


UniversitätsKlinikum Heidelberg

Analyzing adverse events by time-to-event models: The CLEOPATRA study

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Tanja Proctor[1] Martin Schumacher[2]

[1]Institute of Medical Biometry and Statistics, University of Heidelberg
[2]Institute of Medical Biometry and Statistics, University of Freiburg

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CLEOPATRA study

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Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

ABSTRACT

BACKGROUND

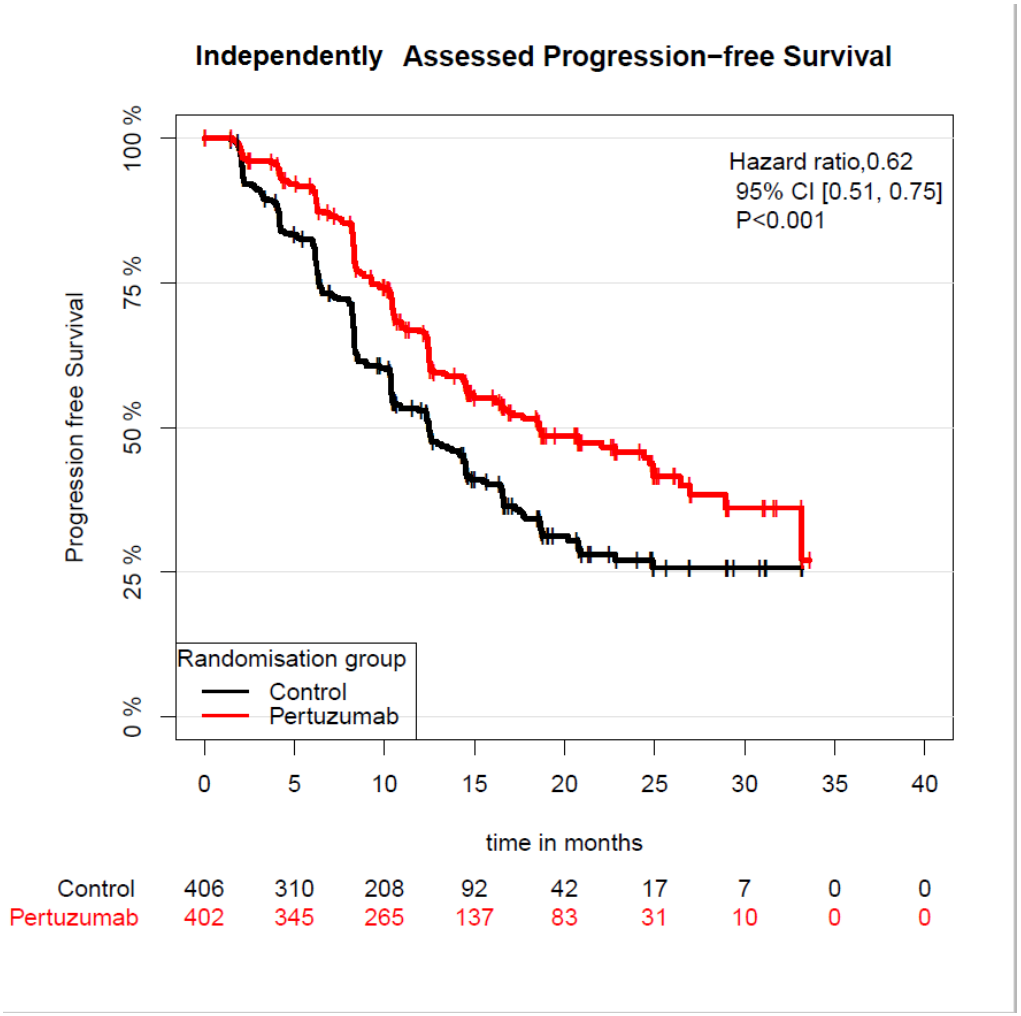
The anti–human epidermal growth factor receptor 2 (HER2) humanized monoclonal antibody trastuzumab improves the outcome in patients with HER2-positive metastatic breast cancer. However, most cases of advanced disease eventually progress. Pertuzumab, an anti-HER2 humanized monoclonal antibody that inhibits receptor dimerization, has a mechanism of action that is complementary to that of trastuzumab, and combination therapy with the two antibodies has shown promising activity and an acceptable safety profile in phase 2 studies involving patients with HER2-positive breast cancer.

From the Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston (J.B.); the Vall d'Hebron Institute of Oncology, Barcelona (J.C.); the Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine (S.-B.K.), the Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine (S.-A.I.), and

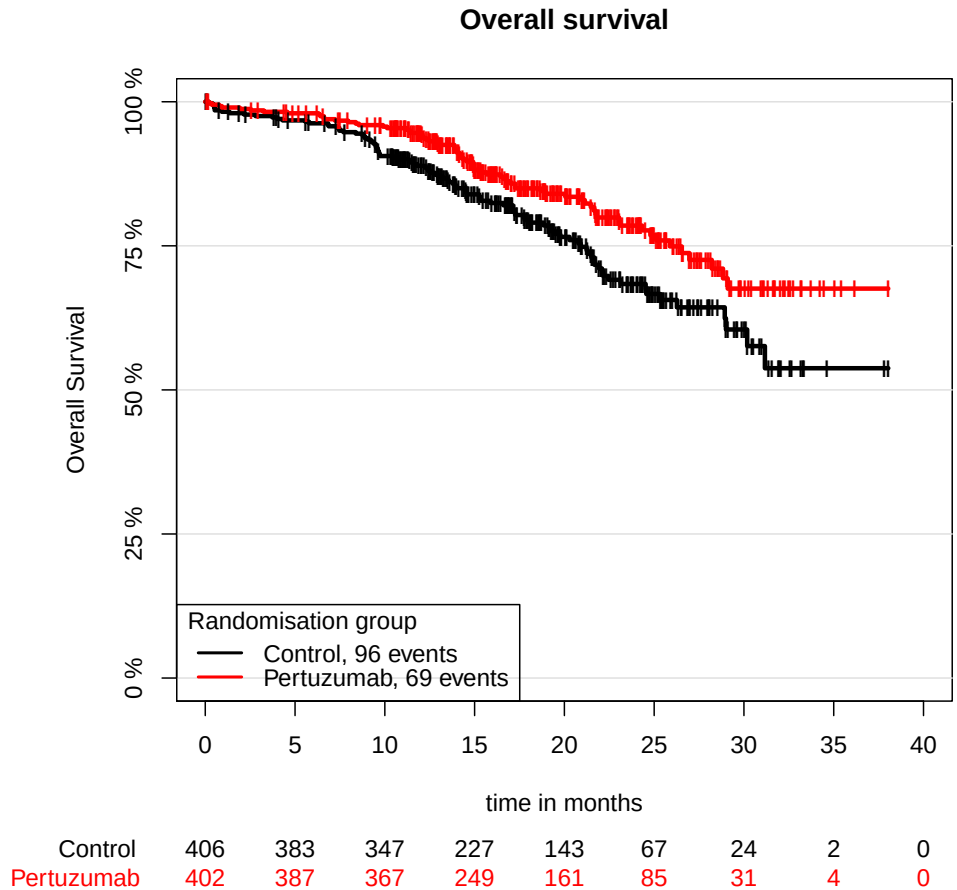
CLEOPATRA study

- Phase 3 study to compare the efficacy and safety of a three-drug regimen (pertuzumab, docetaxel, trastuzumab) to a two-drug regimen (placebo, docetaxel, trastuzumab) in patients with HER2-positive first-line metastatic breast cancer.
- Double-blind randomised trial
- Primary endpoint progression-free survival (assessed independently)
- Secondary endpoints included overall survival, progression-free survival (assessed by investigator), objective response rate and **safety**
- Median follow-up was 30 months
- Data used in the calculation are based on the cut-off date for collection of data in May 2011

Results CLEOPATRA study



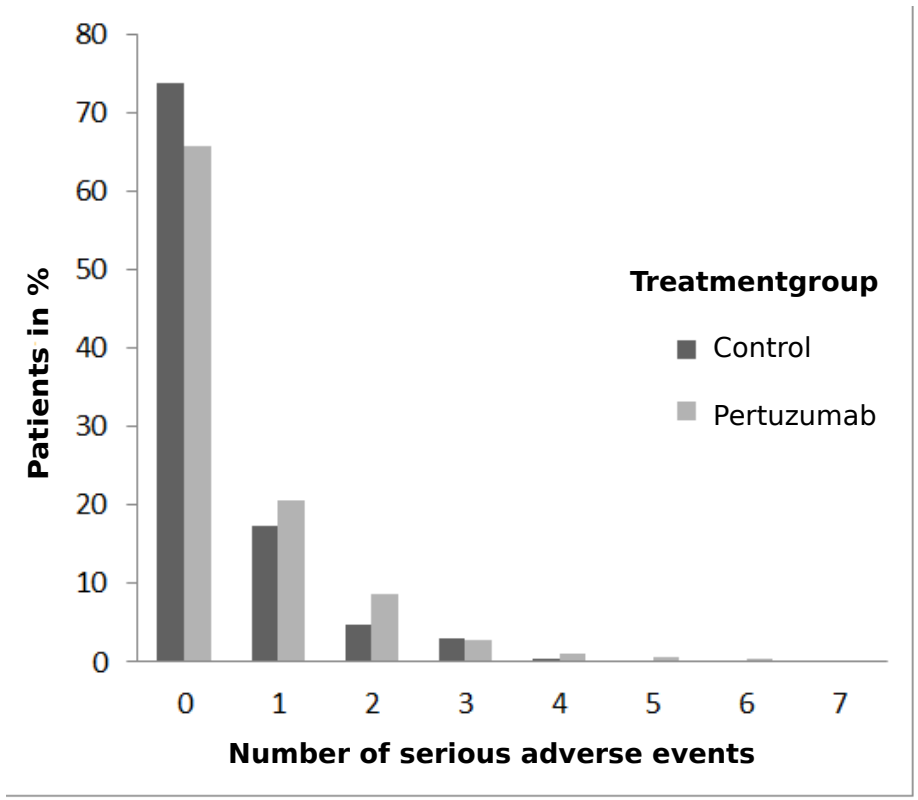
Results CLEOPATRA study



Reporting serious adverse events

- Only serious adverse events (SAEs) are considered; other adverse events are not taken into account.
- All SAEs in the CLEOPATRA study were reported for the period up to 42 days after the last dose of study period, which is defined as the overall treatment period.
- The reporting requirements were reduced after the overall treatment period.
    - e.g. related SAEs had to be reported irrespective of the time period when the SAE occurred and unrelated non-cardiac SAEs were only reported during the overall treatment period.

Barplot


80
70
60
50
40
30
20
10
0
Patients in %
0
1
2
3
4
5
6
7
Number of serious adverse events
Treatmentgroup
Control
Pertuzumab

Results incidence proportion

Safety population!

	Control (n=397)	Pertuzumab (n=407)	Pert. vs. Control RR[95%-CI]
Number of patients with at least one SAE	104 (26.3%)	140 (34.4%)	1.31 [1.06-1.62]

Data are number of patients(%).

Time on treatment:

Study treatment	Control (n=397)	Pertuzumab (n=407)
Time on treatment in months (Median)	11.8	18.1
Difference in median treatment time in months		**6.3**

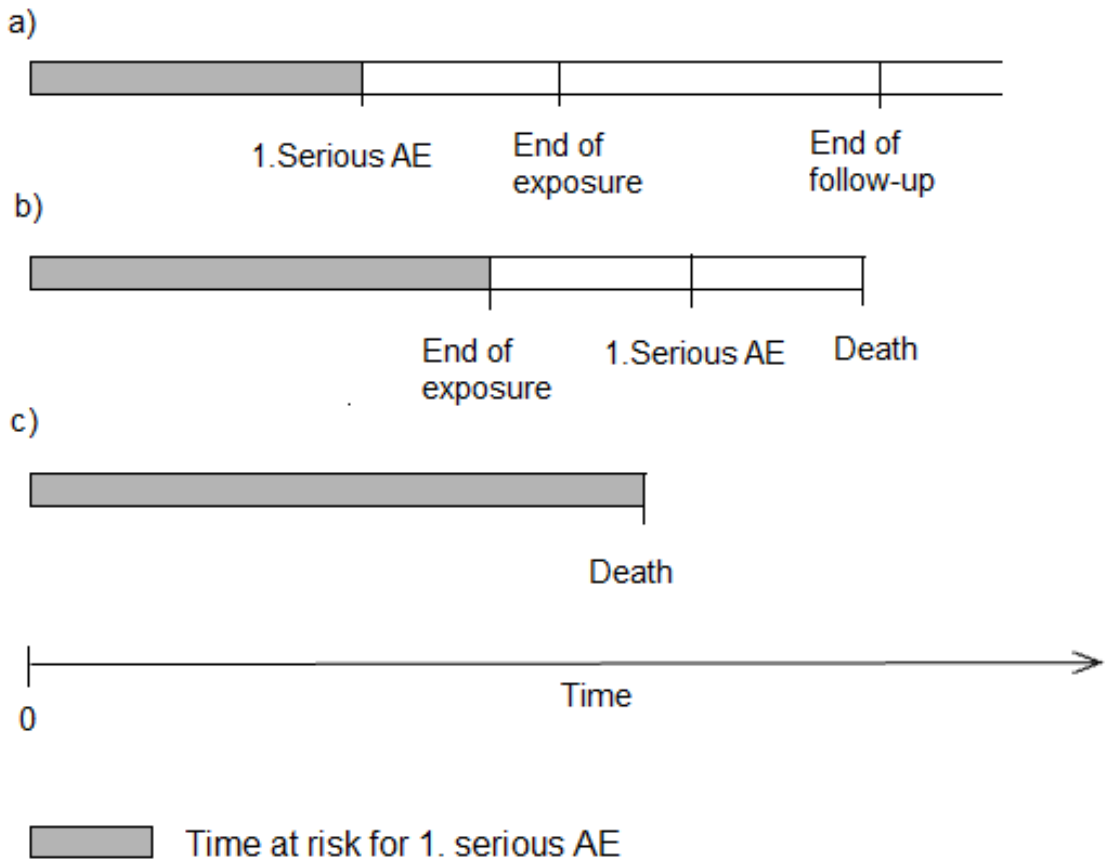
Source: Baselga et al.(2012): Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer.

Incidence rates

IR (Incidence rate): Number of patients experiencing at least one SAE divided by the total *patient-time at risk (of first SAE)* of all patients in each group.

EAIR (Exposure-adjusted incidence rate): Number of patients experiencing at least one SAE divided by the total *patient-exposure-time of first SAE or in case of no SAE patient-exposure-time* of all patients in each group.

Exposure-adjusted incidence rate

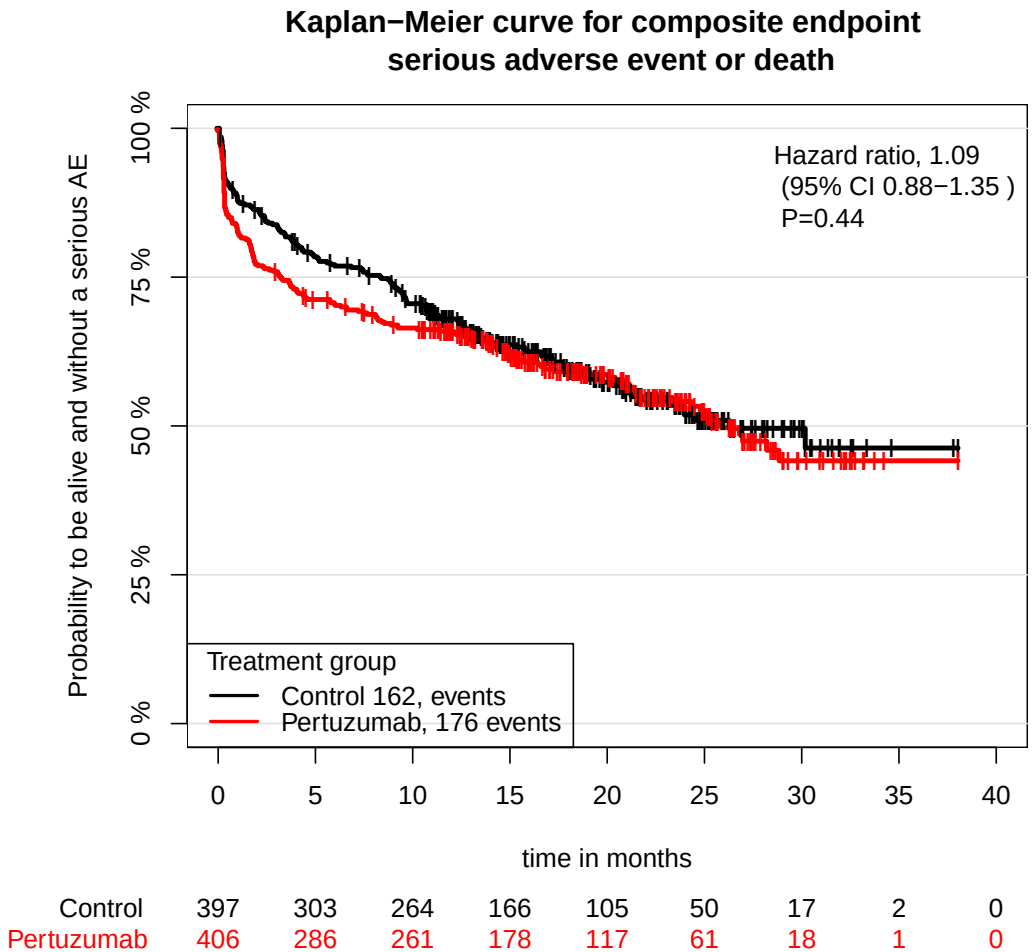


Incidence rate in months

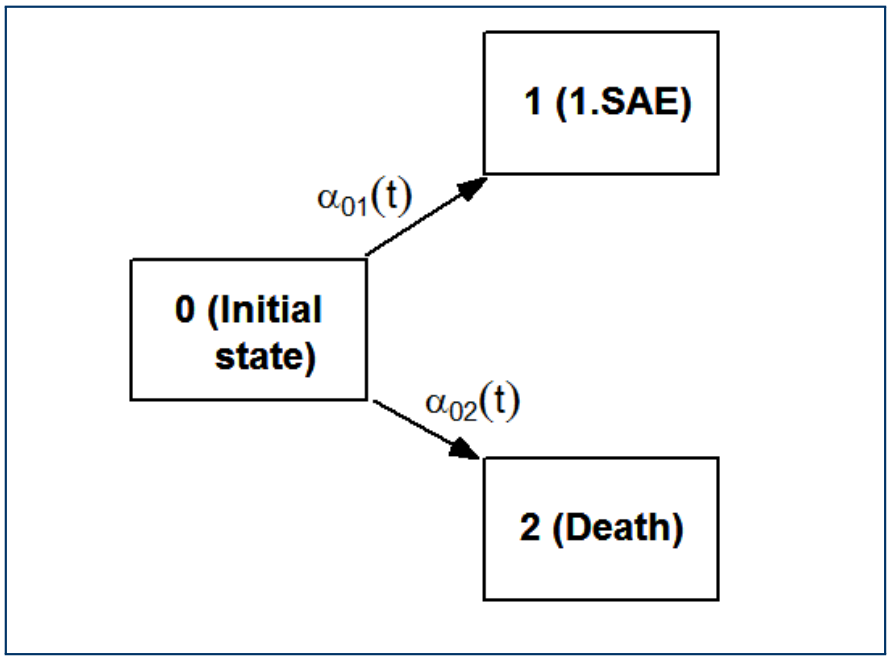
Rates of experiencing SAEs	Control (n=397)	Pertuzumab (n=407)
Proportion of patients experiencing SAEs	104 (26.3%)	140 (34.4%)
RR[95%-CI]	**1.31 [1.06-1.62]**	
Incidence rate per patient-months	0.019	0.026
IRR [95%-CI]	**1.34 [1.04-1.72]**	
EAIR per patient-months	0.027	0.032
HR EAIR [95%-CI]	**1.21 [0.94-1.57]**	

Ratios are given with Pert/Trast/Doce vs. Pla/Trast/Doce

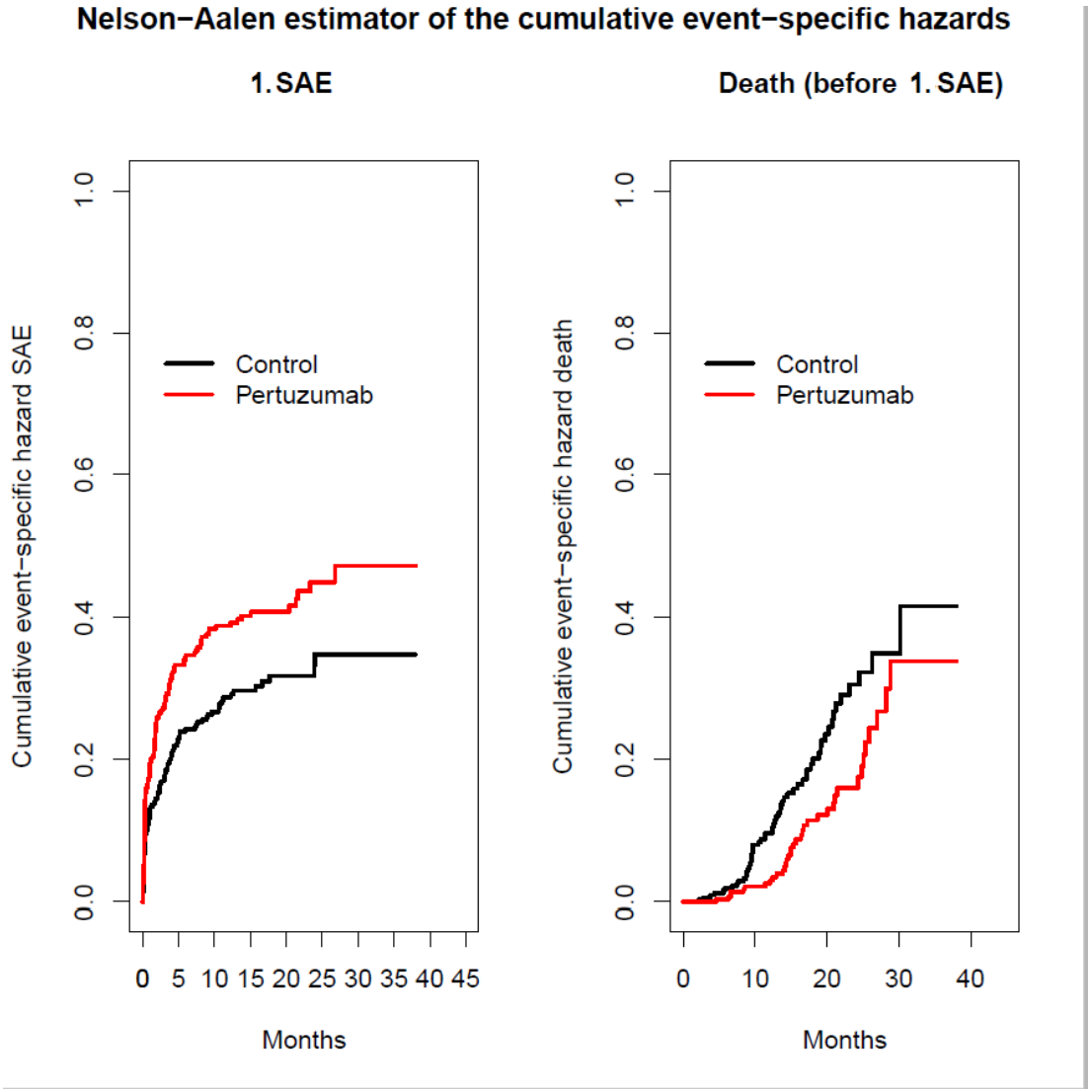
Kaplan-Meier of composite endpoint



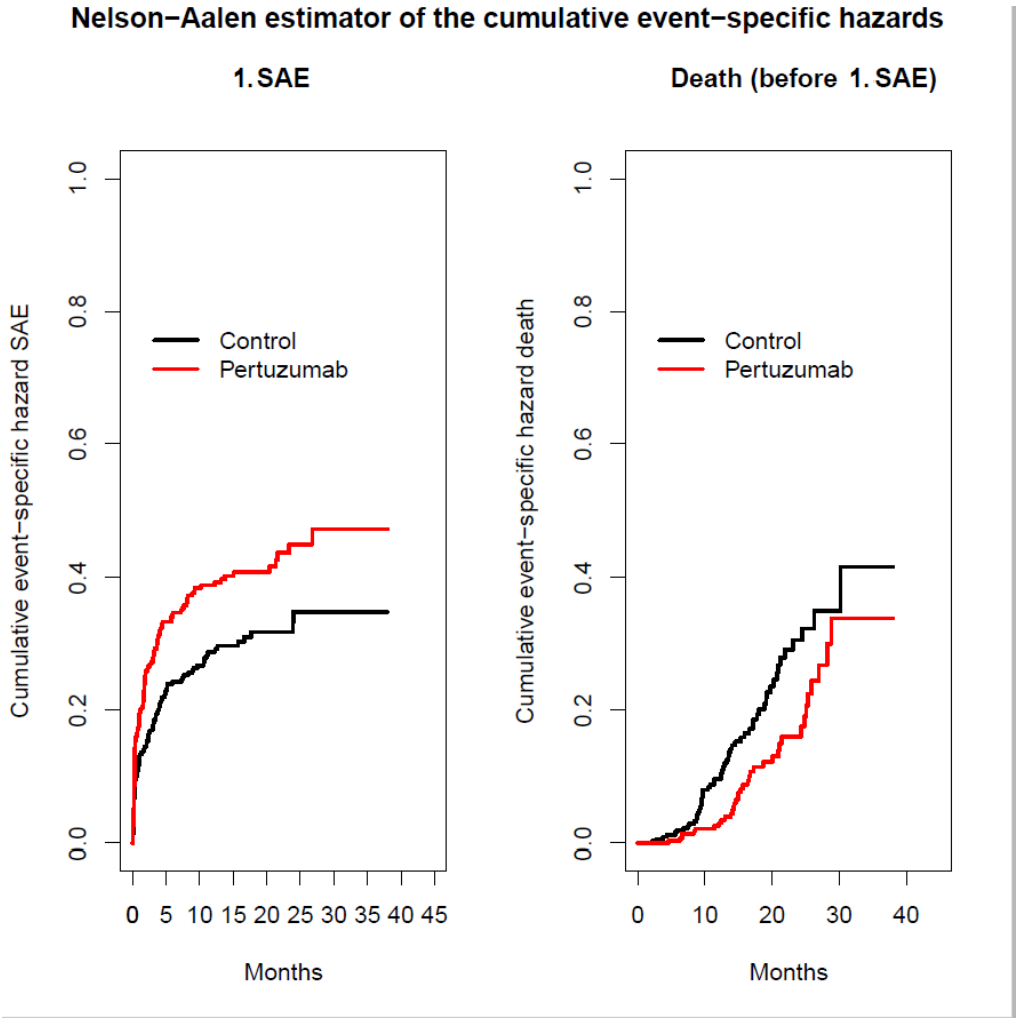
Competing Risks



Cumulative event-specific hazards

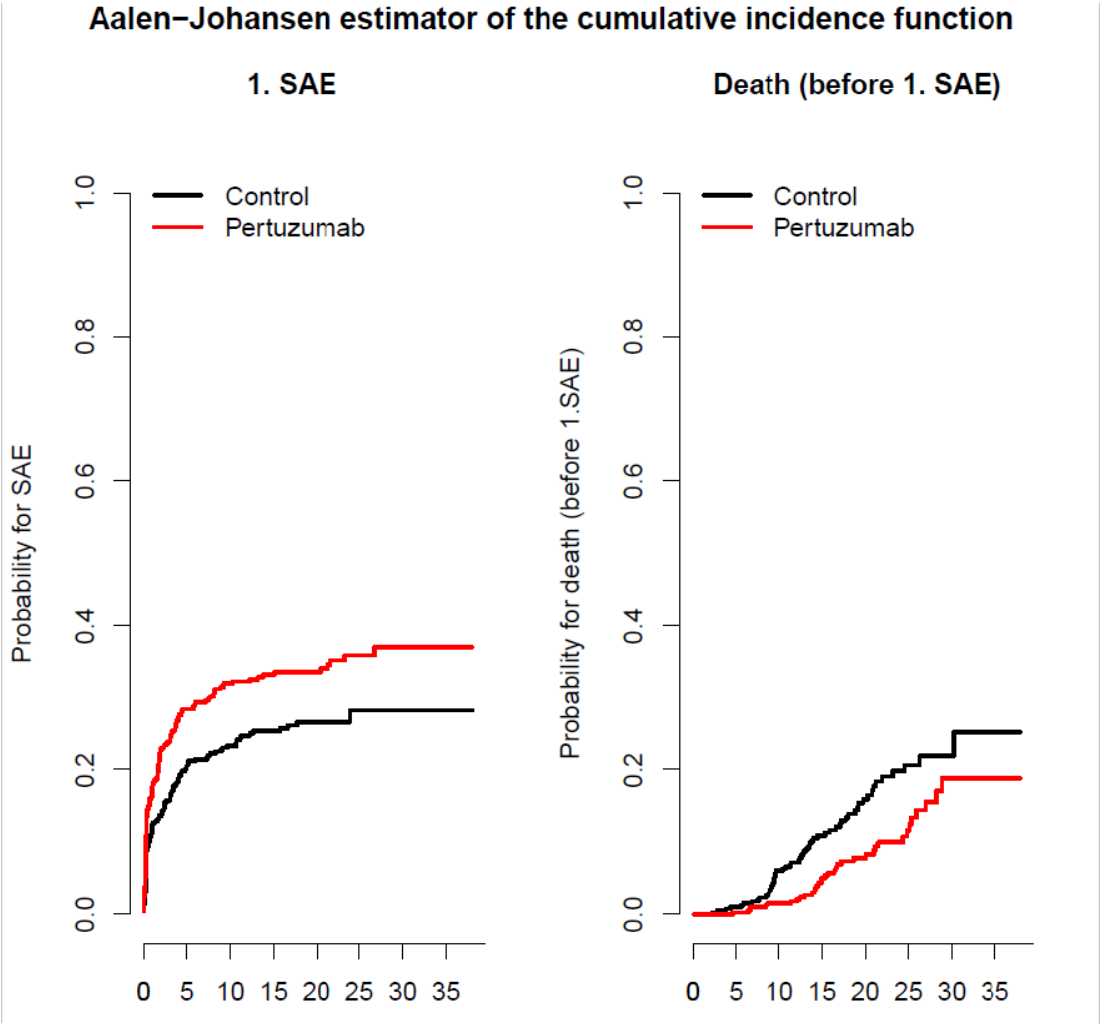


Cumulative event-specific hazards

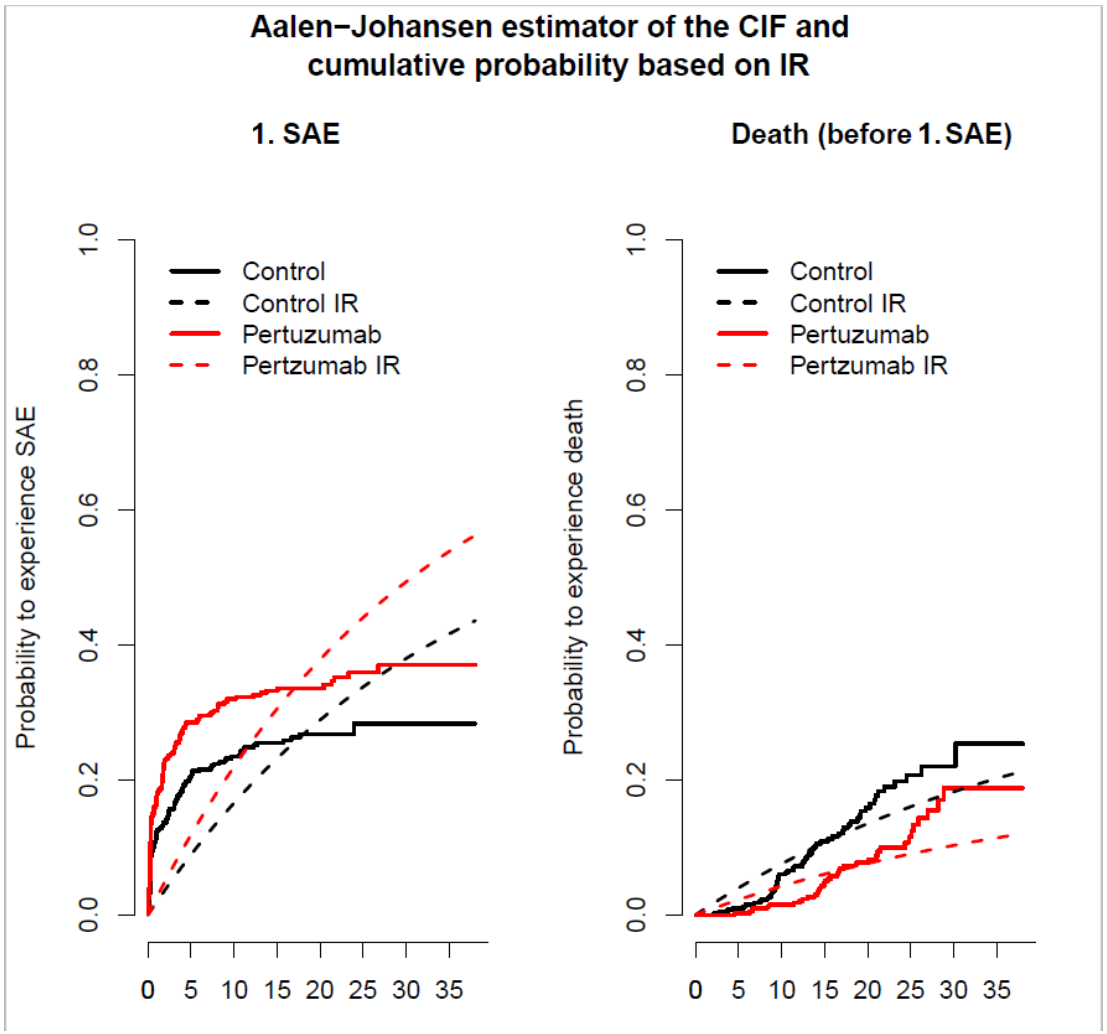


Event-specific hazard:
SAE: $p = 0.0142$ with HR $= 1.37$ and CI-95% [1.07-1.77]
Death: $p = 0.0139$ with HR $= 0.59$ and CI-95% [0.39-0.90]

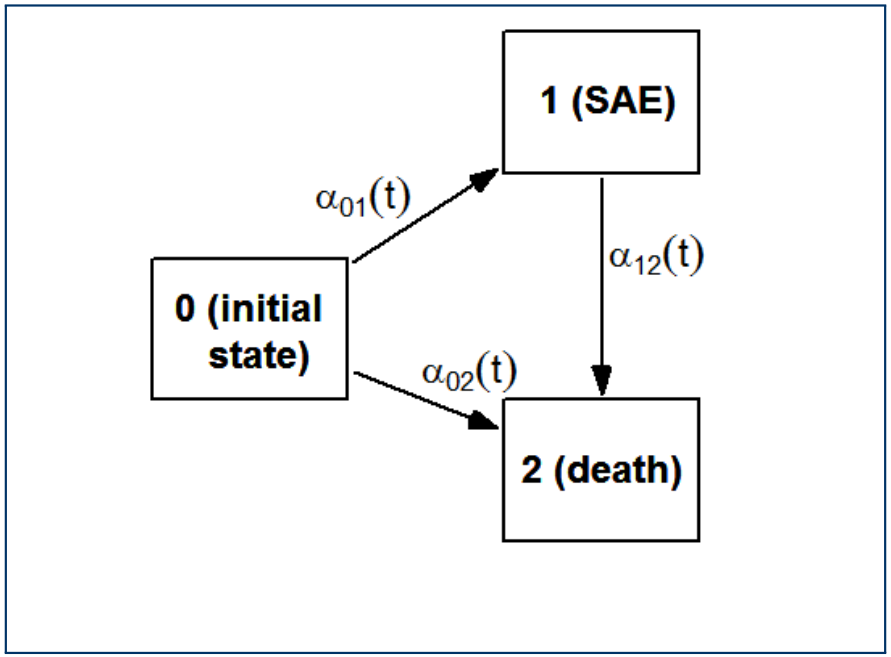
Cumulative incidence function



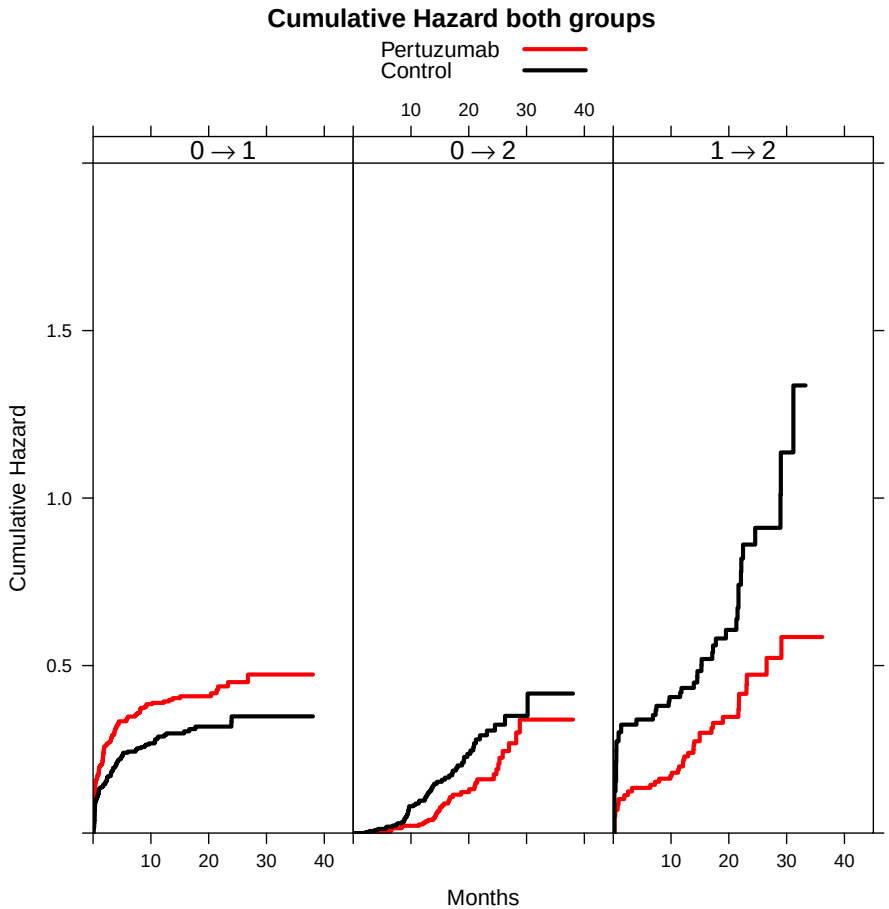
Cumulative incidence function and Incidence rate



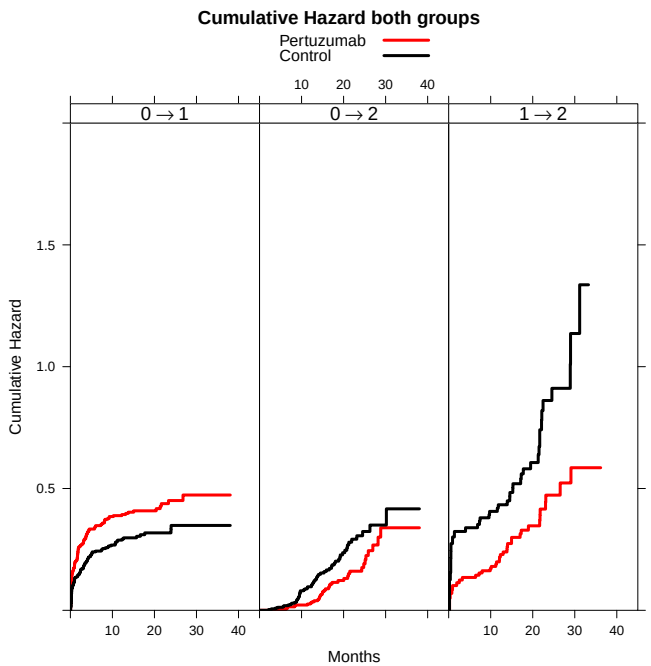
Multi-state Model



Nelson-Aalen estimator of cumulative event-specific hazards in multi-state model



Nelson-Aalen estimator of cumulative event-specific hazards in multi-state model



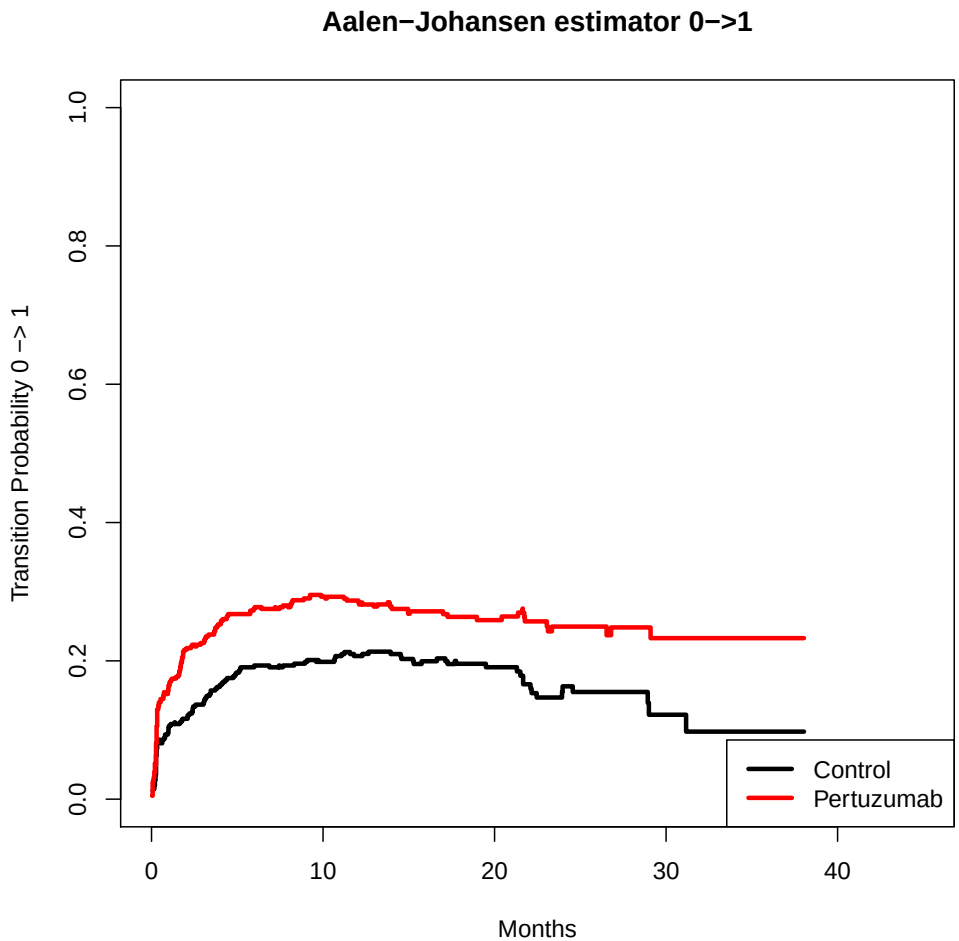
Output transition hazard:

SAE: p = 0.0142,
HR = 1.37
(CI-95% [1.07-1.77])

Death: p = 0.0139,
HR = 0.59
(CI-95% [0.39-0.90])

SAE → Death:
p = 0.034,
HR = 0.60
(CI-95% [0.37-0.96])

Aalen-Johansen estimator of transition probability from initial state to SAE state



Summary Methods

- **Incidence proportion:** Follow-up/exposure time not considered.
- **Incidence rate:** Incidence rate and EAIR consider time-dependence but assume constant hazards.
- **Kaplan-Meier-Plots:** Considers time-dependent occurrence of adverse events. Composite endpoint masks specific effect of competing events death and SAEs.
- **Competing Risks:** Differentiation between hazard for death and hazard for SAEs possible (event-specific hazard), and differentiation between the cumulative probability for death/SAE until month t (cumulative incidence function).
- **Multi-state Model:** Includes the occurrence of competing risk events, hazard of death after a first SAE can be calculated as well.

Summary CLEOPATRA

	SAE	**Death before SAE**	**Death after SAE**
Incidence proportion RR	1.31 [1.06-1.62]	0.60 [0.49-0.92]	-
IRR	1.34 [1.04-1.72]	0.66 [0.49-0.91]	-
Competing Risk HR	1.37 [1.07-1.77]	0.59 [0.39-0.90]	-
Multi-state HR	1.37 [1.07-1.77]	0.59 [0.39-0.90]	0.60 [0.37-0.96]
	SAE	**Disc. or Death**	
EAIRR	1.21 [0.94-1.57]	0.82 [0.41-0.94]	-

Ratios are given with Pertuzumab vs. Control and 95%-CI

Literature

José Baselga, Javier Cortés, Kim Sung Bae, et al.

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

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Ohidul Siddiqui.

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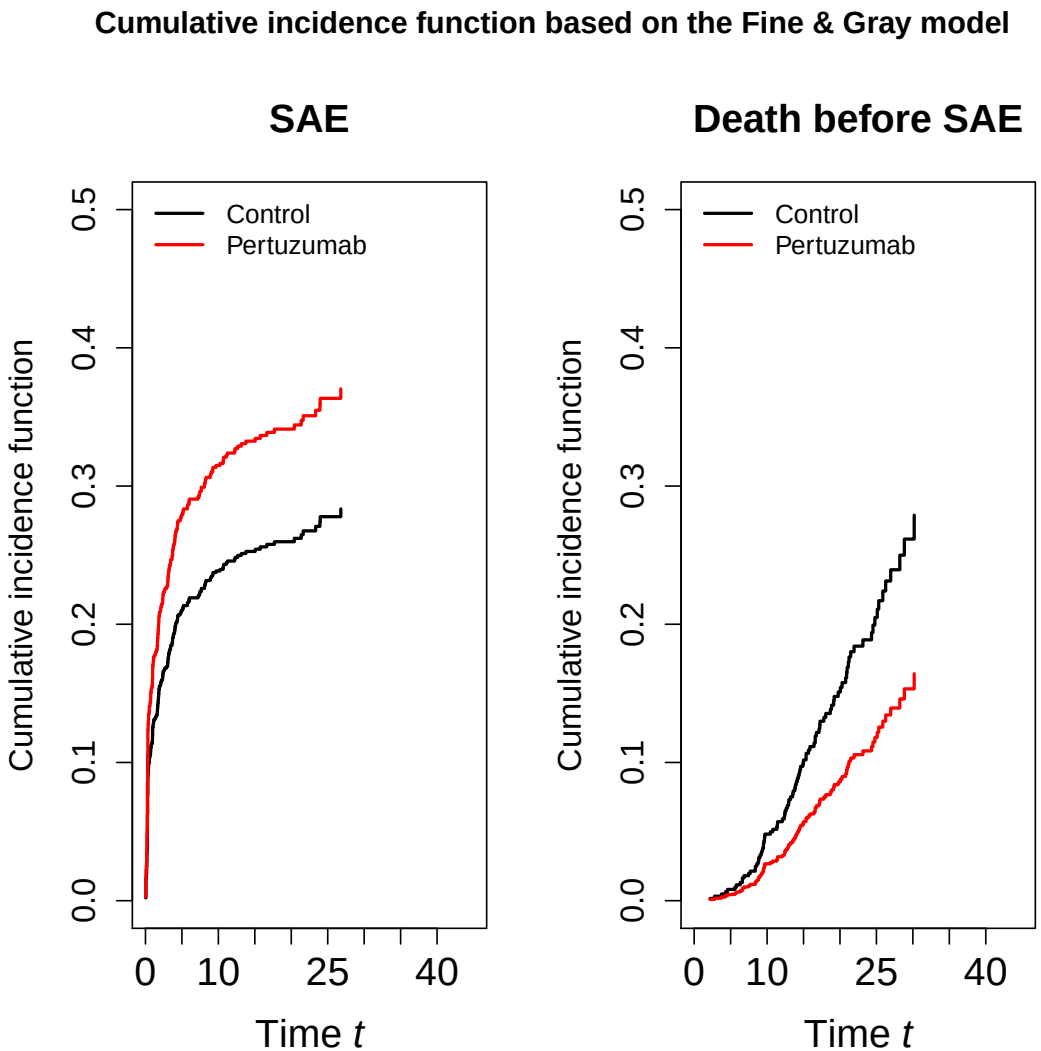
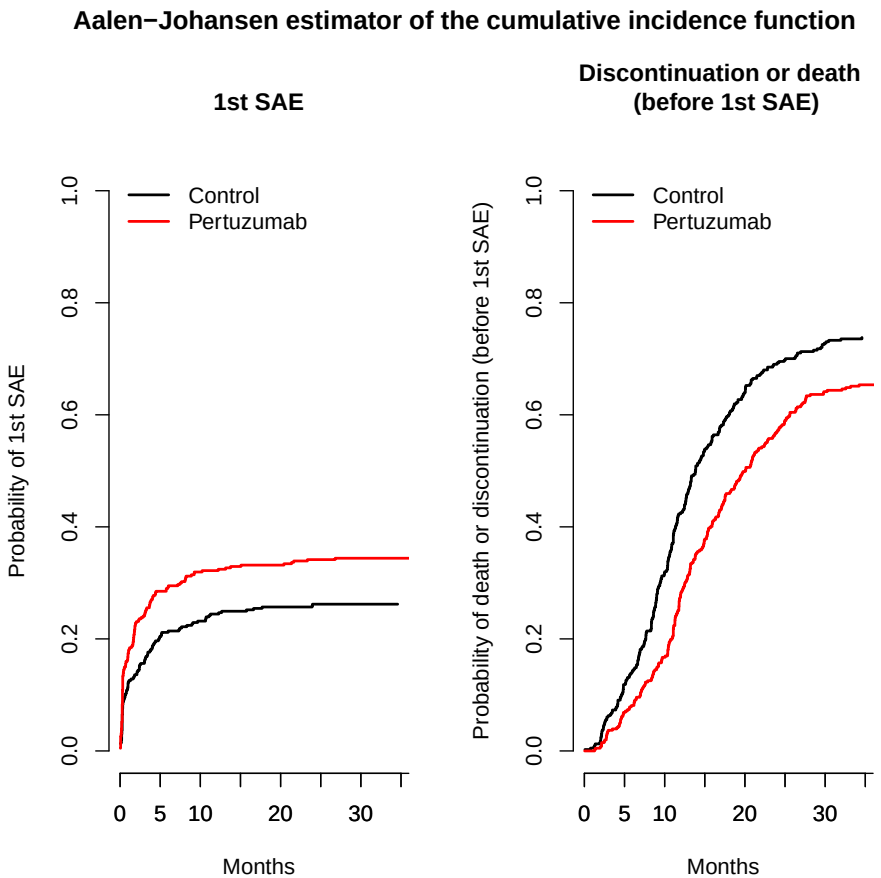
Journal of Biopharmaceutical Statistics,19(5): 889-899, 2009.

Cumulative incidence function based on Fine and Gray model



Competing risks model considering time to discontinuation



Summary CLEOPATRA

	SAE	**Death before 1.SAE**	**Death after 1.SAE**
Incidence proportion RR	1.31 (1.06, 1.62)	0.60 (0.49, 0.92)	-
IRR	1.34 (1.04, 1.72)	0.66 (0.49, 0.91)	-
Competing Risk HR	1.37 (1.07, 1.77)	0.59 (0.39, 0.90)	-
Subdistribution HR	1.39 (1.08, 1.79)	0.55 (0.36, 0.83)	-
Multi-state HR	1.37 (1.07, 1.77)	0.59 (0.39, 0.90)	0.60 (0.37, 0.96)
	SAE	**Disc. or Death**	
EAIRR	1.21 (0.94, 1.57)	0.82 (0.41, 0.94)	
Competing Risk HR	1.32 (1.03, 1.71)	0.72 (0.61, 0.85)	-

Ratios are given with Pertuzumab vs. Control and 95%-CI