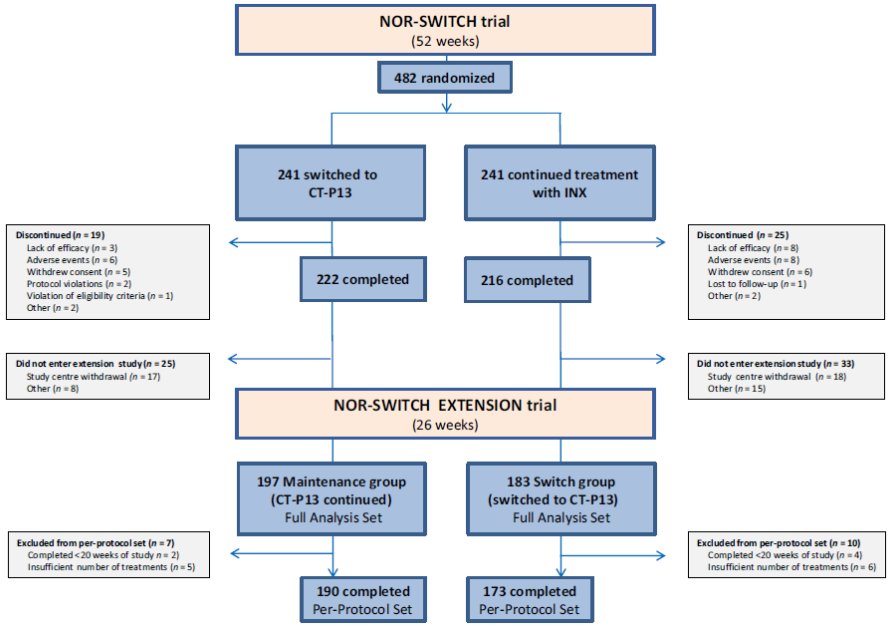
Open Label Follow-up

JIM Original Article

Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial

CONCLUSIONS

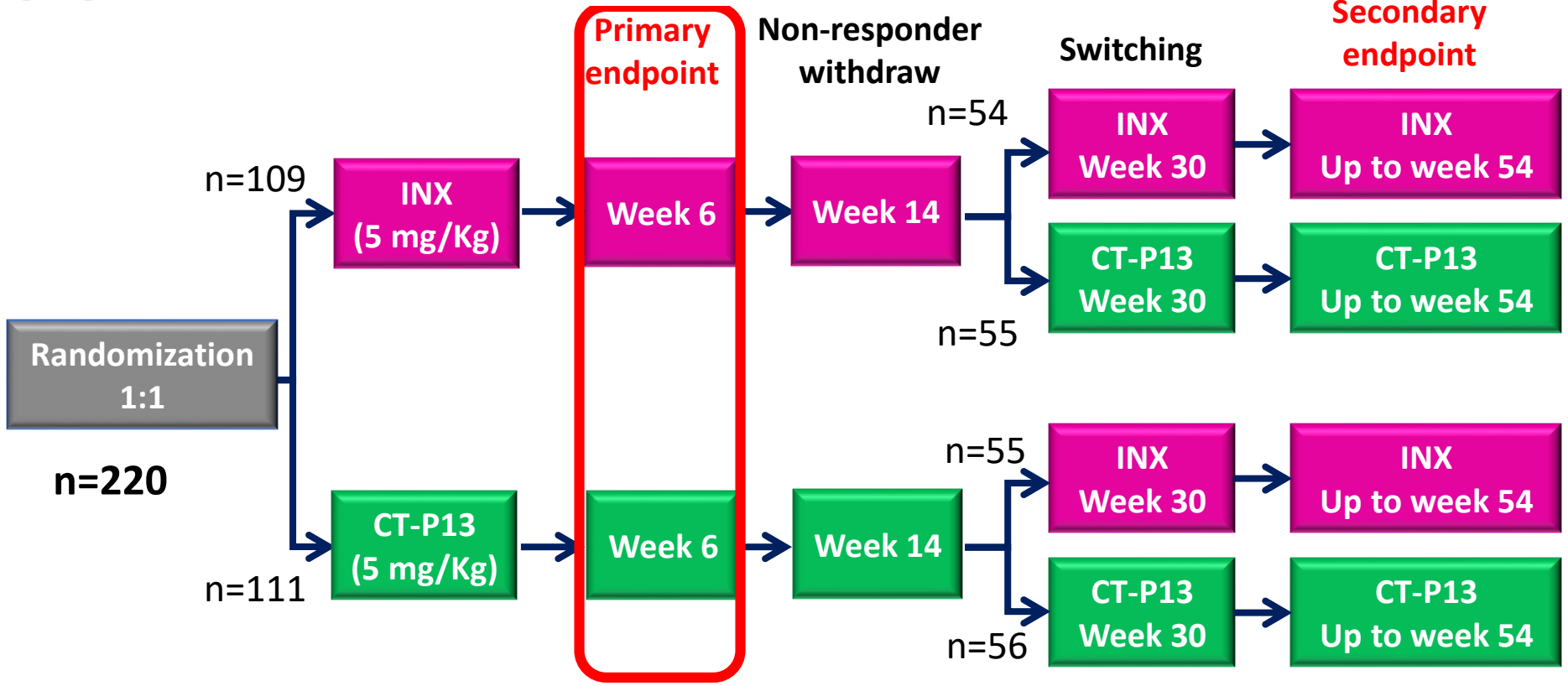
The NOR-SWITCH extension showed no difference in safety and efficacy between patients who maintained CT-P13 and patients who switched from originator infliximab to CT-P13,supporting that switching from originator infliximab to CT-P13 is safe and efficacious



Goll GL et al. J Intern Med. 2019 Jun;285(6):653-669

Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study

Byong Duk Ye, Marina Pesegova, Olga Alexeeva, Marina Osipenko, Adi Lahat, Andriy Dorofeyev, Sigal Fishman, Olena Levchenko, Jae Hee Cheon, Maria Lia Scribano, Radu-Bogdan Mateescu, Kang-Moon Lee, Chang Soo Eun, Sang Joon Lee, Sung Young Lee, HoUng Kim, Stefan Schreiber, Heather Fowler, Raymond Cheung, Young-Ho Kim



- **Primary objective**: To demonstrate that CT-P13 is non-inferior to INX at week 6, in terms of efficacy, as determined by the CDAI-70 response rate
- **Secondary objectives**:
  - To evaluate efficacy of CT-P13 in comparison with INX up to week 54
  - To evaluate overall safety of CT-P13 in comparison with INX up to week 54

The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar

Inflamm Bowel Dis 2017;23:233–243

The PROSIT Cohort of Infliximab Biosimilar in IBD: A Prolonged Follow-up on the Effectiveness and Safety Across Italy

Inflamm Bowel Dis 2019;25: 568-579

CONCLUSIONS

- **No significant issues in terms of safety raised from the study population**
- **The infusion reaction rates observed in patients previously exposed to infliximab is in line with the literature data on the originator**
- **Effectiveness seems to be in line with IFX originator**
- **The safety and effectiveness profile of CT-P13 is not different from the originator in a *real-life* setting**

Position's change

- **British Society of Gastroenterology (BSG)**

Following on extensive and cumulative evidences from biosimilars, gastroenterologists' perceptions and attitudes towards biosimilars have been changed positively.

2016
▪ **There is sufficient evidence to recommend** that patients in a stable clinical status on **RMP therapy can be switched to Remsima or Inflectra** at the same dose and dose interval. ▪ **This should be done after discussion with patients**, with explanation of the reason for switching (which is usually on the grounds of benefit to the overall service by **reduction in costs** of the drug and its administration).
2014
▪ For patients already on therapy, **avoidance of switching** from parent drug to biosimilar, or vice versa, at least until we have safety data. ▪ **Any apparent cost advantage must be balanced against the uncertain efficacy and unknown risk** from the biosimilar.

ECCO Position's change (2013 vs 2016)

- The molecular size and complex structure of biological medicines (and biosimilars) make it extremely difficult to predict therapeutic equivalence, because even subtle changes during development can cause profound differences in clinical efficacy or immunogenicity. Such differences can occur even within the same biological medicine if different manufacturing processes are used (e.g. different cell lines).
- Rules applied to the production of generic chemical medicines cannot be transferred to biosimilars
- Different biological and biosimilar medicines targeting the same molecule are neither identical in efficacy nor toxicity, even in the same clinical entity.
- A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective.
- Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis
- Clinical trials should be of large enough size to detect common adverse events and powered to show equivalence with a reference biological agent, or conventional superiority
- Post-marketing collection of data in both children and adults is necessary to confirm safety by recording less common but important potential adverse effects, as well as identifying any increase in frequency of predictable adverse events contingent on wider access to treatment.
- Any decision to substitute a product should only be made with the prescribing health care provider's specific approval and patient's knowledge[10]
- Names of biosimilars need clearly to differ from their reference biological medicine in order to facilitate the collection of data on safety and efficacy, which would be impossible if confusion between names will occur

1. Biosimilarity is more sensitively characterised by performing suitable *in vitro* assays than clinical studies.
2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.
3. When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics.
4. Demonstration of safety of biosimilars requires large observational studies with long-term follow-up in IBD patients. This should be supplemented by registries supported by all involved stakeholders [manufacturer, healthcare professionals and patients' associations].
5. Adverse events and loss of response due to immunogenicity to a biologic drug cannot be expected to be overcome with a biosimilar of the same molecule.
6. As for all biologics, traceability should be based on a robust pharmacovigilance system and the manufacturing risk management plan.
7. Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients
8. Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

Danese S, et al. *J Crohns Colitis* 2013; Danese S, et al. *J Crohns Colitis* 2017

ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease—An Update

Silvio Danese, Gionata Fiorino, Tim Raine, Marc Ferrante, Karen Kemp, Jaroslaw Kierkus, Peter L. Lakatos,Gerassimos Mantzaris, Janneke van der Woude, Julian Panes, Laurent Peyrin-Biroulet

1. Biosimilarity is more sensitively characterized by performing suitable *in vitro assays than clinical studies.*

2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation.

3. When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product

4. Demonstration of safety of biosimilars requires large observational studies with long-term follow-up in IBD patients.

5. Adverse events and loss of response due to immunogenicity to a biologic drug cannot be expected to be overcome with a biosimilar.

6. As for all biologics, traceability should be based on a robust pharmacovigilance system and the manufacturing risk management plan.

7. Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. **Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients**

8. **Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation**. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

Journal of Crohn's and Colitis, 2017, 26–34

Position Paper

Use of biosimilars in inflammatory bowel disease: a position update of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

Fiorino G et al. DLD 51 (2019) 632–639

Biosimilarity and extrapolation across indications

Statement 1
A biosimilar mAb targeting the same molecule as the originator can be considered **equivalent in terms of efficacy and safety when such equivalence is supported by in vitro assays and clinical studies**. Extrapolation across indications is acceptable when a biosimilar mAb has been tested on one or more approved indications and has been approved and licensed by EMA.

Safety and immunogenicity

Statement 2
Licensed biosimilars can be considered as safe as the originator. However, large observational studies are needed to monitor the long-term safety of biosimilars, and registries supported by all involved stakeholders should be developed

Statement 3
Any event related to **the immunogenicity of a mAb cannot be overcome by a biosimilar** of the same molecule

Interchangeability and switching

Statement 4
Once biosimilarity has been confirmed, **any biosimilar can be considered interchangeable with the reference product**

Statement 5
Switching from the originator to a biosimilar of the same molecule is acceptable**. Switching from one biosimilar to another of the same originator and multiple switches among different molecules should be avoided in the absence of direct evidence of efficacy and safety**

Automatic substitution

Statement 6
Automatic substitution must be avoided. **The clinician alone is responsible for the prescription of a biological drug**, and no pharmacist or other health care operator may assume this responsibility

Patient education about biosimilars

Statement 7
Patients' awareness about biosimilars should be fostered through education and the provision of up-to-date information, to let them make informed choices. **Switching from an originator to a biosimilar should be done only after the patient has received appropriate information and has agreed**

Razionale dello studio

-RCT su psoriasi e AR non hanno mostrato differenze in sicurezza, efficacia e immunogenicità tra Adalimumab originator e suoi biosimilari (SB5, ABP501, BI695501, GP2017)

-Attualmente non sono ancora disponibili dati per i pazienti con IBD

Studio di *real-life* condotto in Toscana su pazienti con IBD sottoposti a terapia con biosimilare di adalimumab SB5 a partire da Novembre 2018.

Gruppi di studio

1. Naïve a adalimumab (mai esposti)
2. Switch da RP (originator)

OBIETTIVI e end-points

- Obiettivo primario:

➢ Valutare la safety del biosimilare di ADA (SB5) in pazienti con IBD

- **Percentuale di EA verso SB5 (totale)**
- **Percentuale di EA gravi che hanno comportato la sospensione di SB5**

- Obiettivi secondari:

➢ Valutare l' efficacia del biosimilare di ADA (SB5) in pazienti con IBD

- **n° pts in remissione (HBI <5 ; PMS <2) a 12, 24 e 52 w**
- **n° pts con stop SB5 per LOR a 12, 24 e 52 w**
- **n° pts con LOR a 12 ,24 e 52 w**
- **n° pts con MH a 24 e 52w (se disponibile)**
- **n° pts con remissione biochimica (Pcr e Calpro) a 12, 24 e 52w (se disponibile)**

➢ Valutare se lo switching da RP a SB5 si associ ad un aumento di Ab anti-farmaco con secondaria riduzione dei TI

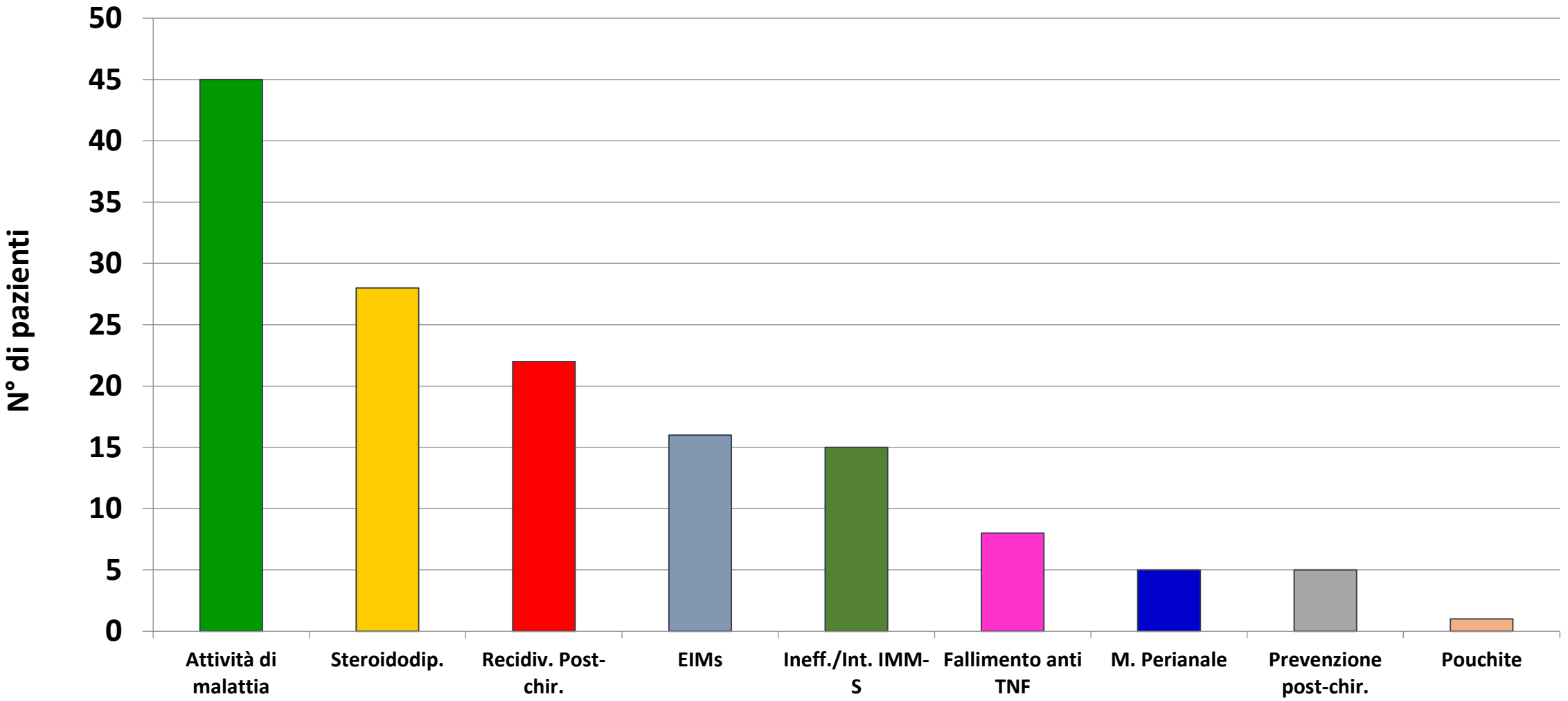
- **TI a (-8-2), 12 , 24 e 52 w dopo lo switch**

Caratteristiche Popolazione

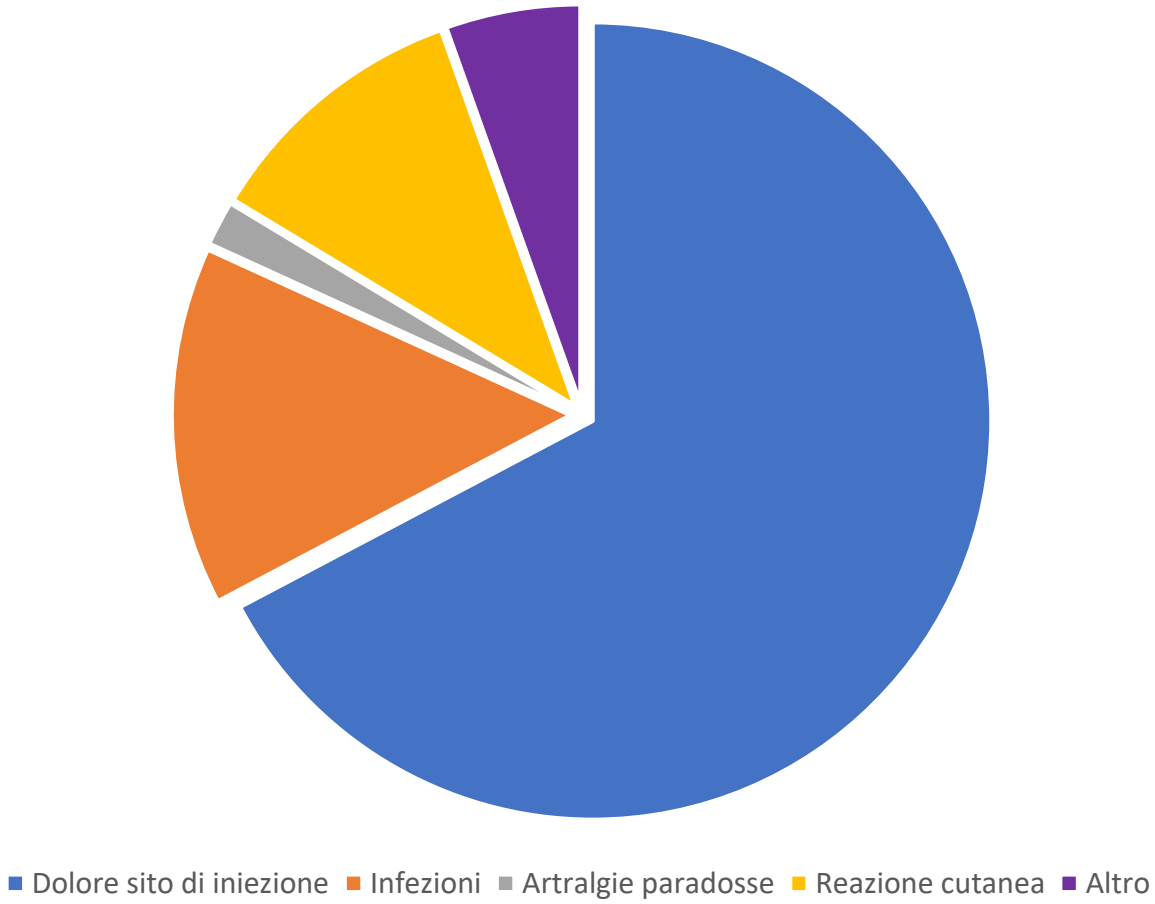
	Overall	CD	UC	IBD-U
N° pazienti	**145**	112	31	2
Naive (%)	**39 (26.89%)**	28	9	2
Switch (%)	**101 (69.65%)**	79	22	0
Exp. a RP(originator)	**5 (3.46%)**	5	0	0
Sesso	**89 M, 56 F**	70 M, 42 F	17 M, 14 F	2 M
Fumo (SI/NO/EX)	**29 - 100 -15**	25 -74 -13	5 - 24 - 2	0 - 2 - 0
Combo Tp.	**2**	2	0	0
Età media allo start/switch SB5 (anni)	**41.9 ± 15.48**	43.81 ± 15.44	40.16 ± 15.66	52.5 ± 15.36
Durata media malattia inizio tp con Adalimumab (anni)	**10.35 ± 9.93**	10.85 ± 9.96	7.83 ± 10.0	17.5 ± 9.59

	Naive	Switch	p
N° pazienti	**39/145 (26.89%)**	**101/145 (69.65%)**	
Diagnosi	CD: 28 (71.79%) UC: 9 (23.07%) IBD-U: 2 (5.12%)	CD: 79 (78.22%) UC: 22 (21.78%) IBD-U: 0 (0%)	0.561 0.950 0.135
Sesso	19 M, 20 F	66 M, 35 F	0.107
Fumo	SI: 10 (25.64%) NO: 25 (64.10%) EX: 4 (10.26%)	SI: 18 (17.83%) NO: 72 (71.28%) EX: 11 (10.89%)	0.424 0.534 0.844
Età media allo start SB5 (anni)	42.35 ± 15.47	42.29 ± 15.64	0.984
Durata media tp Adalimumab ultimo follow-up (settimane)	32.58 ± 14.99	158.81 ± 103.39	**< 0.0001**
2° anti TNF	10 (25.64%)	25 (24.75%)	0.913

Indicazioni alla terapia con Adalimumab



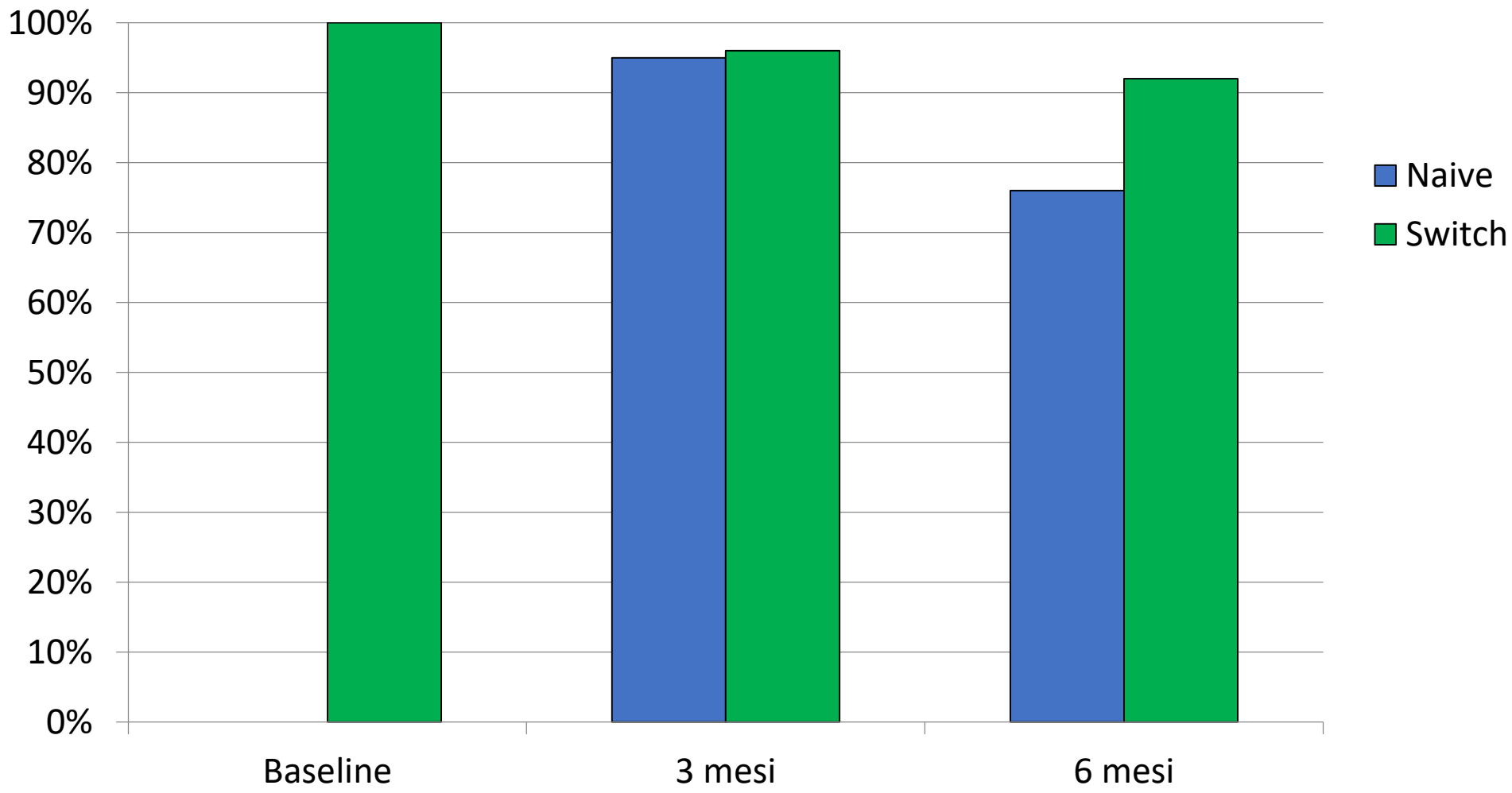
Eventi Avversi



- **11 EA**, di cui **2 gravi (5%)**, nel gruppo dei **naive**;
- **44 EA**, di cui **4 gravi (4%)**, nel gruppo dello **switch**;

Tipo EA	n°
Dolore sito di iniezione	37
Infezioni: - Riattivazione VZV - Febbre persistente - Vie respiratorie - IVU	8 1 1 5 1
Reazioni cutanea	6
Artralgie paradosse	1
Altro: - Cefalea - Dolore retro-orbitale	3 2 1
Totale	**55**

Persistenza di terapia con SB5



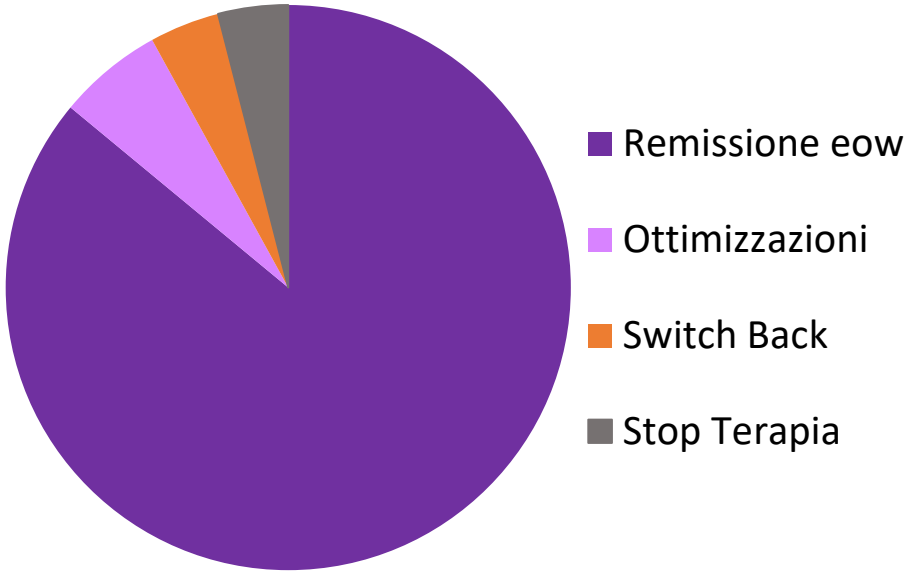
*
- 97/101 (**96.04%**) dei pazienti era in **remissione** al momento dello switch;
- 4/101 (**3.96%**) presentavano solo **risposta** clinica alla terapia con RP;
- 2/101 (1.98%) pazienti erano ottimizzati a monosettimanale al momento dello switch);

Risultati

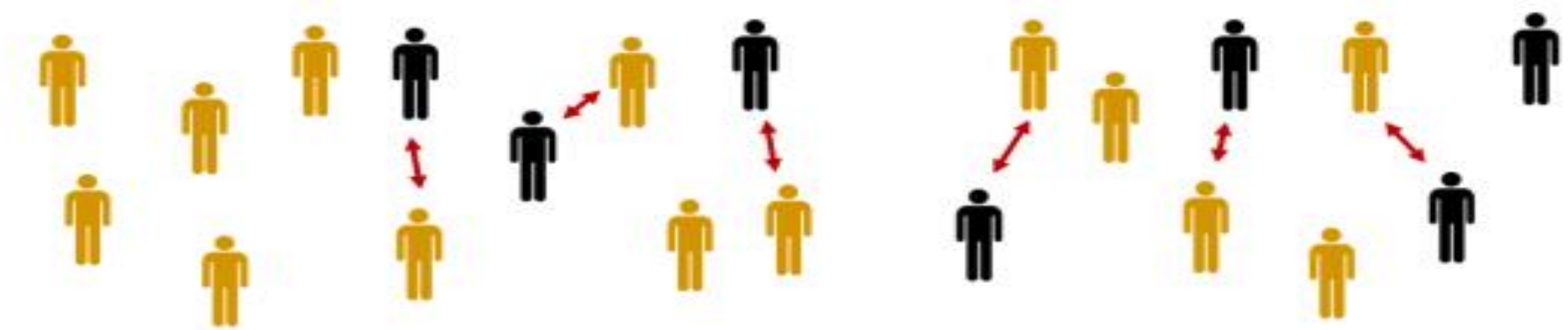
• Il **92%** circa dei pazienti sottoposti a switch ha mantenuto la terapia con SB5 per remissione clinica a 6 mesi; di cui il 6% in terapia eow ha necessitato di una **ottimizzazione terapeutica**, recuperando la risposta clinica.

• 4/101 **(3.96%)** hanno effettuato lo **switch-back** ad Humira®.

- 2/4 (**50%**) per **LOR** recuperando la risposta clinica;
- 1/4 (**25%**) per **reazione cutanea** con miglioramento;
- 1/4 (**25%**) per **dolore sito iniezione,** con miglioramento;



Propensity Score



39
NAIVE

VS

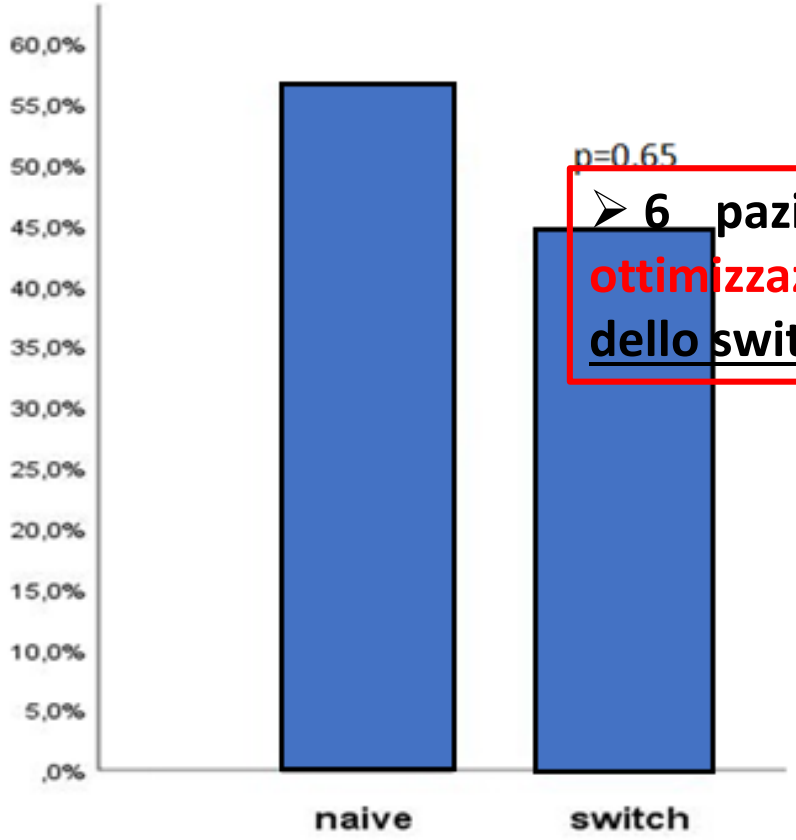
39
SWITCH

- Età al momento di inizio della terapia;
- Diagnosi;
- Sesso;
- Fumo di sigaretta;
- Pregressa esposizione ad anti TNF;
- Durata esposizione al biosimilare;

Outcome clinico a 6 mesi

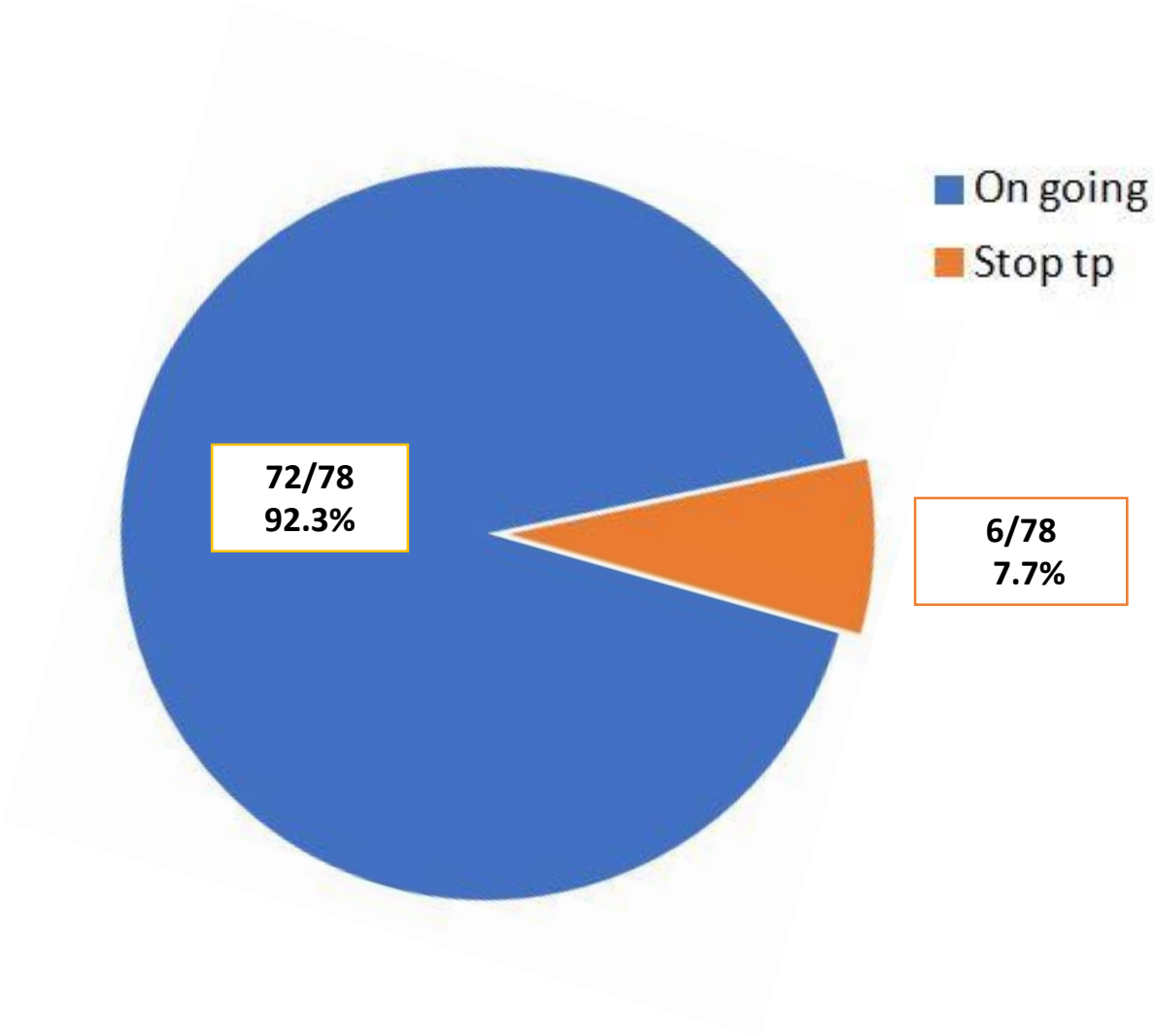
- Nella corte del propensity score, il **79% (62/78)** dei pazienti era in remissione: **30 naive** e **32 switch**;

- 16 pazienti (**20.51%**) non presentavano remissione clinica all'ultimo follow-up: **9 naive** e **7 switch**;



- **6 pazienti** (**7.69%**) hanno necessitato di **ottimizzazione** della terapia, **tutti nel gruppo dello switch;**

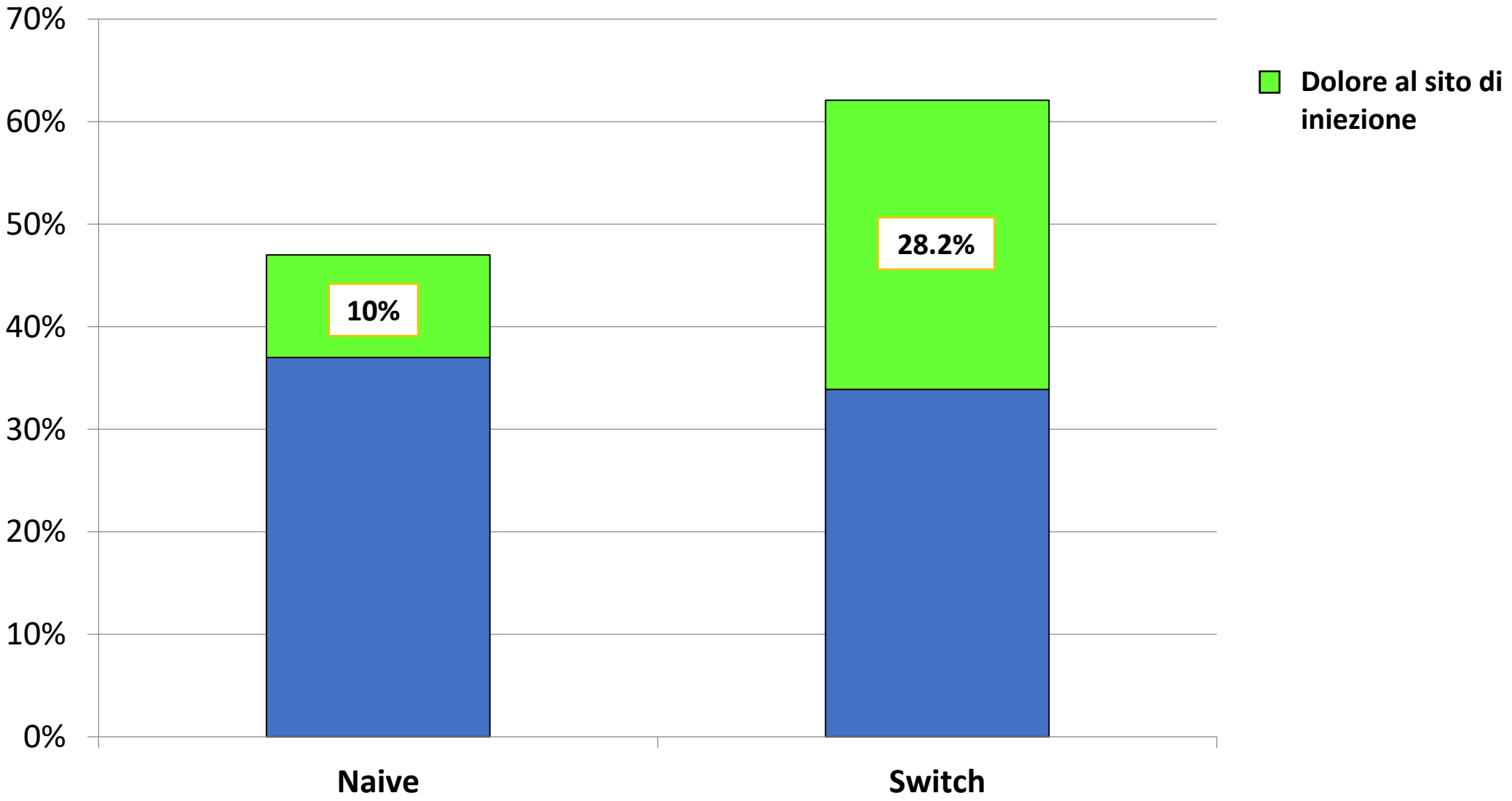
Stop terapia



- **5** del gruppo **naive**:
  - **3 PNR;**
  - **2 EAs;**
- **1** del gruppo **switch**:
  - **deep remission;**

p = 0.089

Eventi avversi



Conclusioni

- **Nessuna differenza significativa è stata osservata in termini di safety tra SB5 e originator**
- **Il dolore nel sito di iniezione è stato l'evento avverso maggiormente osservato nei pazienti dopo lo switch a SB5 ma di breve durata e che non ha determinato la sospensione del farmaco**
- **L'efficacia in termini di persistenza della terapia a 24 settimane dopo lo switch sembra in linea con ADA originator**
- **La necessità di ottimizzare la terapia è stata osservata più frequentemente nei pazienti dopo lo switch senza raggiungere la significatività statistica. Un 4% di pts ha richiesto uno switch-back che ha permesso di recuperare la risposta clinica**