Pharmacovigilance in Oncology

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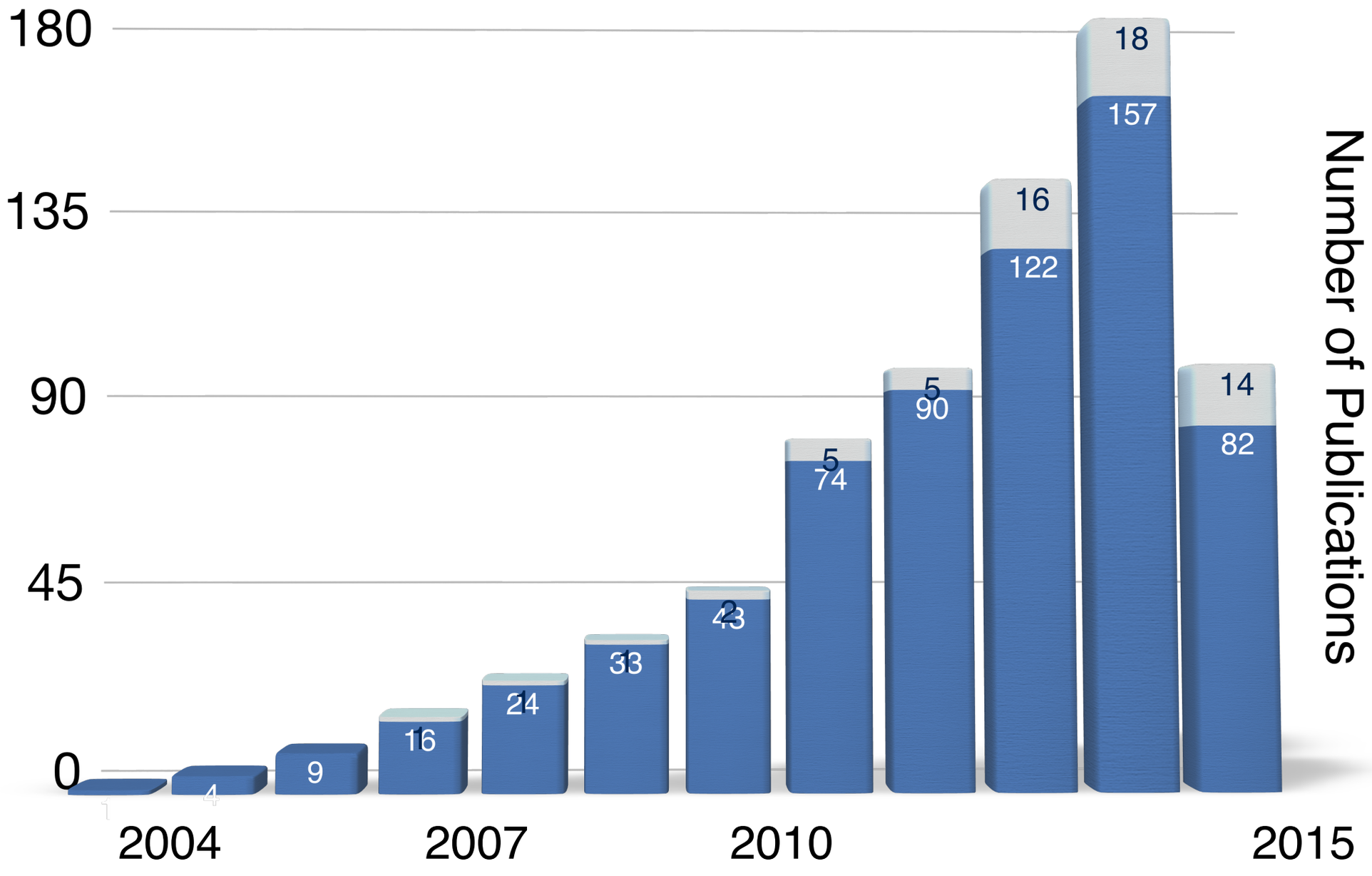
Disclosure

- Director, Center for Oncology and Blood Disorders.
- Secretary, Board of Directors, Texas Society of Clinical Oncology.
- Research Fundings from Merck, EMD serono.
- Consulting for Vaccine program - Merck, Inc.
- Speaker: Merck, Amgen.
- No market stocks or financial interest.

Top 8 blockbuster biologicals 2013

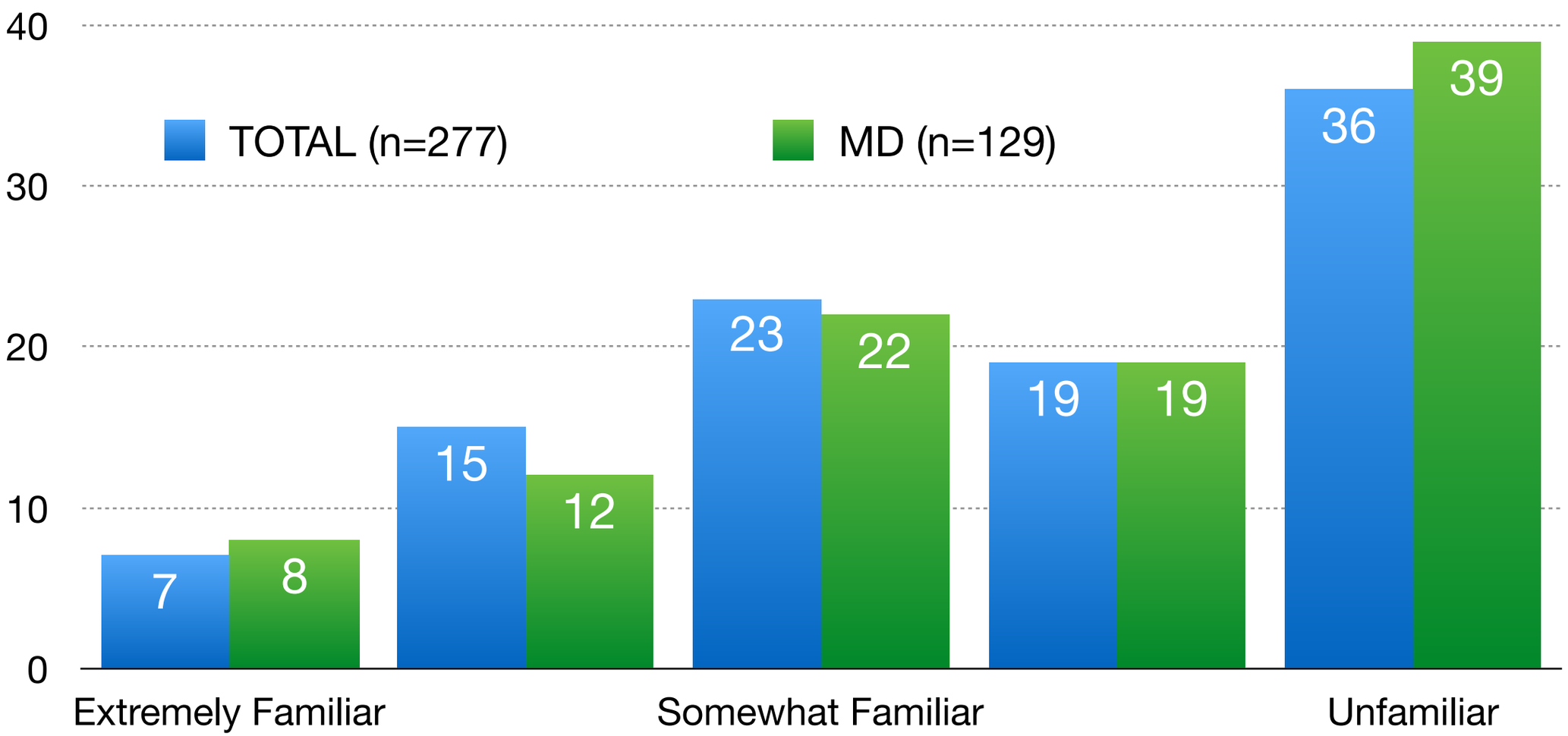
Commercial	Active Ingredient	Type	Class	Indication	Company	Global Sales (US $billion)	Patent Expiration EU/US
Humira	adalimumab	Antibody	TNF Inhibitor	Arthritis	Abbott/Eisai	10.7	Apr 2018/ Dec 2016
Remicade	infliximab	Antibody	TNF Inhibitor	Arthritis	Merck/ Mitsubishi	8.9	Aug 2014/ Sep 2018
Rituximab/ MabThera	**rituximab**	**Antibody**	**Anti-CD20**	**Arthritis / Cancer**	**Roche/ Biogen-Idec**	**8.6**	**Nov 2013/ Dec 2018**
Enbrel	etanercept	Antibody	TNF inhibitor	Arthritis	Amgen/Pfizer/ Takeda	8.3	Feb 2015/ Nov 2018
Lantus	insulin glargine	Protein	Insulin receptor	Diabetes	Sanofi	7.8	2014/2014
Avastin	**bevacizumab**	**Antibody**	**Anti-angiogenesis**	**Cancer**	**Roche**	**7.0**	**Jan 2022/ Jul 2019**
Herceptin	**trastuzumab**	**Antibody**	**Anti-HER2**	**Cancer**	**Roche**	**6.8**	**Jul 2014/ Jun 2019**
Neulasta	**pegfilgrastim**	**Protein**	**G-CSF**	**Neutropenia**	**Amgen**	**4.4**	**Aug 2007/ Oct 2015**

Biosimilars Publications (n=592)



PUBMED May 2015

Physician familiarity



NCCN survey: Please rate your familiarity with biosimilars and recent developments

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Zelenetz AD: J Natl Compr Canc Netw. 2011

Pharmacovigilance (PV)

Pharmacovigilance is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”.

EMA and FDA have clear requirements regarding PV in the biosimilar application dossier.

PV is a critical component of marketing programs for approved drugs.

Prescription Drug User Fee Act (PDUFA III)

- **June 12, 2002**. US Congress approved the PDUFA III. FDA agreed to further implement good PV practices and pharmacoepidemiologic assessment (**PV guidance**)

- Provides authority to the FDA to collect additional resources (fee from industry) and enables the FDA to accelerate its drug evaluation process WO compromising the quality of reviews.

http://www.fda.gov/cder/guidance/index.htm - March 2005

Prescription Drug User Fee Act (PDUFA III)

Committee to provide guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).

(1) safety signal identification

(2) pharmacoepidemiologic assessment and safety signal interpretation

(3) pharmacovigilance plan development.

Risk Management Guidance

The **Premarketing Guidance** and the **Pharmacovigilance Guidance** focus on risk assessment. The **RiskMAP Guidance** focuses on risk minimization.

Risk Management: Risk assessment and risk minimization together.

(1) assessing a product's benefit-risk balance.

(2) developing and implementing tools to minimize its risks while preserving its benefits.

(3) evaluating tool effectiveness and reassessing the benefit-risk balance.

(4) making adjustments as appropriate, to the risk minimization tools to further improve the benefit-risk balance.

Safety Signals

1. Pharmacovigilance principally involves the **identification and evaluation of safety signals**.
2. **Safety signal** refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use.
3. Signals generally indicate the **need for further investigation**, which may or may not lead to a conclusion as to whether or not the product caused the event.

http://www.fda.gov/cder/guidance/index.htm - March 2005

Under-reporting of toxicities in clinical trials

- Assessment of toxicities by physicians may not represent **patient's perception**.
- AEs may be detected but **not appropriately reported** by investigators, or influenced by sponsors.
- Short-term follow up might not detect **long term** and potentially serious effects.

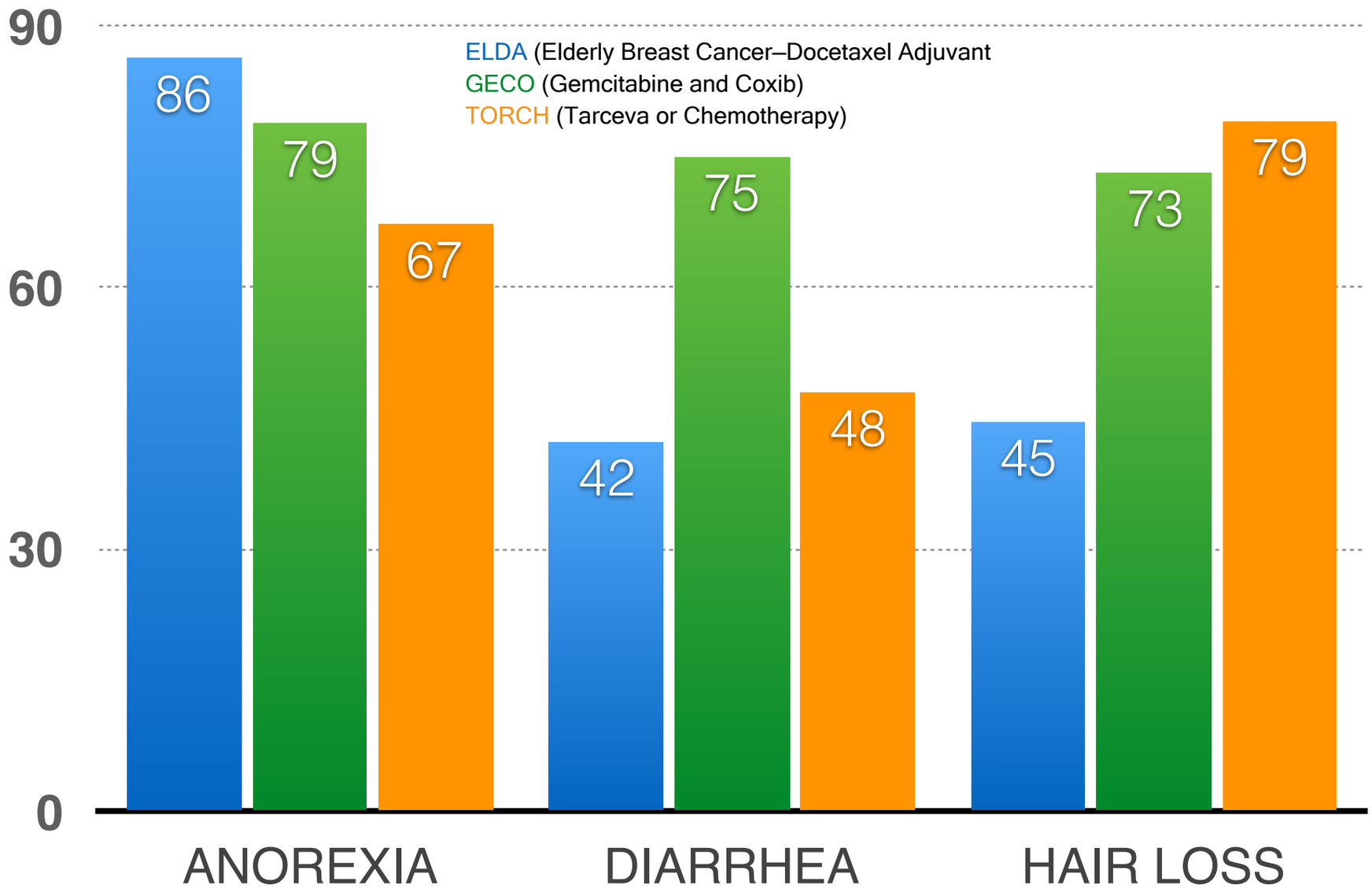
Serge B et al. Lancet Oncol. May 2016

Potential Factors Affecting Assessment of Toxicities

- Common Terminology Criteria by NCI (CTCAE) may not accurately **capture toxicities**.
- **Insufficient time** during patient's visits to assess AEs.
- Under-reporting of symptoms by patients to **continue study participation**.
- Downgrading AEs by physicians to **justify treatment continuation**.

Serge B et al. Lancet Oncol. May 2016

Differences Reporting AEs between Patients and Physicians



ELDA n= 299
GECO n= 400
TORCH n= 760

1090/1459 Patients eligible.

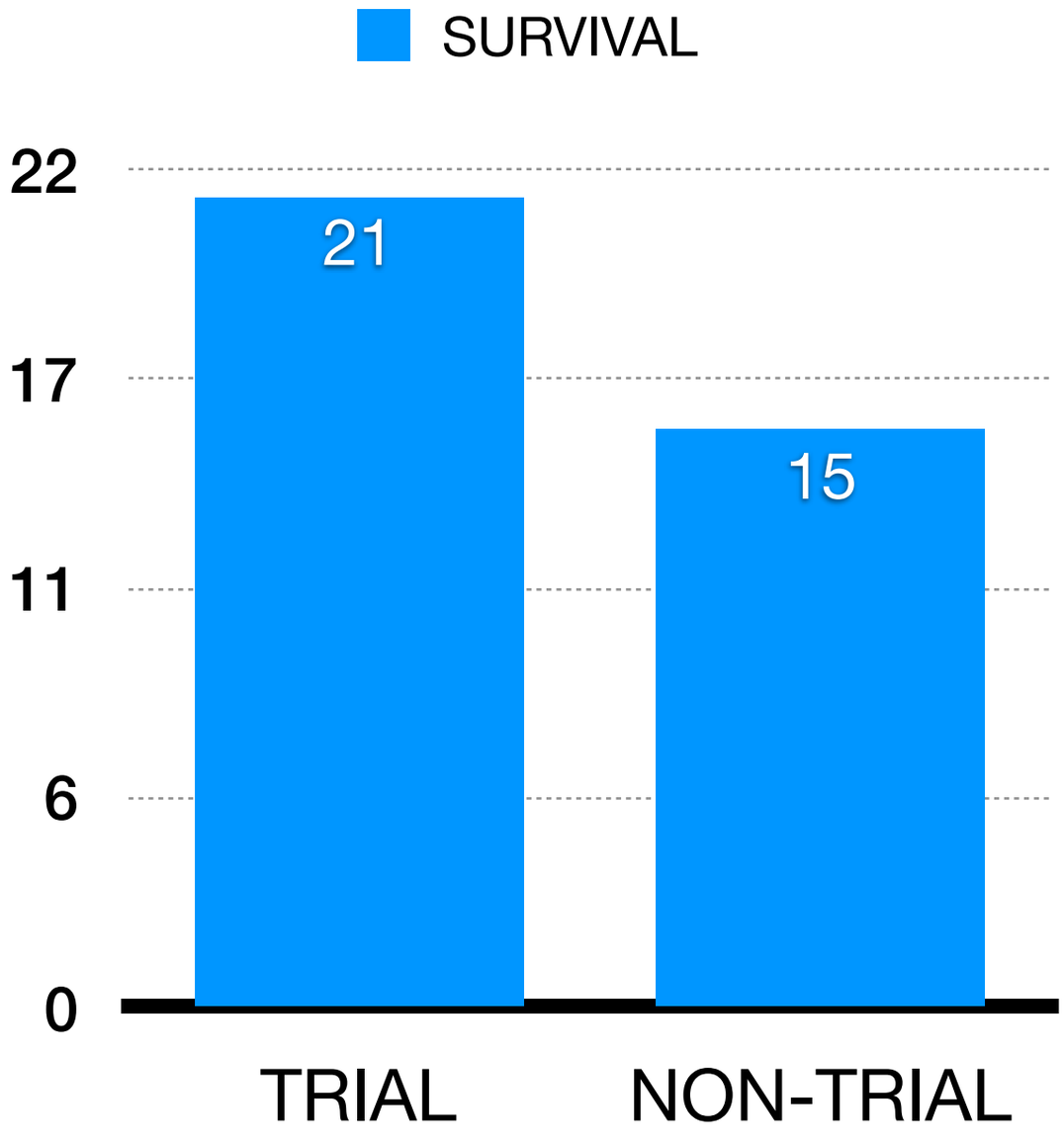
Any toxicity varied 40-74%
"Very much": 13-50%

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Di Maio M et al. J Clin Oncol 2015

Survival Difference according to Trial Participation

- Patients (**n=764**) with **metastatic colorectal cancer** were screened
  Norway (296)
  Denmark (330)
  Sweden (134).
- **36%** were enrolled in clinical trials.
- **69%** were ineligible.
- **Poor performance** was main exclusion and survival was **2.1 months**.



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Sorbye H. et al. Cancer 2009

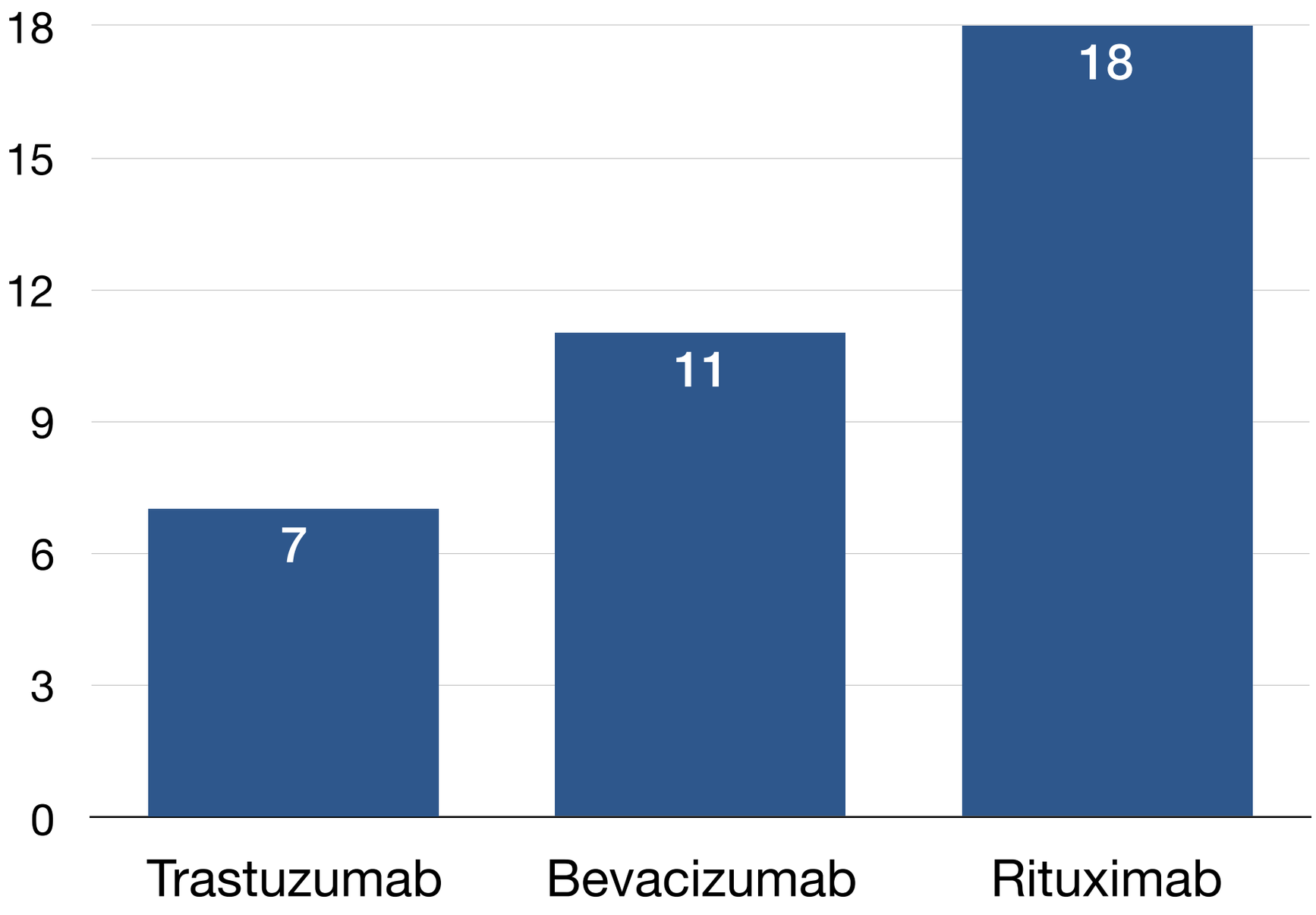
Pharmacovigilance Challenges

1. Orphan diseases.
2. Often used only in hospital settings.
3. Biologicals are often used in multiple indications with different dose regimens.
4. Occasionally, difficult to define the ‘at-risk window’.
5. Often used in second line where patients are usually sicker and confounding symptoms may be present.

Pharmacovigilance in Oncology

1. Neoplastic disorders may be associated with large symptom burden and PV assessment maybe more challenging.
2. The approval process for reference biologicals requires larger clinical trials than the process for biosimilars.
3. Communication of label warnings to patients and health care providers is a slow process.
4. The publication rate of postmarketing AEs is exceedingly low.

Post-marketing AE reports



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Camacho & Pai: J. Pharmacovigilance. 2015

Summary

- Large **educational efforts** are most needed to build the **trust** in the development and approval of biosimilars in oncology.

- The success of biosimilars in oncology is intimately associated with the strength of its **safety assessment and pharmacovigilance programs**.

- Beyond FDA encouragement, mandatory requirements should be in place for sponsors to **periodically publish postmarking AEs** of an agent.



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