An exemplar of a systems pharmacology approach for a detailed investigation of an adverse drug event as a result of drug-drug interactions

Poster #: PT-012

ASCPT Annual Meeting 2017
Washington, DC

Sarah Kim[1], Gezim Lahu[2], Lawrence J. Lesko[1], Mirjam N. Trame[1,*]

[1] Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, University of Florida, Orlando, FL
[2] Takeda Pharmaceuticals International GmbH, Zurich, Switzerland
[*]Corresponding author: mtrame@cop.ufl.edu

Systems Approach to Drug Safety utilizing Adverse Event Databanks

Systems Approach to Drug Safety utilizing Adverse Event Databanks

FAERS

- Post-market surveillance databank of ADR by the FDA
- Rich source of ADR information submitted voluntarily by drug manufacturers, healthcare professionals and consumers
- ADR reports evaluated by clinical reviewers at the CDER or CBER

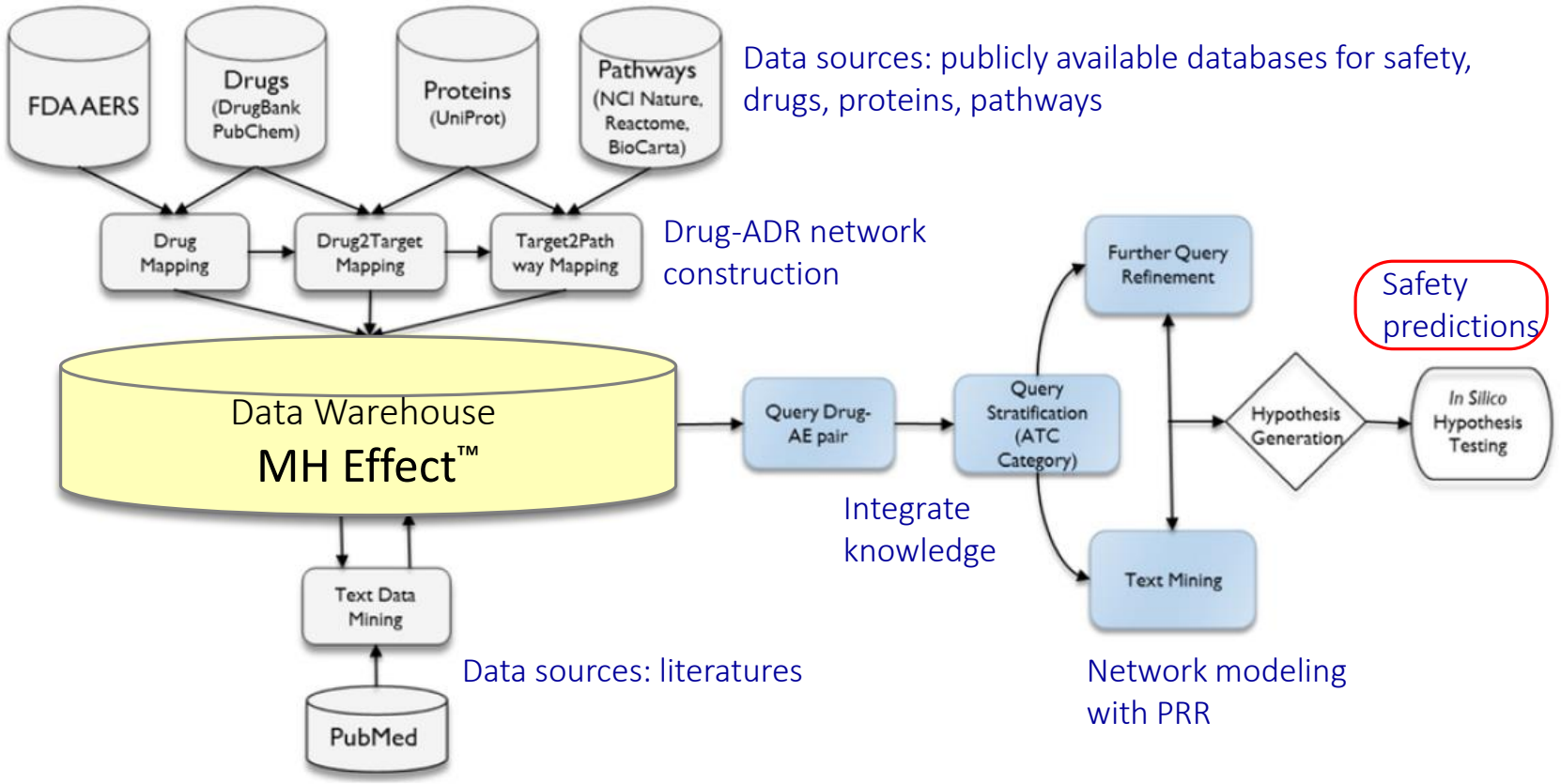
Evidex™
Advera Health

- Maps FAERS to AE and outcome costs
- Provides RxCosts® to determine direct costs of adverse events, RxSignal® for predictive notification of pending regulatory action, and RxScore® - a drug safety scorecard

MH Effect™
Molecular Health

- Maps FAERS to chemical and biological sources to integrate knowledge for hypothesis generation towards the underlying molecular pathways and targets of the ADR

Systems Approach to Drug Safety utilizing Adverse Event Databanks



The objective of the following analysis was to select a prototype ADR to develop a systems pharmacology platform for drug safety

MH Effect™
Systems Approach to Analyze Drug-ADR

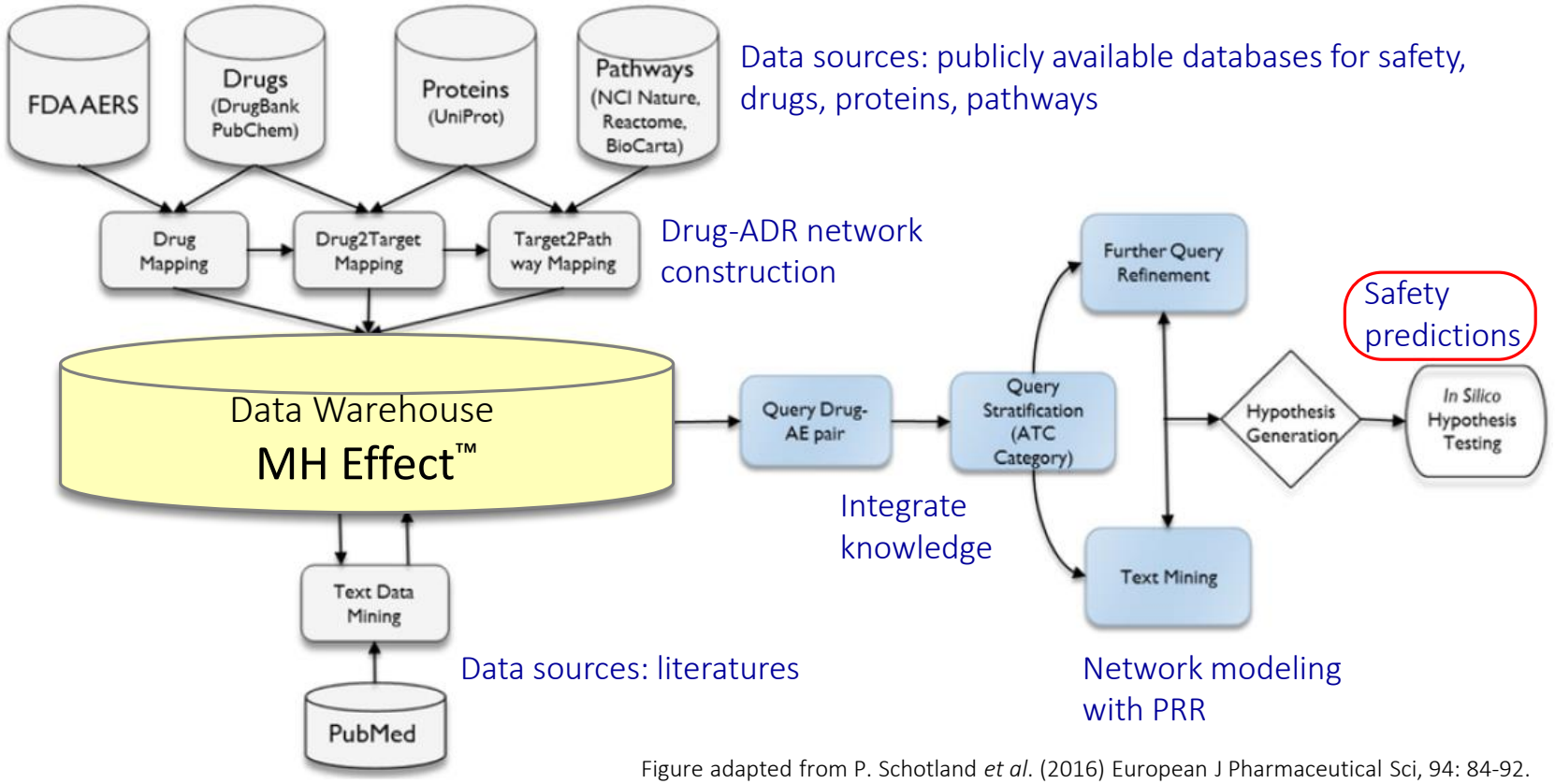


Figure adapted from P. Schotland *et al.* (2016) European J Pharmaceutical Sci, 94: 84-92.

Mapping FAERS to chemical and biological sources integrates knowledge for hypothesis generation towards the underlying molecular pathways and targets of the ADR for safety predictions.

Proportional Reporting Ratio (PRR):

a statistical method used to assess statistical associations between drugs and events of interest using number of case reports

	N w/ event of interest	N w/o event of interest
N w/ drug of interest	a	b
N w/o drug of interest	c	d

N = number of case reports.

$$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}.$$

Reference: S.J. Evans *et al.* (2001) Pharmacoepidemiology and Drug Safety, 10(6): 483-486.

Facts

- 1/3 of new FDA drug approvals are in oncology since 2014 with several of these being categorized as targeted therapy drugs (TTDs)

- **Clinical response** of cancer patients **to TTDs depends on**:
  1) Efficacy (benefit) variables → on-target effects
     - Influenced by sensitivity of tumor cells, molecular properties of tumors, and tumor microenvironment
  2) Safety (risk) variables → off-target effects
     - Influenced by sensitivity of the host, including intrinsic factors such as genetic metabolic polymorphisms and renal function, and extrinsic factors such as drug-drug interactions

Reference: T. Force *et al*. (2007) Nat Rev Cancer, 7(5): 332-344.

Efficacy of TTDs compromised by one additional host factor

- 96% of cancer patients are concomitantly given 1-6 additional medications → serious drug-drug interactions

Reference: M.H. Hanigan *et al*. (2008) J Oncol Pharm Practice, 14: 123-130.

Case Study

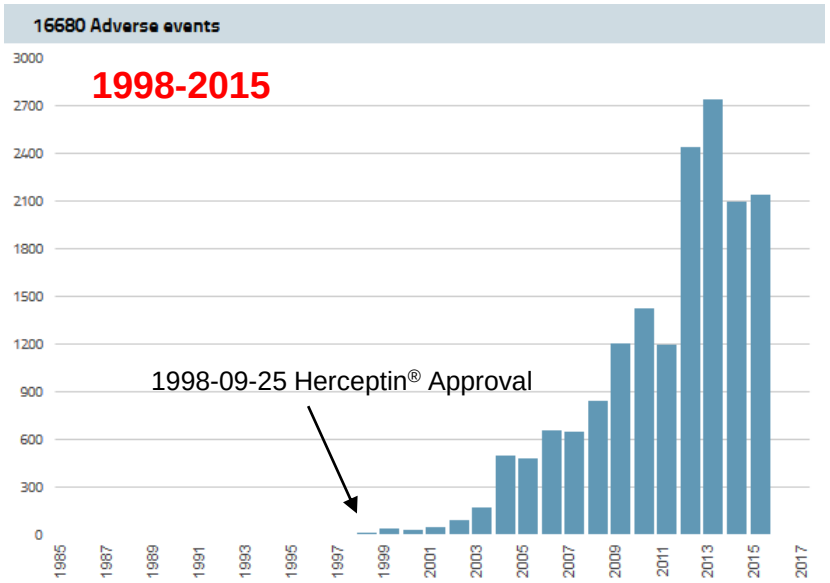
- Starting with a case study of a typical breast cancer patient receiving the following prescriptions:
  - **Trastuzumab** (Herceptin®) TTD (Target: HER2/neu)
  - **Doxorubicin** (Doxil® and Adriamycin®) Chemotherapy, Anthracycline
  - **Tamoxifen** (Nolvadex® and Soltamox®) Hormonal therapy
  - **Paroxetine** (Paxil®, Pexeva®, and Brisdelle®) Antidepressant
  - **Lapatinib** (Tykerb®) TTD (Target: HER2/neu, EGFR)

Cardiotoxicity → Heart Failure

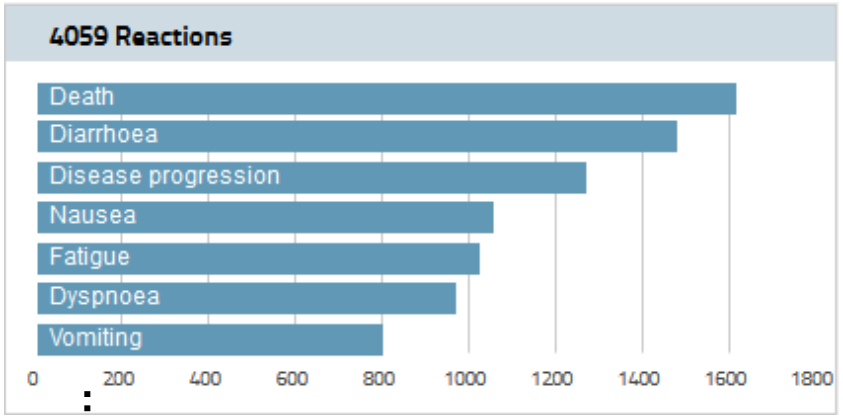
Safety Assessment Overview

Cohort Search Term:
Trastuzumab (#1)

- **Number of AEs per year**

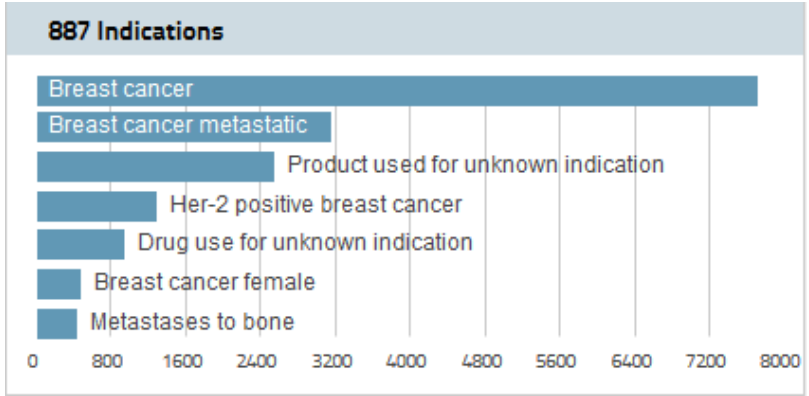


- **Top AEs (ranked by the number of cases (N))**

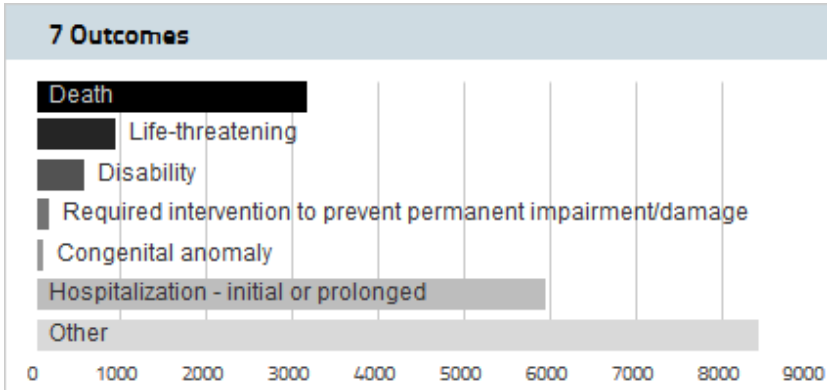


Cardiotoxicity: N = 196 (Ranking 69),
PRR = 47.06 (Ranking 2 among the top 69)

- **Top 7 Indications for which Trastuzumab is prescribed**

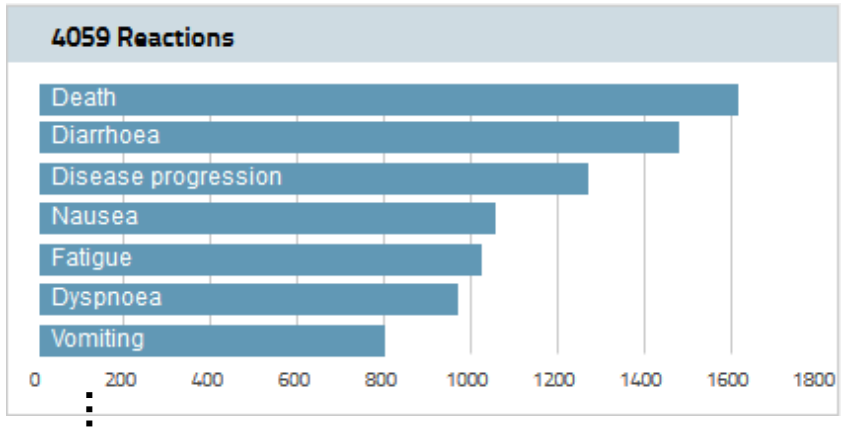


- **Final patient outcome due to AEs**



Safety Assessment Overview

- **Top AEs (ranked by the number of cases (N))**

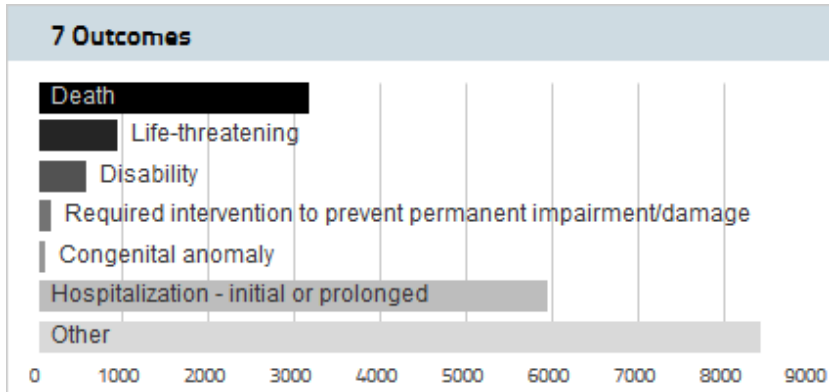


Cardiotoxicity: N = 196 (Ranking 69),
PRR = 47.06 (Ranking 2 among the top 69)

Cohort	Total N of all AEs	N of Cardiotoxicity	PRR with Cardiotoxicity	95% CI PRR with Cardiotoxicity
Trastuzumab	16680	196	47.06	**40.59** - 54.56
Doxorubicin	35850	263	30.63	**26.87** - 34.91
Com. T+D	1157	36	113.12	**81.73** - 156.57

N = number of case reports, AE = adverse event, PRR = Proportional Reporting Ratio, CI = confidence interval.

- **Final patient outcome due to AEs**



Major Molecular Mechanisms of Trastuzumab-induced Cardiotoxicity

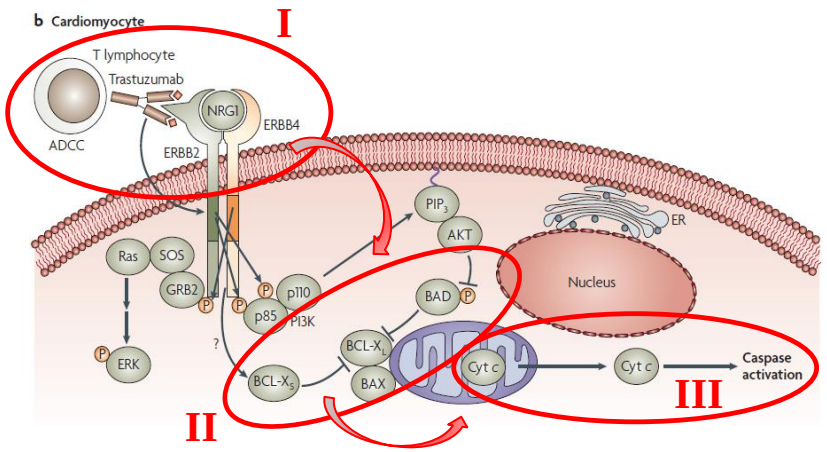


Figure from T. Force *et al*. (2007) Nat Rev Cancer, 7(5): 332-344.

	Ranking	Molecular Mechanism	PRR (95% CI)
I	1	Signaling by ERBB2 (HER2)	141.63 (140.31 – 142.96)
	4	Signaling by ERBB4	64.04 (63.64 – 64.44)
	9	ERBB receptor signaling network	62.40 (62.01 – 62.78)
	29	ERBB4 signaling events	25.42 (25.32 – 25.52)
		cont'd…	
II	34	Bh3-only proteins associate with and inactivate anti-apoptotic BCL-2 members	18.84 (16.42 – 21.61)
		cont'd…	
	37	Activation of BAD and translocation to mitochondria	18.71 (16.31 – 21.46)
		cont'd…	
III	40	Role of mitochondria in apoptotic signaling	18.10 (15.78 – 20.76)

PRR = Proportional Reporting Ratio, CI = confidence interval

- ∃ **Total 549 molecular mechanisms**
- **Ranked by PRR**

Combination Therapy: Trastuzumab and Doxorubicin

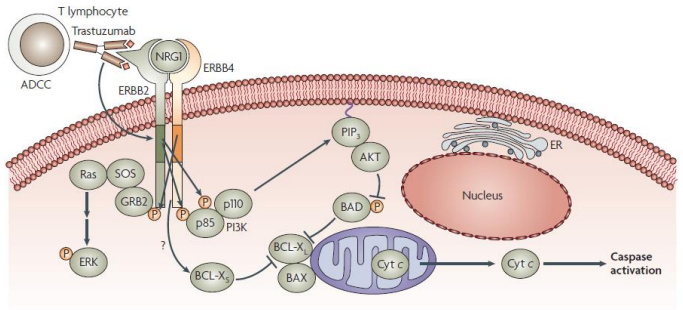


Figure from T. Force *et al.*, Nat Rev Cancer (2007) 7(5): 332-344.

Loss of mitochondrial membrane potential through **BCL-2 family**

Loss of **PGC-1α and PGC-1β proteins** which are critical for mitochondrial biogenesis and function

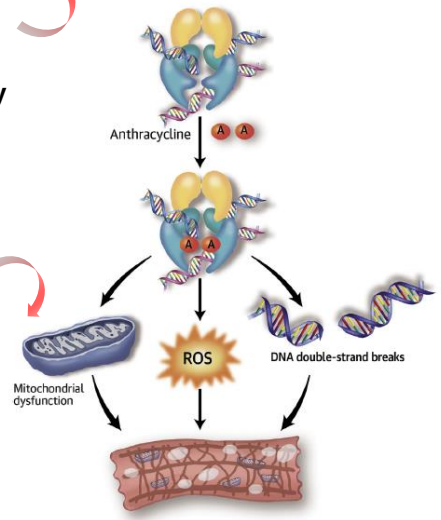


Figure from P. Vejpongsa and E.T.H. Yeh J American College Cardiol (2014) 64(9): 938-945.

Cohort	Molecular Mechanism	N	PRR	95% CI PRR
Trastuzumab	BH3-only proteins associated with and inactivate anti-apoptotic BCL-2 members	100	18.84	**16.42** – 21.61
Doxorubicin		42	5.89	4.47 – 7.78
Com. T+D		24	24.60	▲ **19.53** – 31.0
Trastuzumab	Activation of BAD and translocation to mitochondria	100	18.71	**16.31** – 21.46
Doxorubicin		42	5.85	4.44 – 7.72
Com. T+D		24	24.43	▲ **19.39** – 30.78
Trastuzumab	PPARα activates gene expression	35	0.58	**0.43** – 0.78
Doxorubicin		94	1.15	0.98 – 1.35
Com. T+D		4	0.36	▼ **0.14** – 0.90
Trastuzumab	Role of mitochondria in apoptotic signalling	100	18.10	**15.78** – 20.76
Doxorubicin		42	5.66	4.29 – 7.47
Com. T+D		24	23.64	▲ **18.76** – 29.79

N = number of case reports, PRR = Proportional Reporting Ratio, CI = confidence interval, ▲ = higher than Cohort-Trastuzumab, ▼= lower than Cohort-Trastuzumab, orange = harmful effect, green = protective effect.

Poster #: PT-012

Discussion and Conclusions

Hypothesis: The combination therapy of trastuzumab and doxorubicin may induce a synergistic effect of mitochondrial dysfunction in cardiomyocytes through different molecular pathways of the BCL-2 family, PPARα and PPARβ proteins, leading to an increased risk of developing cardiotoxicity.

What did this Systems-based approach provide versus a non-mechanistic approach?

- This **systems-based approach** provides a process to better map the mechanism of **drug-drug interactions** to targets and pathways

Inform Drug Development Pipelines

Poster #: PT-012

Acknowledgement

Thank you very much for your attention!

Dr. Mirjam N. Trame

Dr. Lawrence J. Lesko

Dr. Sonja Hartmann

Dr. Gezim Lahu

Dr. Majid Vakilynejad