MADRID 2014 ESMO congress

Symptomatic toxicities experienced during anti-cancer treatment: comparison of patients' and physicians' reporting in 3 randomized controlled trials

Massimo Di Maio*, Maria Carmela Piccirillo, Gennaro Daniele, Francesco Nuzzo, Cesare Gridelli, Vittorio Gebbia, Fortunato Ciardiello, Sabino De Placido, Anna Ceribelli, Adolfo Favaretto, Andrea de Matteis, Ronald Feld, Charles Butts, Natasha Leighl, Alessandro Morabito, Jane Bryce, Simona Signoriello, Ciro Gallo and Francesco Perrone

* Clinical Trials Unit

National Cancer Institute – "G.Pascale" Foundation, Napoli, Italy

Disclosure

- I have no conflicts of interest to declare.

Background

- Information available about symptomatic toxicities of anti-cancer treatments is based on reports made by clinicians, not on direct reporting by patients. [1]
- Therefore, some side effects could be under-reported. [2,3]
- Reflecting an increasing focus on a patient-centered approach, scientific interest in the integration of patient-reported outcomes into drug safety evaluation is growing. [4]

[1] Basch E. J Natl Cancer Inst 103: 1808-10, 2011.
[2] Petersen MA. Eur J Cancer 42: 1159-66, 2006.
[3] Fromme EK. J Clin Oncol 22: 3485-90, 2004.
[4] Basch E. Annu Rev Med 65: 307-17, 2014.

Aim of the study

- To describe patients' and physicians' reporting of 6 symptomatic toxicities occurred during anti-cancer treatment, based on data prospectively collected in randomized trials, in order to evaluate:
  - the **agreement** between patients and physicians
  - the rate of possible **under-reporting** by physicians

Patients

Patients enrolled in 3 multicenter, randomized trials (coordinated by the Clinical Trials Unit, NCI Naples)

Trial	Enrolment years	Setting	Treatments
ELDA [1] (NCT00331097)	2003 – 2011	Early breast cancer, pts 65 – 79 yrs	• CMF • Docetaxel
GECO [2] (NCT00385606)	2003 – 2005	Advanced NSCLC, pts < 70 yrs	Cisplatin/Gemcitabine +/- Rofecoxib
TORCH [3] (NCT00349219)	2006 – 2009	Advanced NSCLC, pts < 70 yrs (Italy), no age limit (Canada)	• Cisplatin/Gemcitabine • Erlotinib

[1] Perrone F. ESMO 2014 (abstract 256O).
[2] Gridelli C. Lancet Oncol 8: 500-12, 2007.
[3] Gridelli C. J Clin Oncol 30: 3002-11, 2012.

Methods (1)

Trial	Adverse events reporting	QoL questionnaires
ELDA (NCT00331097)	NCI-CTC v2.0	EORTC QLQ C30 + BR23
GECO (NCT00385606)	NCI-CTC v2.0	EORTC QLQ C30 + LC13
TORCH (NCT00349219)	CTCAE v3.0	EORTC QLQ C30 + LC13

- **Adverse events** prospectively collected by physicians → any grade during each cycle
- **Quality of life (QoL)** questionnaires filled in by patients at the end of each treatment cycle → any severity during last week

Methods (2)

- Analysis was limited to the first 3 cycles.
- Rates of **6 toxicities** reported by patients and physicians were described:
  - Anorexia
  - Nausea
  - Vomiting
  - Constipation
  - Diarrhea
  - Hair loss
- **Agreement** between patients' and physicians' evaluation was assessed by Cohen's κ.
- **Relative under-reporting** was calculated (toxicity reported by patients but not by physicians).

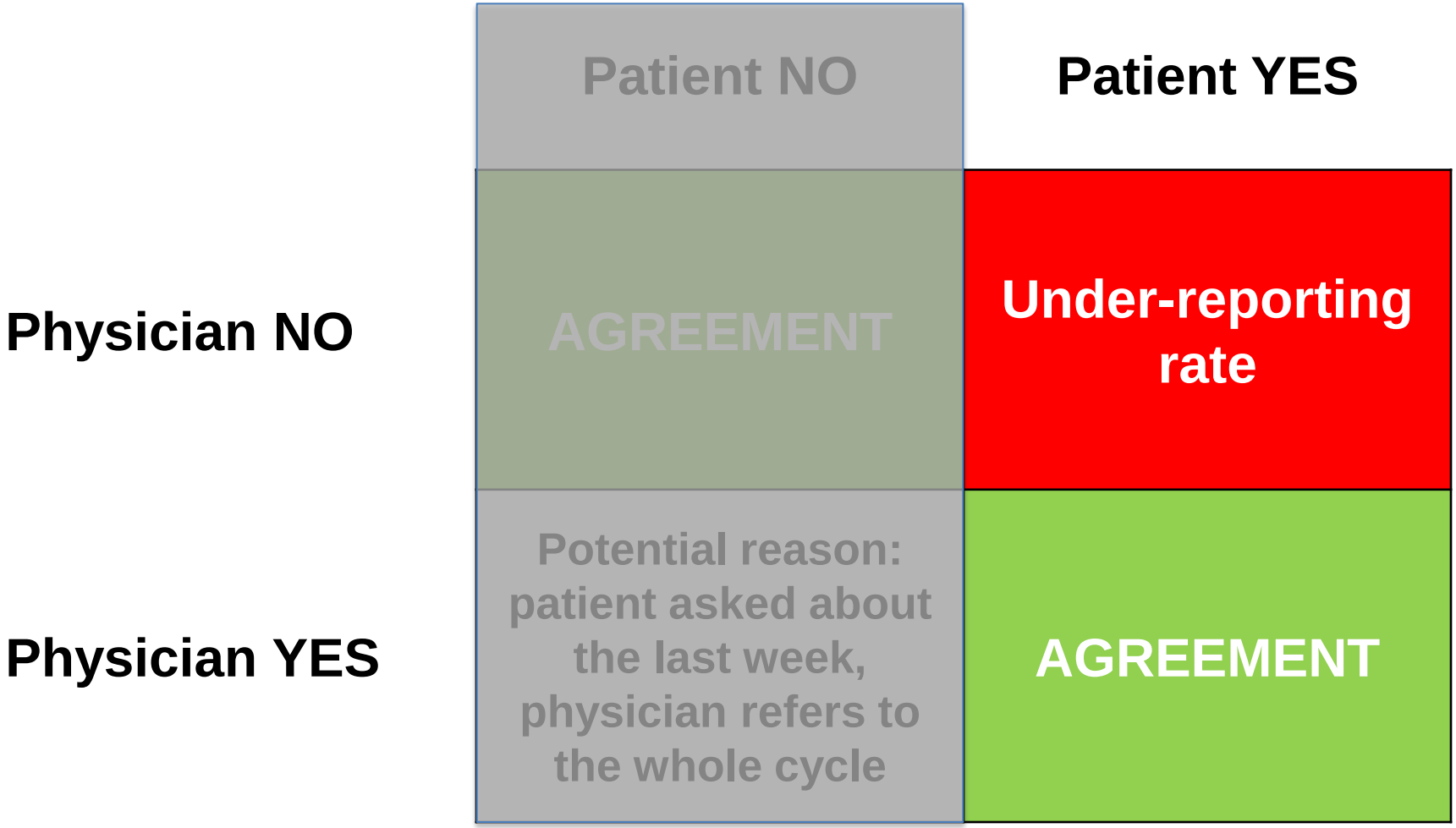
Agreement of patients' and physicians' reporting

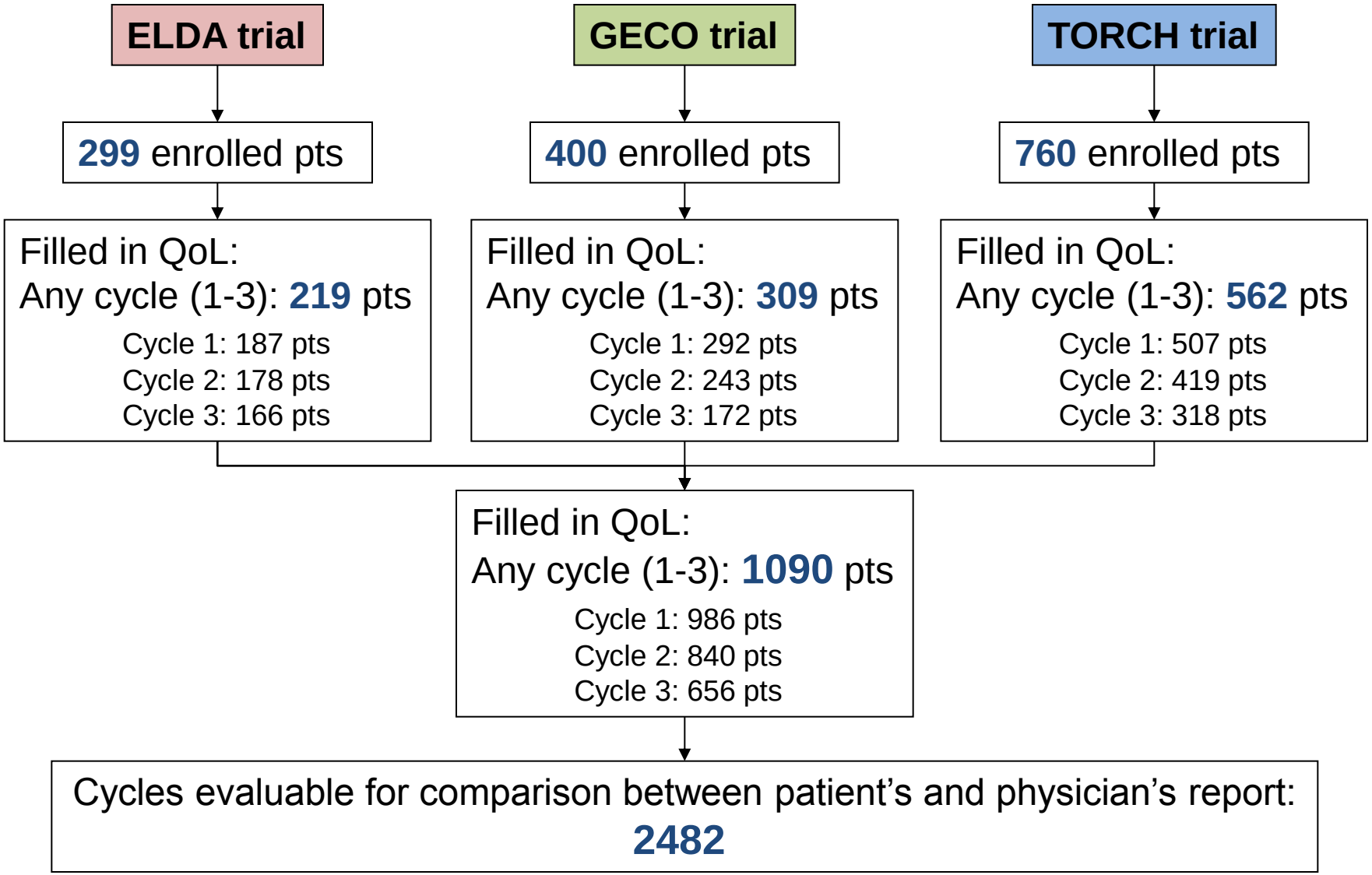
	Patient NO	Patient YES
Physician NO	AGREEMENT	NO AGREEMENT
Physician YES	NO AGREEMENT	AGREEMENT

Agreement of patients' and physicians' reporting

	Patient NO	Patient YES
Physician NO	AGREEMENT	NO AGREEMENT
Physician YES	Potential reason: patient asked about the last week, physician refers to the whole cycle	AGREEMENT

Under-reporting by physicians




ELDA trial
299 enrolled pts
Filled in QoL:
Any cycle (1-3): 219 pts
Cycle 1: 187 pts
Cycle 2: 178 pts
Cycle 3: 166 pts
GECO trial
400 enrolled pts
Filled in QoL:
Any cycle (1-3): 309 pts
Cycle 1: 292 pts
Cycle 2: 243 pts
Cycle 3: 172 pts
TORCH trial
760 enrolled pts
Filled in QoL:
Any cycle (1-3): 562 pts
Cycle 1: 507 pts
Cycle 2: 419 pts
Cycle 3: 318 pts
Filled in QoL:
Any cycle (1-3): 1090 pts
Cycle 1: 986 pts
Cycle 2: 840 pts
Cycle 3: 656 pts
Cycles evaluable for comparison between patient's and physician's report:
2482

Patients' characteristics (n=1090)

Age	Median (range)	64	(29 – 81)
Gender	Males	618	(56.7%)
	Females	472	(43.3%)
ECOG performance status	0	642	(58.9%)
	1	448	(41.1%)
Country	Italy	957	(87.8%)
	Canada	133	(12.2%)
Type of disease	Early breast cancer	219	(20.1%)
	Advanced NSCLC	871	(79.9%)
Treatment	Cisplatin + gemcitabine	469	(43.0%)
	Cis + gem + rofecoxib	116	(10.6%)
	Erlotinib	286	(26.2%)
	CMF	116	(10.6%)
	Docetaxel	103	(9.4%)

Agreement

Association between patient reporting (any severity) and physician reporting (any grade) – 2482 cycles

	Anorexia	Nausea	Vomiting	Constipation	Diarrhea	Hair loss
Toxicity reported by:						
Patient: NO Physician: NO	51.4%	44.5%	76.7%	59.3%	73.1%	55.6%
Patient: NO Physician: YES	2.4%	10.1%	6.4%	3.2%	4.2%	1.7%
Patient: YES Physician: NO	37.0%	24.6%	9.7%	29.7%	13.9%	28.8%
Patient: YES Physician: YES	9.2%	20.8%	7.2%	7.8%	8.9%	13.9%
Cohen's κ*	0.162	0.280	0.377	0.183	0.396	0.323

* κ>0.75: excellent agreement; κ=0.40-0.75: fair to good agreement; κ<0.40: poor agreement.
(Fleiss JL . New York: John Wiley 1981)

Association between patient reporting (any severity) and physician reporting (any grade) – 1090 patients

	Anorexia	Nausea	Vomiting	Constipation	Diarrhea	Hair loss
Toxicity reported by:						
Patient: NO Physician: NO	35.1%	30.8%	64.2%	46.1%	59.1%	47.8%
Patient: NO Physician: YES	2.6%	9.2%	9.8%	2.9%	5.2%	1.4%
Patient: YES Physician: NO	46.3%	9.8%	12.3%	35.3%	18.1%	33.1%
Patient: YES Physician: YES	16.0%	2.9%	13.7%	15.6%	17.6%	17.7%
Cohen's κ*	0.153	0.342	0.407	0.244	0.447	0.316

* κ>0.75: excellent agreement; κ=0.40-0.75: fair to good agreement; κ<0.40: poor agreement.
(Fleiss JL . New York: John Wiley 1981)

Under-reporting

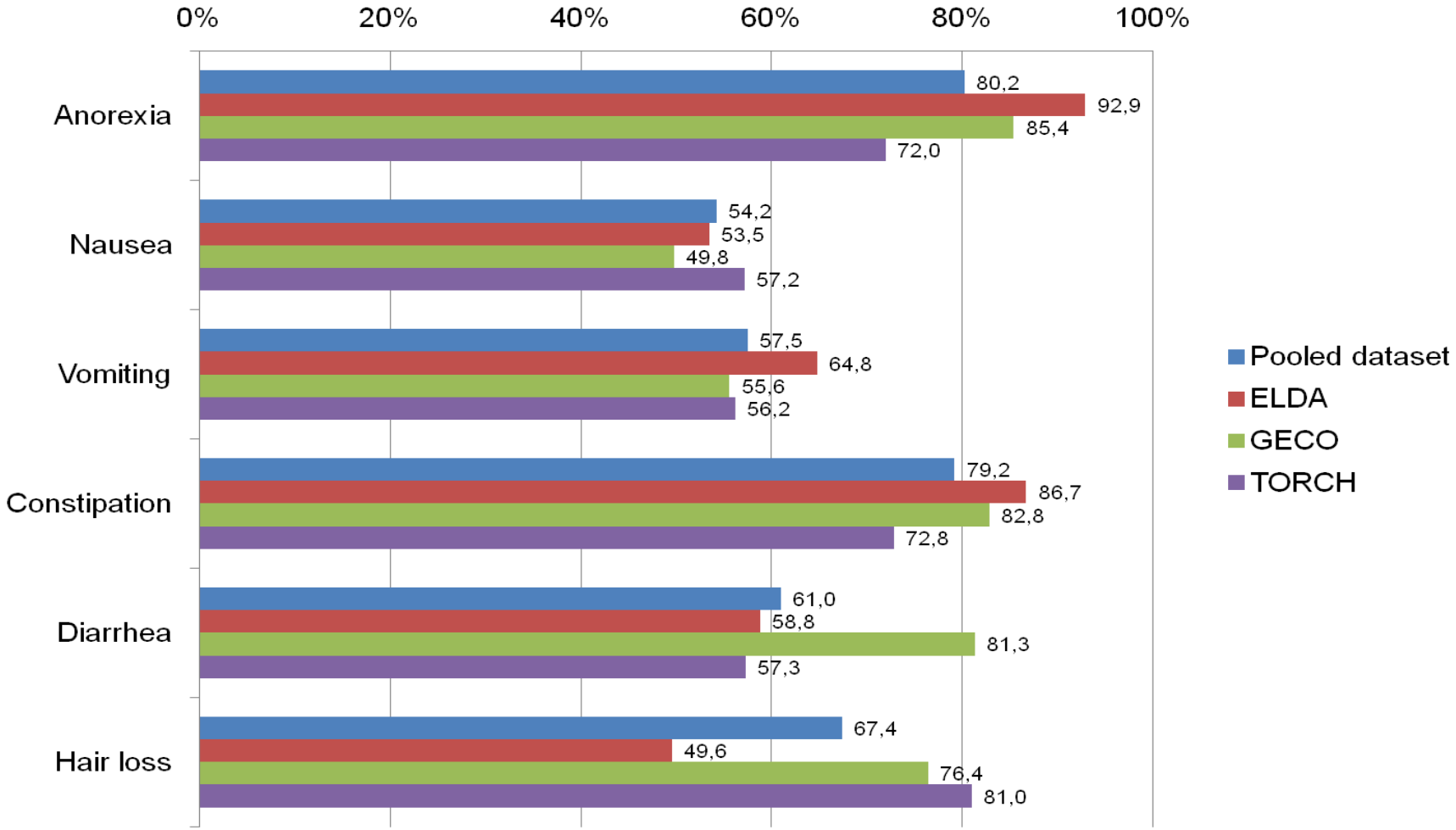
Association between patient reporting (any severity) and physician reporting (any grade) – 2482 cycles

	Anorexia	Nausea	Vomiting	Constipation	Diarrhea	Hair loss
Toxicity reported by:						
Patient: NO Physician: NO	51.4%	44.5%	76.7%	59.3%	73.1%	55.6%
Patient: NO Physician: YES	2.4%	10.1%	6.4%	3.2%	4.2%	1.7%
Patient: YES Physician: NO	37.0%	24.6%	9.7%	29.7%	13.9%	28.8%
Patient: YES Physician: YES	9.2%	20.8%	7.2%	7.8%	8.9%	13.9%
Under-reporting by physicians	**80.2%**	**54.2%**	**57.5%**	**79.2%**	**61.0%**	**67.4%**

Association between patient reporting (any severity) and physician reporting (any grade) – 1090 patients

	Anorexia	Nausea	Vomiting	Constipation	Diarrhea	Hair loss
Toxicity reported by:						
Patient: NO Physician: NO	35.1%	30.8%	64.2%	46.1%	59.1%	47.8%
Patient: NO Physician: YES	2.6%	9.2%	9.8%	2.9%	5.2%	1.4%
Patient: YES Physician: NO	46.3%	9.8%	12.3%	35.3%	18.1%	33.1%
Patient: YES Physician: YES	16.0%	2.9%	13.7%	15.6%	17.6%	17.7%
Under-reporting by physicians	**74.4%**	**40.7%**	**47.3%**	**69.3%**	**50.8%**	**65.2%**

Relative under-reporting by physicians by trial (any severity reported by patients)



Relative under-reporting: proportion of cycles with toxicity (any severity) reported by patient but not reported at all by physician

"Very much" toxicity reported by patients: association between patient reporting and physician reporting (any grade)

Per cycle analysis

	Anorexia (93 cycles)	Nausea (75 cycles)	Vomiting (27 cycles)	Constipation (95 cycles)	Diarrhea (34 cycles)	Hair loss (146 cycles)
Any grade toxicity reported by physician:						
YES	48.4%	58.7%	77.8%	37.9%	73.5%	53.4%
NO (under-reporting by physician)	**51.6%**	**41.3%**	**22.2%**	**62.1%**	**26.5%**	**46.6%**

"Very much" toxicity reported by patients: association between patient reporting and physician reporting (any grade)

Per patient analysis

	Anorexia (76 pts)	Nausea (62 pts)	Vomiting (23 pts)	Constipation (77 pts)	Diarrhea (29 pts)	Hair loss (103 pts)
Any grade toxicity reported by physician:						
YES	50.0%	74.2%	87.0%	65.8%	75.9%	57.3%
NO (under-reporting by physician)	**50.0%**	**25.8%**	**13.0%**	**44.2%**	**24.1%**	**42.7%**

Results (summary)

- **Agreement was low**
  - Toxicity rates reported by physicians were always lower than those reported by patients

- **Under-reporting by physicians was high**
  - ranging from 54.2% to 80.2% of cycles when patients reported "any severity" toxicity
  - ranging from 22.2% to 62.1% examining only cycles when patients reported "very much" toxicity

Conclusions

- Subjective toxicities are at high risk of **under-reporting** by physicians, even when prospectively collected within randomized trials and even if perceived as “very much” by the patient.
- Our findings strongly support **the incorporation of patient-reported information** into reporting of adverse events in clinical trials.

Acknowledgments

- All the patients participating in the ELDA, GECO and TORCH trials.

- All the investigators at 78 Institutions in Italy and Canada.