

Integrating safety information from beyond the first treatment cycle

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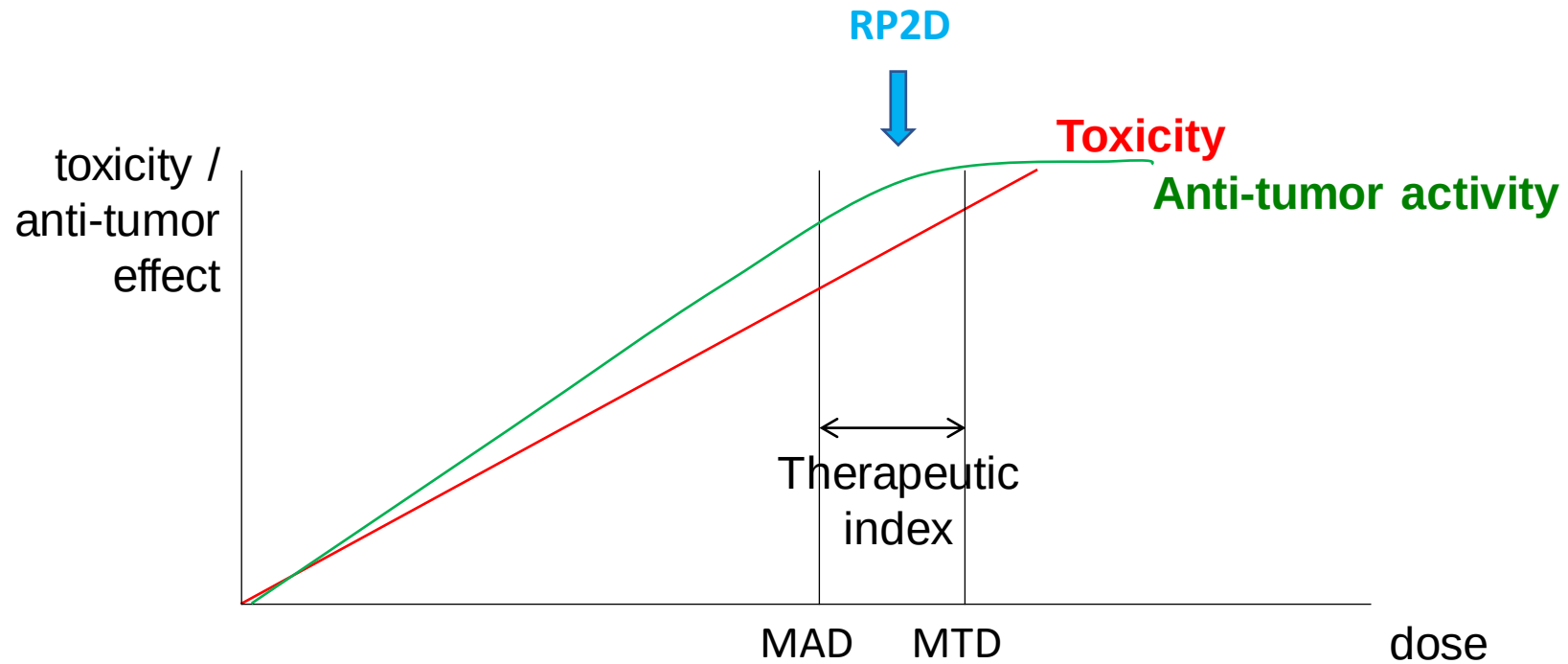
Cancer Drug Development Forum

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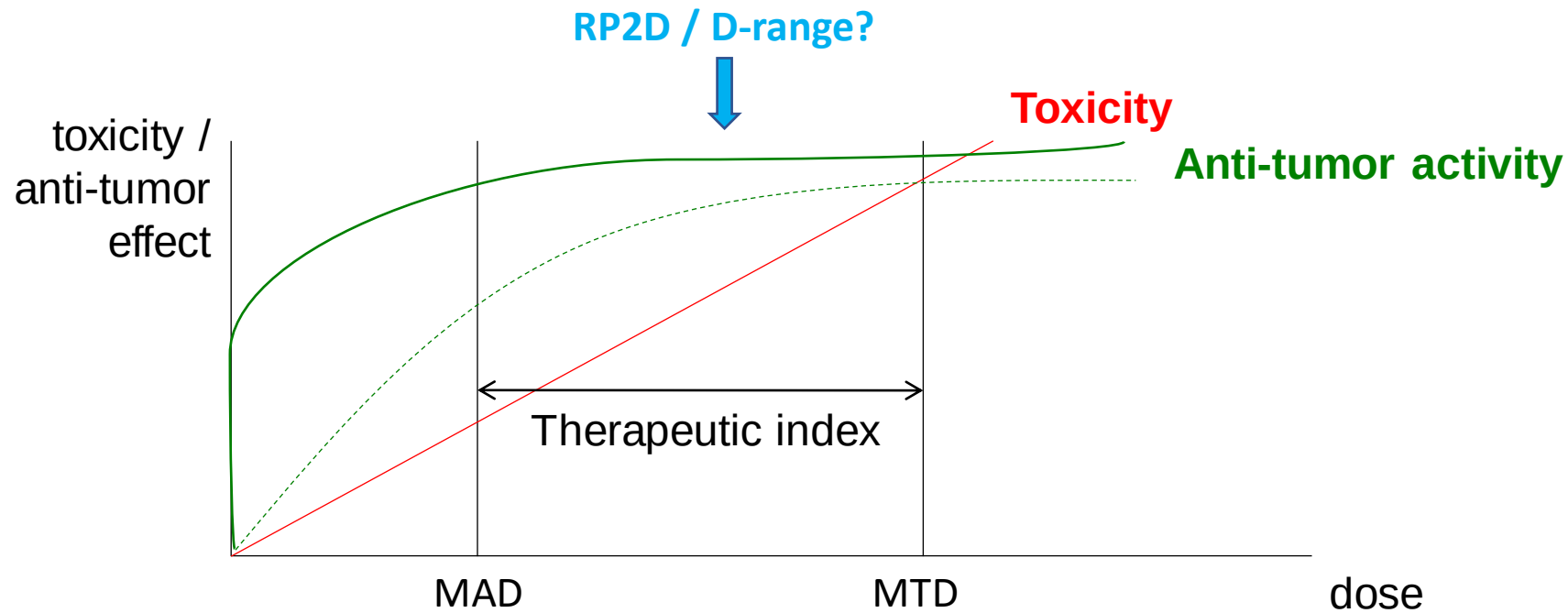
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Conventional chemotherapy: Therapeutic index & RP2D



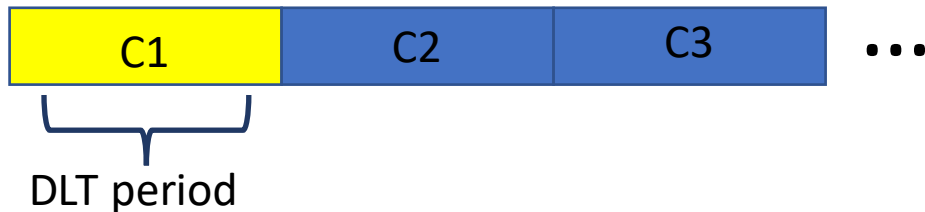
MTAs & immunotherapy: Therapeutic index & RP2D / dose-range?



On the definition of MTD and RP2D

MTD: MAXIMUM TOLERATED DOSE

- Is defined by the rate of observed DLTs (20-30%)
- DLTs are per definition **specific toxicities** observed at **cycle 1**



RP2D: RECOMMENDED PHASE 2 DOSE

- Is guided by MTD
- Inconstantly also take into account **toxicities** observed beyond **cycle 1**

Usually $RP2D \leq MTD$

- Traditionally mostly **G3-5 toxicities**

Example of MTA and ICB toxicity profile



Grade 2 folliculitis with EGFR-inhibitors

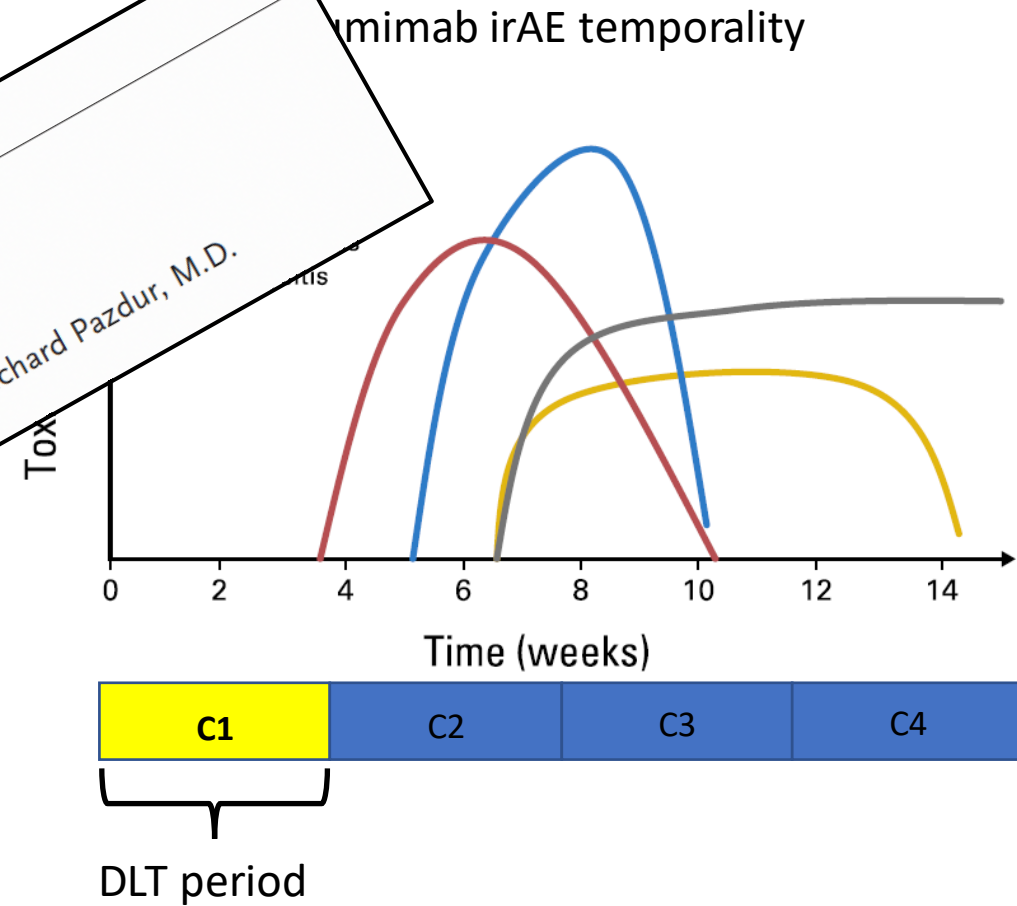
Robert C, Semin Oncol 2012



Grade 2 HFSR with sorafenib

Adverse event	Grade	Management
Diarrhea	Grade 2	Increase in frequency over baseline
Dry mouth	Grade 2	Moderate intake alterations, e.g. copious water, lubricants, diet limited to purees and/or other soft, moist foods

The Drug-Dosing Conundrum in Oncology
— When Less Is More
Mirat Shah, M.D., Atiqur Rahman, Ph.D., Marc R. Theoret, M.D., and Richard Pazdur, M.D.



DLT-TARGETT

Pilot study

445 patients / 2 centres / 36 trials
2609 toxic events (skin, GI, renal only)

- > 50% of the G3-4 toxicities
and
- > 50% of the worst toxicities
occur after the 1st cycle,
i.e. after the DLT period

-> Suggestion of considering
acute vs chronic DLT

Postel-Vinay et al, JCO 2011

VOLUME 29 · NUMBER 13 · MAY 1 2011

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ORIGINAL REPORT

Phase I Trials of Molecularly Targeted Agents: Should We Pay More Attention to Late Toxicities?

Sophie Postel-Vinay, Carlos Gomez-Roca, L. Rhoda Molife, Bhavesh Anghan, Antonin Levy, Ian Judson, Johann De Bono, Jean-Charles Soria, Stan Kaye, and Xavier Paoletti



**Definition of NEW METHODS for the
determination of DOSE LIMITING TOXICITIES
and
RECOMMENDED DOSE for Molecularly
Targeted Agents**

Severity
Grade

Cycles to
consider

Relative
dose-
intensity

Postel-Vinay et al, EJC 2014

Patients and Methods

Patients and studies

- 54 studies / 37 MTA monotherapy
 - Small molecules (72%)
 - Antibody (14%)
- Feb 1997 – May 2013
- Solid tumors

→ 2 084 evaluable patients

MTD reached in 43 trials
RP2D defined in 40/54 trials

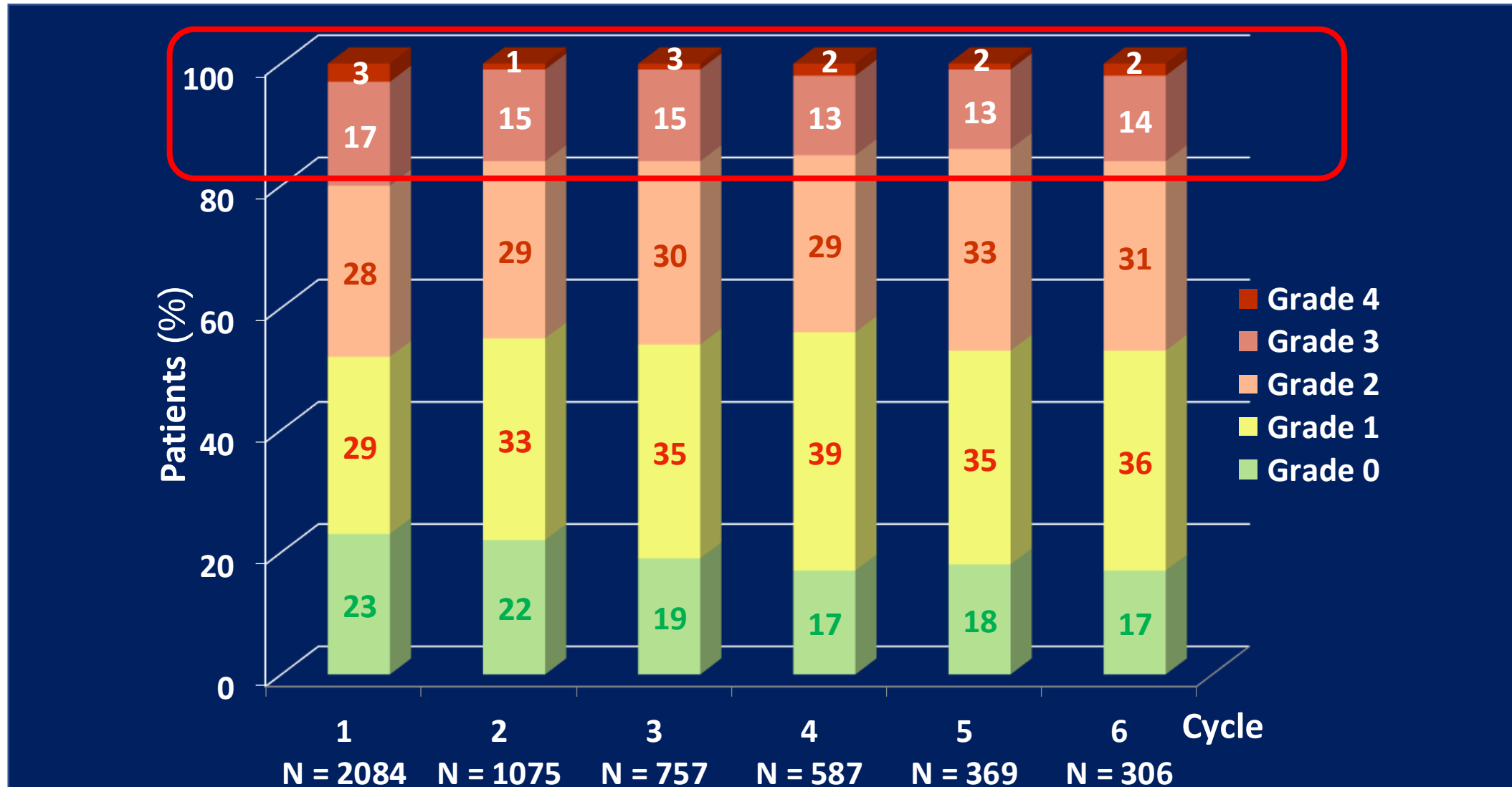
Adverse events (AEs):

- Reported during **cycles 1-6**
- At least **possibly related** to the drug
- Not present at same or higher grade at entry

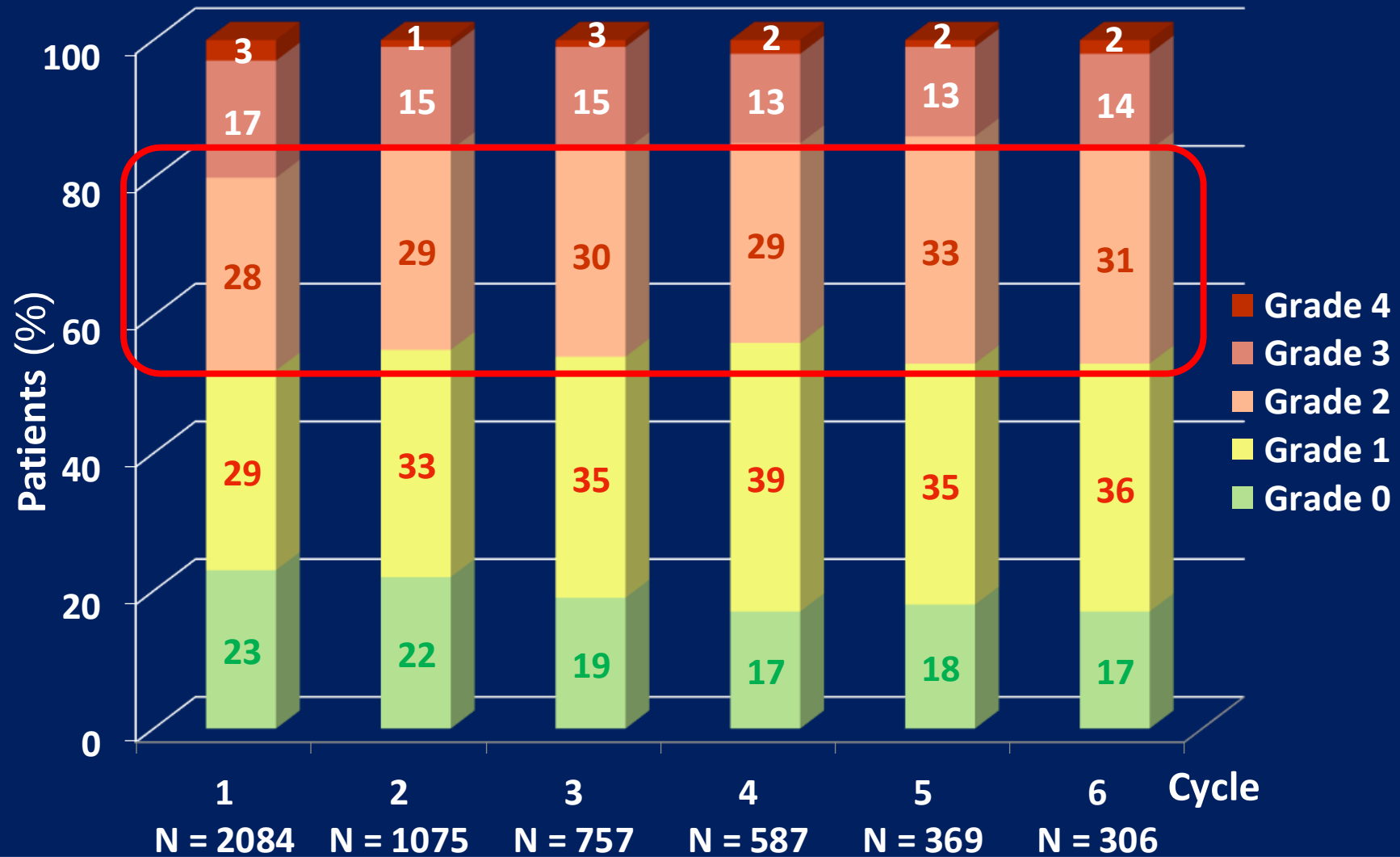
→ 25 076 AEs

161/2084 (7.7%)
patients experienced DLTs

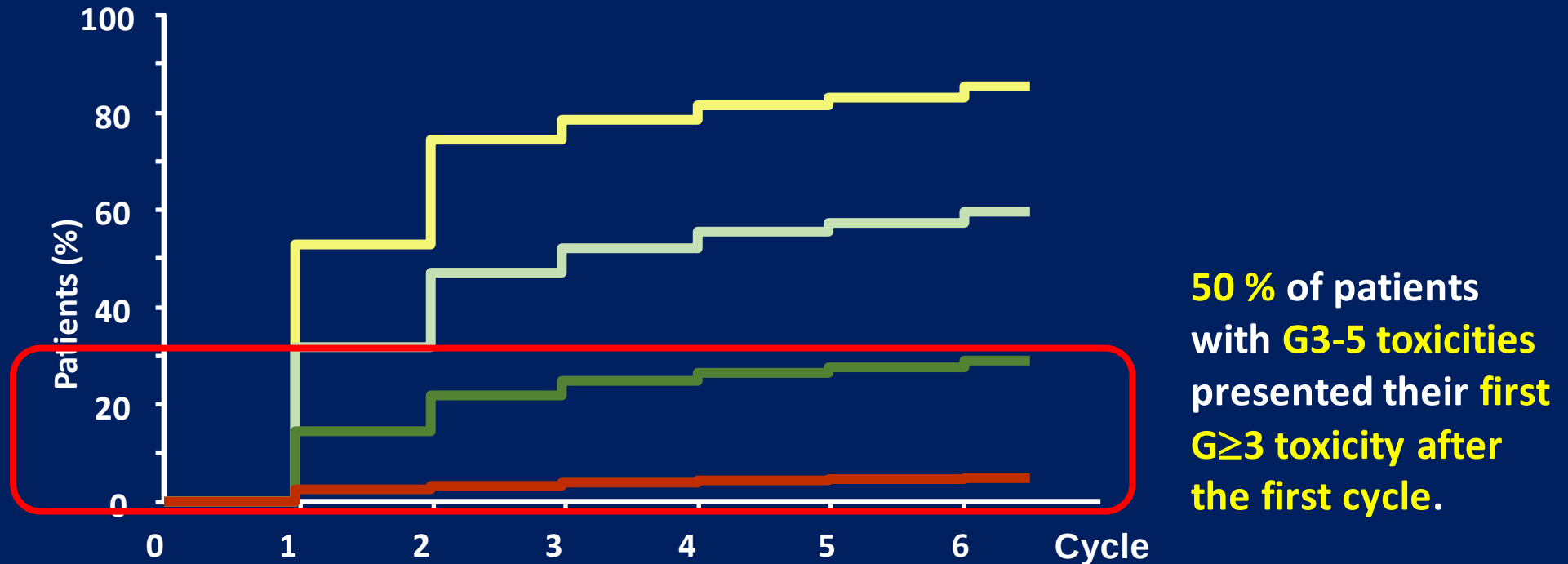
Worst grade AE over time



Worst grade AE over time



Time to first toxicity



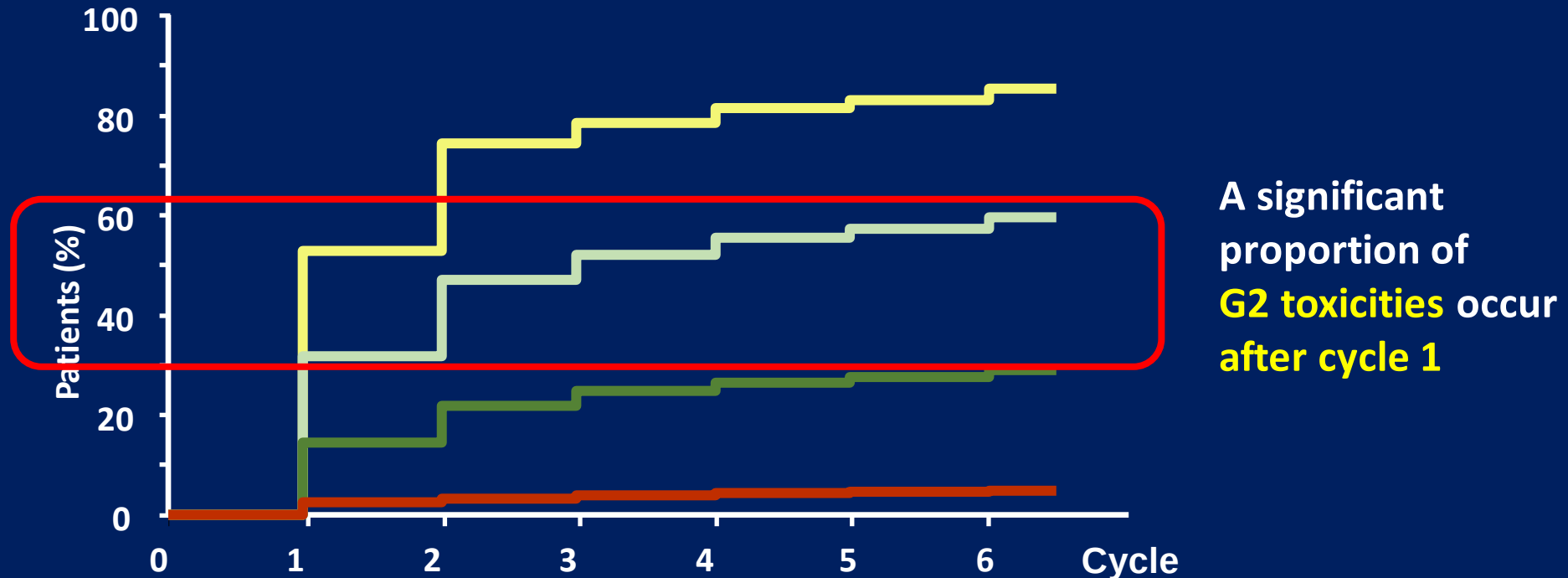
Number of patients at risk :

N of events

2084	894	303	200	116	77	1776
2084	1264	534	375	212	154	1242
2084	1489	684	515	317	247	599
2084	1589	747	580	365	301	100

- Grade $\geq$ 1
- Grade $\geq$ 2
- Grade $\geq$ 3
- Grade $\geq$ 4

Time to first toxicity

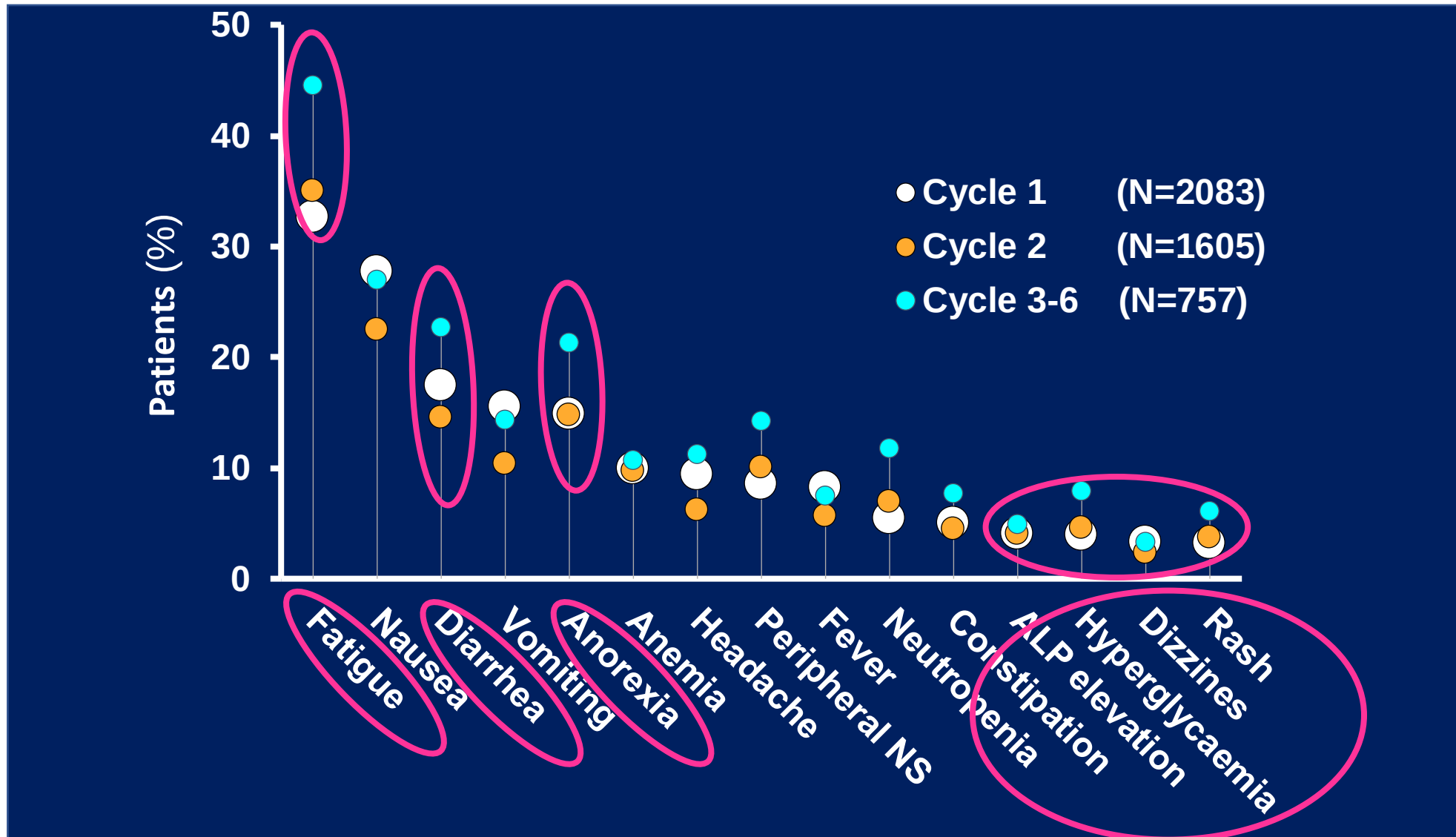


Number of patients at risk :

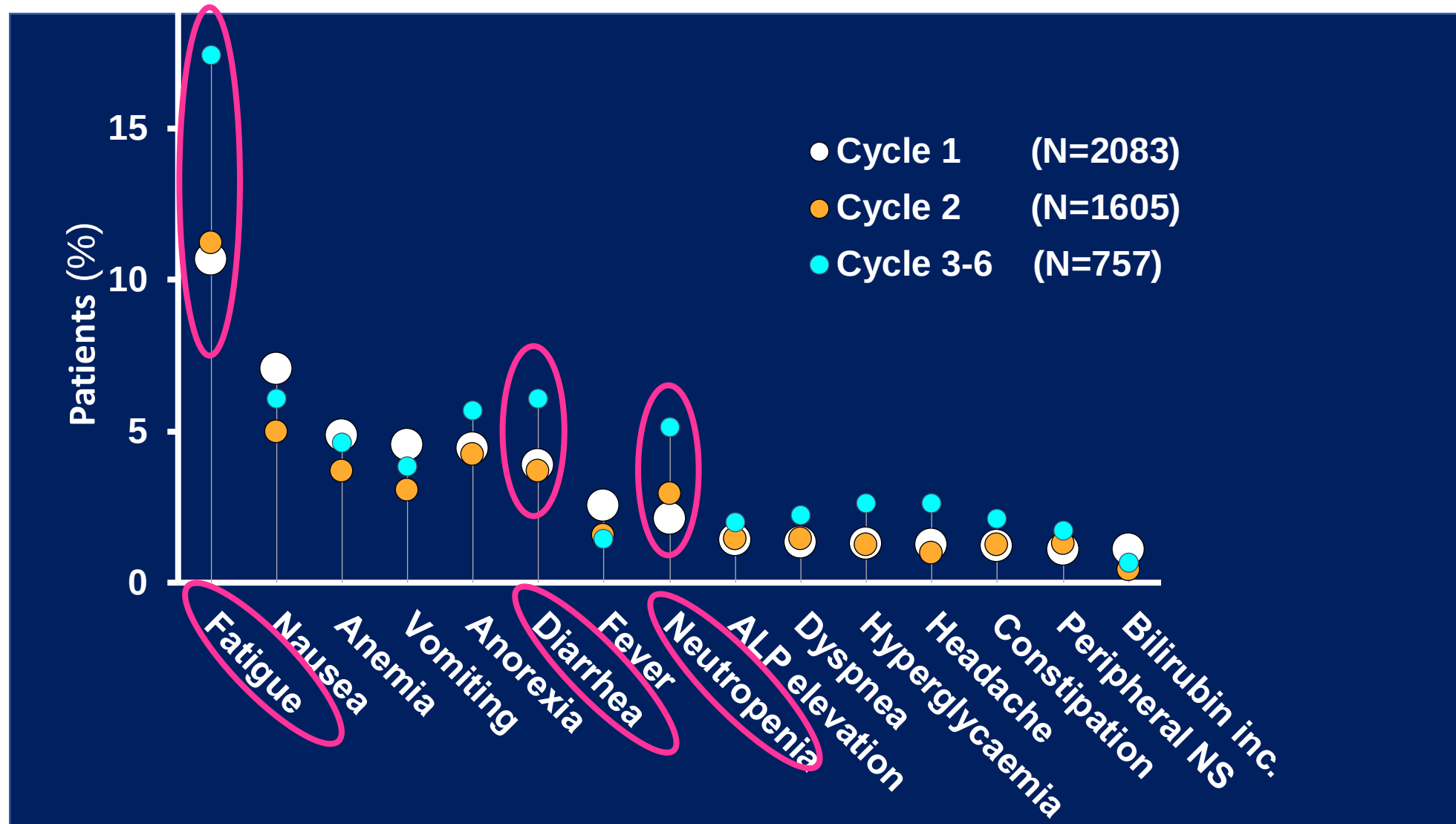
N of events

2084	894	303	200	116	77	1776	Grade >= 1
2084	1264	534	375	212	154	1242	Grade >= 2
2084	1489	684	515	317	247	599	Grade >= 3
2084	1589	747	580	365	301	100	Grade >= 4

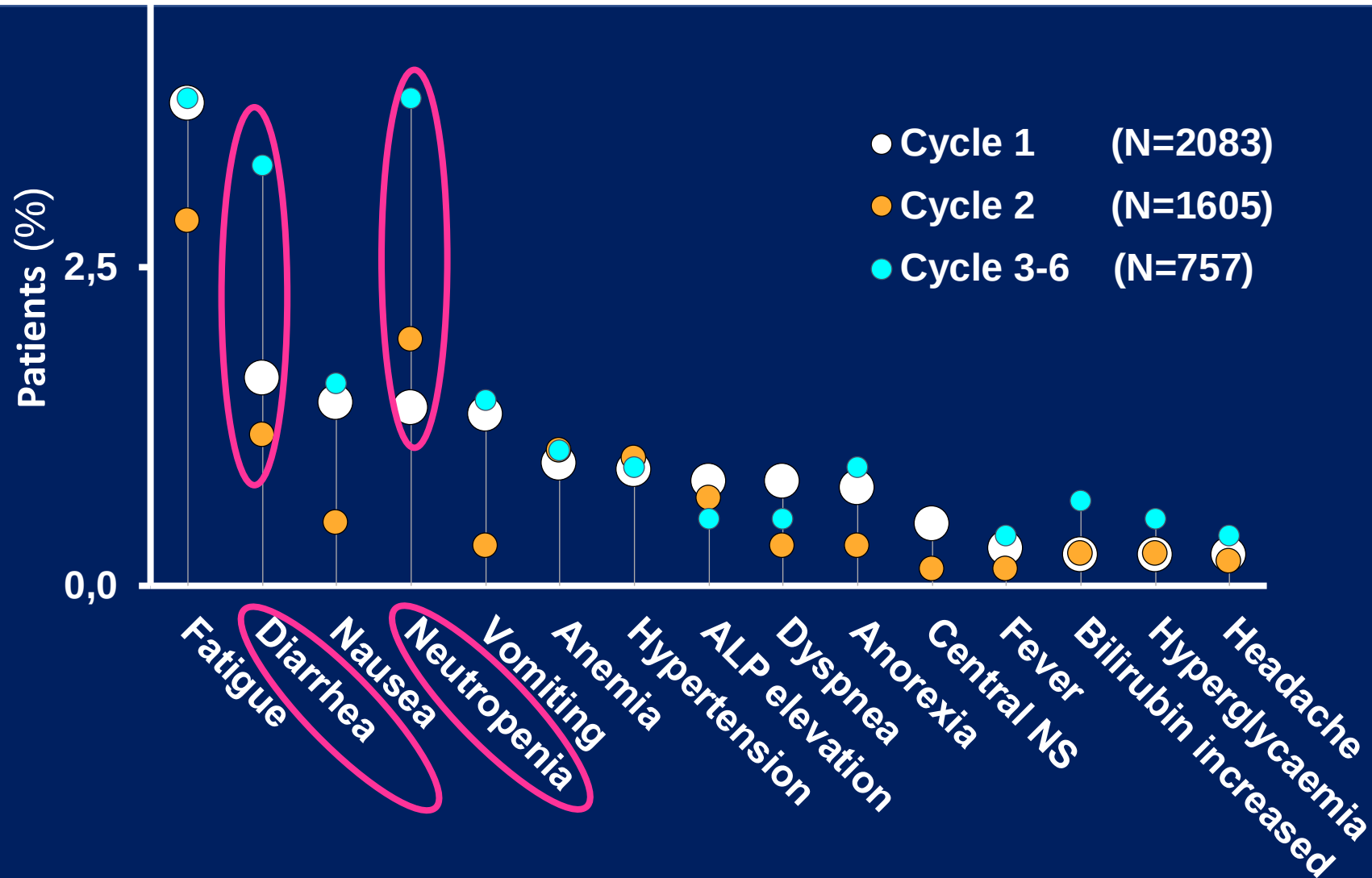
AEs of any grade over time



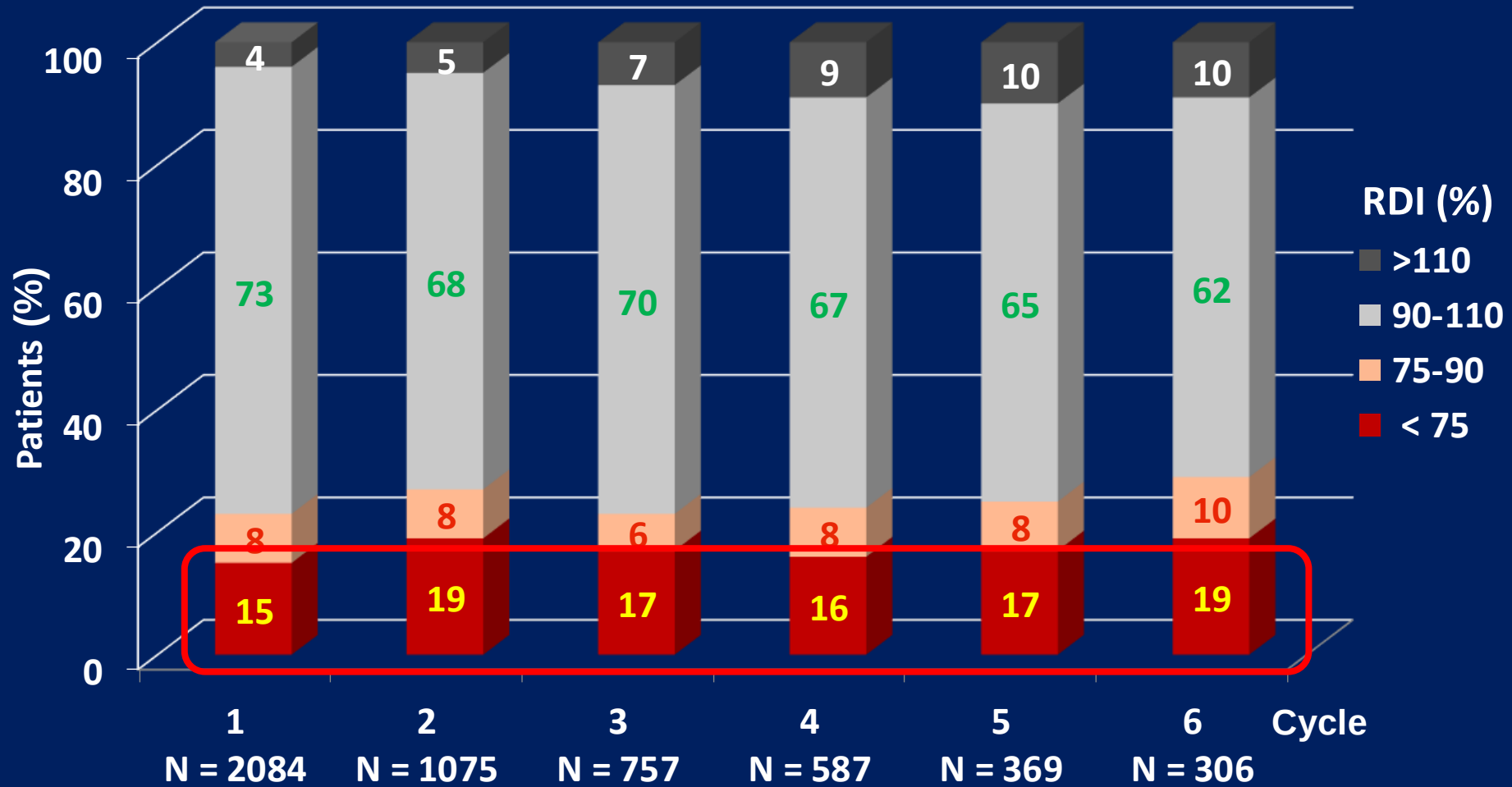
Grade 2 AEs over time



Grade 3 AEs over time

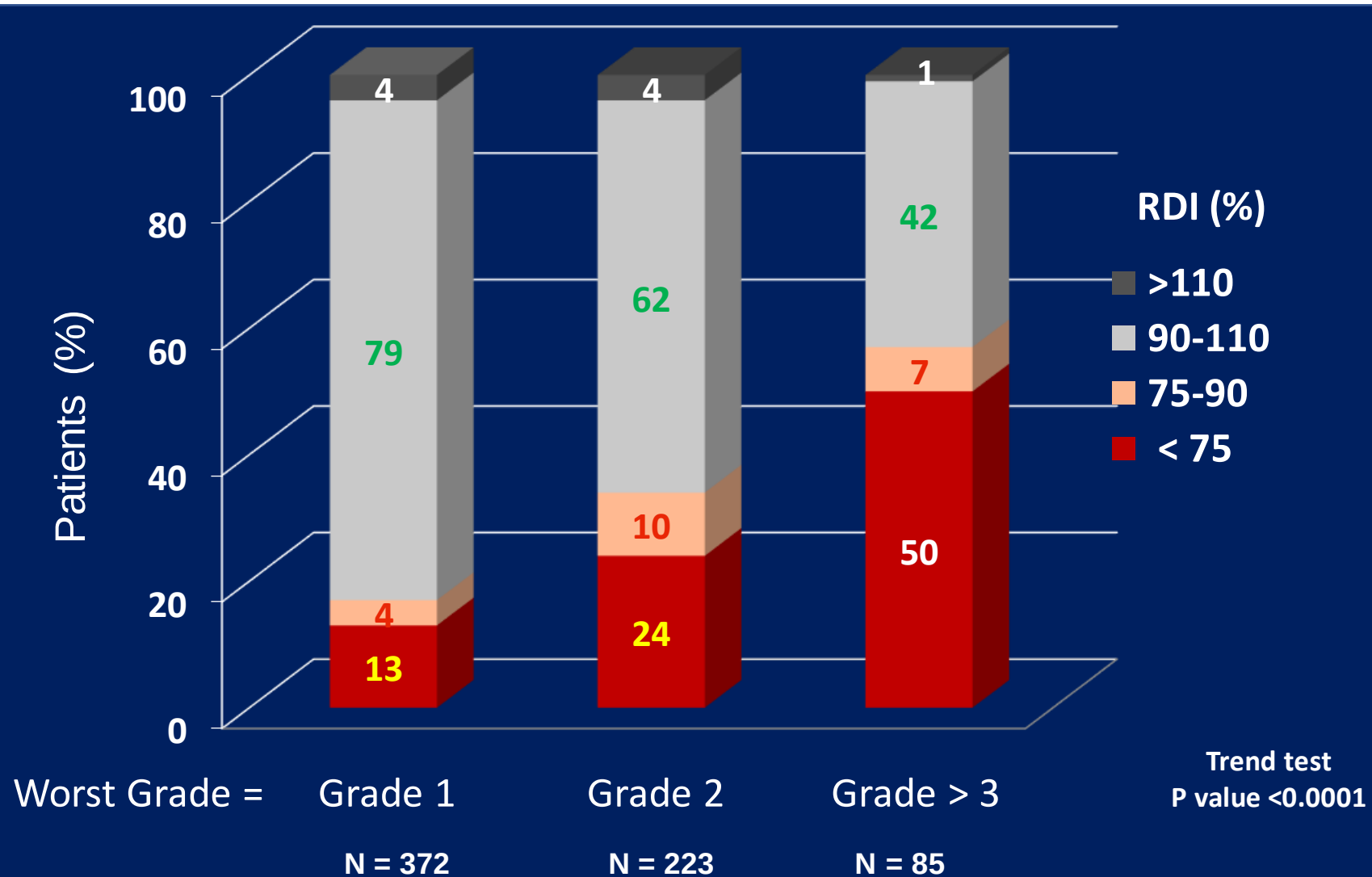


Relative Dose Intensity (RDI)*



* RDI = theoretical dose / effective administered dose per cycle

Fatigue and RDI at cycle 1



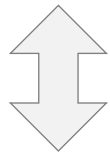
Acute vs Chronic DLT definition?

Cycle	1	2	3	4	5	6
Coefficient	1	0.5*		0.33*		
Toxicities	G3-4 +/- intol. G2	G3-4 + intol. G2 +/- chronic or repeated G2				
a/cDLT	acute	chronic				

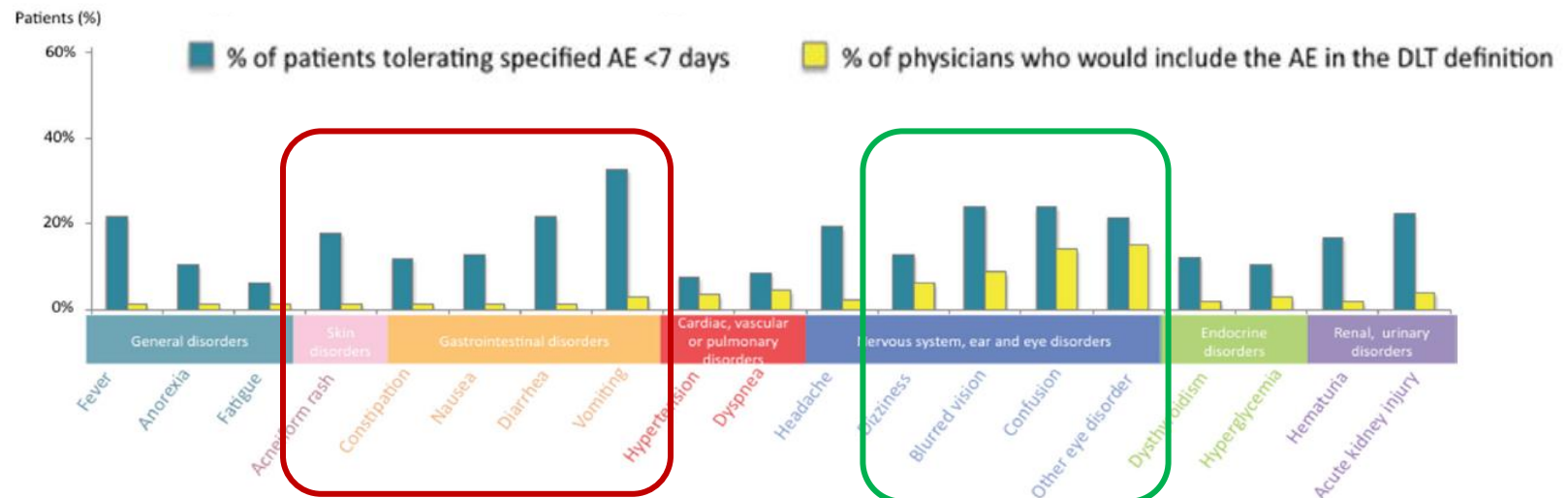
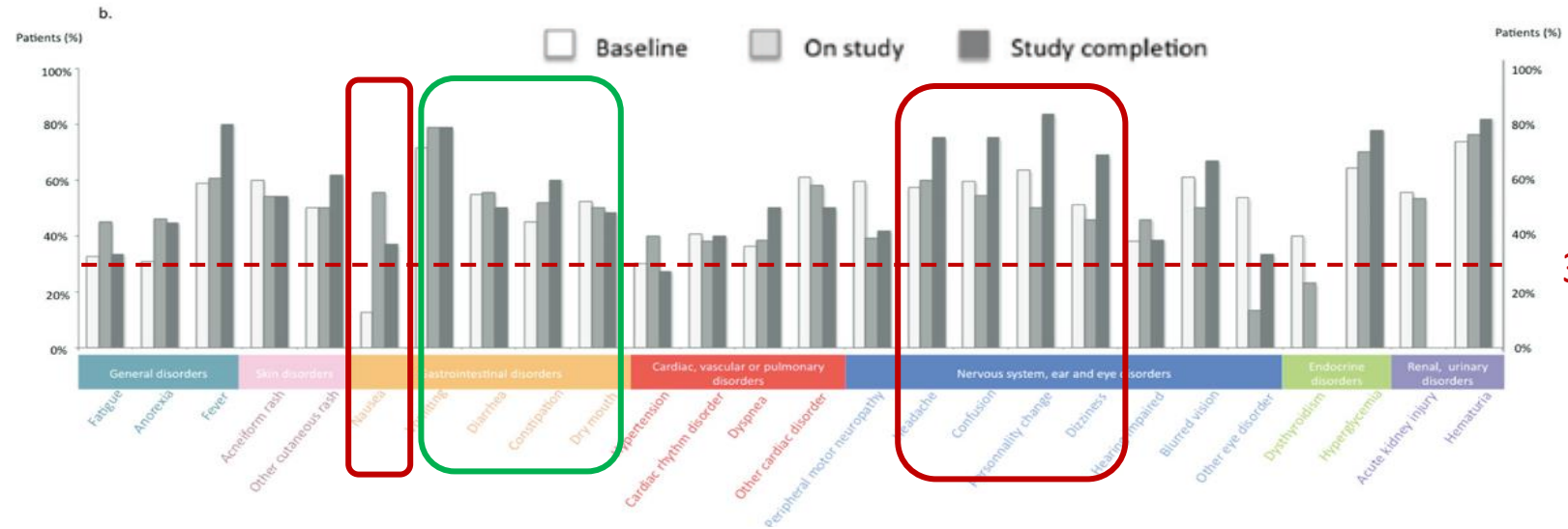
Determines
stopping rule for
dose escalation

Patients' vs physicians' perception of tolerability

- 52 patients
- 30 items
- 9000 responses



- 65 investigators
- 15 items



Conclusions

- > 50% of patients with **G3-5 toxicities** present their **first toxicity after the first cycle**
- Significant proportion of patients require **dose-reduction** for **selected G≤2 toxicities** as early as cycle 1
- **Collaboration** with **industry** is key to build meaningful databases

-> Main Recommendations:

1. Dose-escalation

- Timing : based on data from **C1 only**
- **Dose-increment** recommendation: consider **all available information**, including late toxicities

2. **Report all toxicities** comprehensively, even if not occurring during the DLT period

3. **Recommended Dose** should

- incorporate **all available** information, notably toxicities observed after C1
- be based on **achieving > 75% RDI**

Perspectives

- **Flexible designs**
 - Intra-patient dose-escalation , back-filling, etc.
 - Specific populations
 - Randomized dose confirmation
- Implementation of **Patient-Reported Outcomes**
- Specific challenges of **combinations**
- Early involvement of **Regulatory Authorities**

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