Clinical trial results:
Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma (MPM) with or without hemithoracic radiotherapy. A randomized multicenter phase II trial

Summary

EudraCT number	2006-000445-19
Trial protocol	DE BE
Global end of trial date	18 May 2017

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	SAKK 17/04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00334594
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakkcc@sakk.ch

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2017
Global end of trial reached?	Yes
Global end of trial date	18 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial are to evaluate the short-term outcomes and feasibility of neoadjuvant chemotherapy and extrapleural pneumonectomy in Part 1, and long-term outcomes and feasibility of hemithoracic radiotherapy in patients with R0 and R1 resection in Part 2.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continous assessment of laboratory values and vital signs.

Background therapy:

None.

Evidence for comparator:

Not applicable. The study investigated the effect of hemithoracic radiotherapy (Arm B) versus no radiotherapy (Arm A) after treatment with pemetrexed/cisplatin and subsequent extrapleural pneumonectomy.

Actual start date of recruitment	07 December 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Switzerland: 139
Worldwide total number of subjects	151
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	108
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between December 2005 and November 2012, 153 patients were included into the trial at 14 centers in Switzerland (12 centers), Germany (1 center) and Belgium (1 center).

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fullfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled. Of the 153 registered patients, two patients were excluded due to direct refusal after registration and missing information about chemotherapy during external treatment.

Pre-assignment period milestones

Number of subjects started	153[1]
Number of subjects completed	151

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Missing information about chemotherapy: 1
Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two patients (one patient from Switzerland and one patient from Germany) were excluded (see pre-assigment period for details).

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Baseline

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed 500 mg/m2 i.v. over approximately 10 minutes on day 1 every 21 days.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 75 mg/m2 as an infusion, over approximately 2 hours on day 1 of each 21-day cycle beginning approximately 30 minutes after the end of administration of pemetrexed.

Number of subjects in period 1	Baseline
Started	151
Completed	151

Period 2	
Period 2 title	Chemotherapy (Pemetrexed / Cisplatin)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Chemotherapy

Arm description:

3 cycles of chemotherapy prior to extrapleural pneumonectomy (and hemithoracic radiotherapy).

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed 500 mg/m2 i.v. over approximately 10 minutes on day 1 every 21 days.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 75 mg/m2 as an infusion, over approximately 2 hours on day 1 of each 21-day cycle beginning approximately 30 minutes after the end of administration of pemetrexed.

Number of subjects in period 2	Chemotherapy
Started	151
Completed	145
Not completed	6
Symptomatic deterioration	1
Other	2

Progression	3

Period 3	
Period 3 title	Surgery (extrapleural pneumonectomy)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Extrapleural pneumonectomy
Arm description: Extrapleural pneumonectomy	
Arm type	Surgical intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Extrapleural pneumonectomy
Started	145
Completed	125
Not completed	20
Consent withdrawn by subject	3
Toxicity	1
Other	3
Progression	10
Unknown	1
Infiltration of other organs	2

Period 4	
Period 4 title	Macroscopic resection (R0/R1)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Patients with macroscopic resection R0/R1
Arm description: Patients with chemotherapy and extrapleural pneumonectomy showing macroscopic resection R0/R1.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	Patients with macroscopic resection R0/R1
Started	125
Completed	99
Not completed	26
Macroscopic resection not (R0/R1)	26

Period 5	
Period 5 title	Eligibility assessment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Eligibility assessment
Arm description: Patients after chemotherapy and extrapleural pneumonectomy with macroscopic resection status R0/R1.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 5	Eligibility assessment
Started	99
Completed	54
Not completed	45
Consent withdrawn by subject	20
Not eligible	10
Death	8
Other	7

Period 6	
Period 6 title	Hemithoracic radiotherapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Without RT

Arm description:

No radiotherapy after 3 cycles of chemotherapy and extrapleural pneumonectomy.

Arm type	No RT

No investigational medicinal product assigned in this arm

Arm title	Hemithoracic RT

Arm description:

Hemithoracic radiotherapy after 3 cycles of chemotherapy and extrapleural pneumonectomy.
Schedule 1: 25 x 1,8 Gy = 45 Gy to PTV1 followed by 7 x 1,8 Gy = 12, 6 Gy to PTV2 total 57,6 Gy, alternatively a schedule with 2 Gy single fraction was possible.
Schedule 2: 23 x 2 Gy = 46 Gy to PTV1 followed by 5 x 2 Gy to PTV 2 total 56 Gy.
Schedule 3 for intensity-modulated RT with or without integrated simultaneous boost: 26 x 1.75 Gy to PTV1 (45,5 Gy) including simultaneous internal boost to PTV2: 26 x 2.15 Gy (55,9 Gy).

Arm type	Hemithoracic RT

No investigational medicinal product assigned in this arm

Number of subjects in period 6	Without RT	Hemithoracic RT
Started	27	27
Completed	27	25
Not completed	0	2
Death	-	1
Symptomatic deterioration and PD	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline	

Reporting group values	Baseline	Total	
Number of subjects	151	151	
Age categorical Units: Subjects			
Adults (18-64 years)	108	108	
From 65-84 years	43	43	
Gender categorical Units: Subjects			
Female	14	14	
Male	137	137	

Subject analysis sets	
Subject analysis set title	Part B: Non-randomized patients with CT and surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with chemotherapy and extrapleural pneumonectomy who were not randomized.	
Subject analysis set title	Part B: Arm A - No radiotherapy
Subject analysis set type	Full analysis
Subject analysis set description: Randomized patients with chemotherapy and extrapleural pneumonectomy receiving no radiotherapy.	
Subject analysis set title	Part B: Arm B - Hemithoracic radiotherapy
Subject analysis set type	Full analysis
Subject analysis set description: Randomized patients with chemotherapy and extrapleural pneumonectomy receiving hemithoracic radiotherapy.	
Subject analysis set title	Part A: Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Patients of Part A (Chemotherapy and extrapleural pneumonectomy)	

Reporting group values	Part B: Non-randomized patients with CT and surgery	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy
Number of subjects	97	27	27
Age categorical Units: Subjects			
Adults (18-64 years)	71	19	18
From 65-84 years	26	8	9
Gender categorical Units: Subjects			
Female	10	3	1
Male	87	24	26

Reporting group values	Part A: Full Analysis Set		
Number of subjects	151		
Age categorical Units: Subjects			
Adults (18-64 years)	108		
From 65-84 years	43		
Gender categorical Units: Subjects			
Female	14		
Male	137		

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: Baseline	
Reporting group title	Chemotherapy
Reporting group description: 3 cycles of chemotherapy prior to extrapleural pneumonectomy (and hemithoracic radiotherapy).	
Reporting group title	Extrapleural pneumonectomy
Reporting group description: Extrapleural pneumonectomy	
Reporting group title	Patients with macroscopic resection R0/R1
Reporting group description: Patients with chemotherapy and extrapleural pneumonectomy showing macroscopic resection R0/R1.	
Reporting group title	Eligibility assessment
Reporting group description: Patients after chemotherapy and extrapleural pneumonectomy with macroscopic resection status R0/R1.	
Reporting group title	Without RT
Reporting group description: No radiotherapy after 3 cycles of chemotherapy and extrapleural pneumonectomy.	
Reporting group title	Hemithoracic RT
Reporting group description: Hemithoracic radiotherapy after 3 cycles of chemotherapy and extrapleural pneumonectomy. Schedule 1: 25 x 1,8 Gy = 45 Gy to PTV1 followed by 7 x 1,8 Gy = 12, 6 Gy to PTV2 total 57,6 Gy, alternatively a schedule with 2 Gy single fraction was possible. Schedule 2: 23 x 2 Gy = 46 Gy to PTV1 followed by 5 x 2 Gy to PTV 2 total 56 Gy. Schedule 3 for intensity-modulated RT with or without integrated simultaneous boost: 26 x 1.75 Gy to PTV1 (45,5 Gy) including simultaneous internal boost to PTV2: 26 x 2.15 Gy (55,9 Gy).	
Subject analysis set title	Part B: Non-randomized patients with CT and surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with chemotherapy and extrapleural pneumonectomy who were not randomized.	
Subject analysis set title	Part B: Arm A - No radiotherapy
Subject analysis set type	Full analysis
Subject analysis set description: Randomized patients with chemotherapy and extrapleural pneumonectomy receiving no radiotherapy.	
Subject analysis set title	Part B: Arm B - Hemithoracic radiotherapy
Subject analysis set type	Full analysis
Subject analysis set description: Randomized patients with chemotherapy and extrapleural pneumonectomy receiving hemithoracic radiotherapy.	
Subject analysis set title	Part A: Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Patients of Part A (Chemotherapy and extrapleural pneumonectomy)	

Primary: PE | Part 1: Complete macroscopic resection

End point title	PE | Part 1: Complete macroscopic resection[1]
End point description: Complete resection defined as macroscopic resection R0/R1. 125 out of 151 patients underwent surgery.	
End point type	Primary

End point timeframe:

After extrapleural pneumonectomy.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Part A of this study contained only one arm. Thus no comparative statistical analyses are available for the primary endpoint of this part.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Patients (%)				
number (confidence interval 95%)				
All Subgroup - operated patients	63.6 (55.9 to 71.3) 85 (78.4 to 91.6)			

Statistical analyses

No statistical analyses for this end point

Primary: PE | Part 2: Loco-regional relapse-free survival

End point title	PE | Part 2: Loco-regional relapse-free survival[2]

End point description:

Loco-regional relapse free survival was calculated for all patients with R0 or R1 resection from surgery until the first occurrence of loco-regional relapse (relapse in the ipsilateral hemithorax) according to the definitions below or until death.
Local relapse: Relapses in the region of the former pleura, the pleura replacement, the thoracic wall and the mediastinum.
Regional relapse: Lymph node metastases (=N2) in the mediastinum, ipsilateral.

Out of 27 patients per arm, 26 patients showed an LR RFS event (Arm A: Relapse/progression = 24; Death = 2 || Arm B: Relapse/progression = 20; Death = 6).

End point type	Primary

End point timeframe:

From surgery until first occurrence of loco-regional relapse or death.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparative statistical analyses have been performed for this endpoint.

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Relapse free survival (months)				
median (confidence interval 95%)	7.6 (4.5 to 10.7)	9.4 (6.5 to 11.9)		

Statistical analyses

No statistical analyses for this end point

Primary: PE | Part 2: Loco-regional relapse-free survival rate at year 1 to 3

End point title	PE | Part 2: Loco-regional relapse-free survival rate at year 1 to 3[3]

End point description:

Percentage of patients with loco-regional relapse-free survival at year one, two and three.

End point type	Primary

End point timeframe:

At year one, two and three.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparative statistical analyses have been performed for this endpoint.

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Patients (%)				
number (confidence interval 95%)				
1-year LR RFS	29.2 (13.6 to 46.7)	29.6 (14.4 to 47.0)		
2-year LR RFS	8.3 (1.5 to 23.1)	18.5 (6.7 to 34.8)		
3-year LR RFS	4.2 (0.3 to 17.5)	7.4 (1.3 to 21.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Response to chemotherapy

End point title	SE | Part 1: Response to chemotherapy

End point description:

Response to chemotherapy (objective response rate, ORR) defined as complete response (CR) or partial response (PR).

End point type	Secondary

End point timeframe:

From start of chemotherapy until end of chemotherapy.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Patients (%)				
number (confidence interval 95%)	34.4 (26.8 to 42.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Operability

End point title	SE | Part 1: Operability

End point description:

Proportion of patients remaining operable after completing chemotherapy. This was a decision taken on clinical grounds by the thoracic surgeon. In cases where the patient had become inoperable, the reason was recorded.

End point type	Secondary

End point timeframe:

At time point of surgery.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Patients (%)				
number (confidence interval 95%)	84.8 (79.0 to 90.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Randomization rate

End point title	SE | Part 1: Randomization rate

End point description:

Patients eligible for randomization. Reasons for non-randomization included macroscopic incomplete resection, patients' refusal or patient inability to be subjected to RT within 10 weeks after surgery.

End point type	Secondary

End point timeframe:

At time point of randomization.

End point values	Eligibility assessment	Part A: Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	99	151		
Units: Randomizable patients (%)				
number (confidence interval 95%)	54.6 (44.7 to 64.4)	35.8 (28.1 to 43.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Relapse/progression free survival

End point title	SE | Part 1: Relapse/progression free survival

End point description:

From the 151 patients, 145 showed events (relapse progression = 119; death = 26) and the remaining 6 patients were censored.

End point type	Secondary

End point timeframe:

From registration until progression/relapse (loco-regional or distant) or death for all registered patients.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: PFS (months)				
median (confidence interval 95%)	8.4 (7.1 to 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Relapse/progression free survival rates at year 1 to 5

End point title	SE | Part 1: Relapse/progression free survival rates at year 1 to 5

End point description:

Percentage of patients with PFS at year one to year five.

End point type	Secondary

End point timeframe:

At year one to year five.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Patients (%)				
number (confidence interval 95%)				
1-year PFS	35.6 (28.0 to 43.3)			
2-year PFS	13.1 (8.2 to 19.1)			
3-year PFS	8.9 (5.0 to 14.2)			
4-year PFS	4.1 (1.7 to 8.3)			
5-year PFS	2.1 (0.6 to 5.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 2: Feasibility of radiotherapy

End point title	SE | Part 2: Feasibility of radiotherapy

End point description:

Proportion of patients receiving at least 90% of planned RT dose. Out of the 27 patients receiving radiotherapy, six (22.2%) patients received RT schedule 1, five (18.5%) patients received RT schedule 2, twelve (44.4%) patients received RT schedule 3 and four (14.8%) patients received an other RT schedule.

End point type	Secondary

End point timeframe:

At time-point of radiotherapy.

End point values	Part B: Arm B - Hemithoracic radiotherapy			
Subject group type	Subject analysis set			
Number of subjects analysed	23[4]			
Units: Patients (%)				
number (confidence interval 95%)	70.4 (49.8 to 86.3)			

Notes:

[4] - Four patients received „other" schedule , so its feasibility could not be evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 2: Relapse-free survival (for randomized patients)

End point title	SE | Part 2: Relapse-free survival (for randomized patients)

End point description:

RFS calculated from registration until progression/ relapse (loco-regional or distant) or death for all

randomized patients. 26 Events per arm were observed (Arm A: Relapse/progression = 24; Death = 2; Arm A: Relapse/progression = 20; Death = 6), one patient in each arm was censored.

End point type	Secondary

End point timeframe:

From registration until progression/ relapse (loco-regional or distant) or death.

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: RFS (months)				
median (confidence interval 95%)	5.7 (3.5 to 8.8)	7.6 (5.2 to 10.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 2: Relapse-free survival rate at year 1 to 3 (for randomized patients)

End point title	SE | Part 2: Relapse-free survival rate at year 1 to 3 (for randomized patients)

End point description:

Percentage of randomized patients with RFS at year one to year three.

End point type	Secondary

End point timeframe:

At year one, two and three.

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Patients (%)				
number (confidence interval 95%)				
1-year RFS (randomized patients)	25.0 (10.6 to 42.5)	29.6 (14.1 to 47.0)		
2-year RFS (randomized patients)	4.2 (0.3 to 17.5)	18.5 (6.7 to 34.8)		
3-year RFS (randomized patients)	4.2 (0.3 to 17.5)	7.4 (1.3 to 21.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 2: Psychological distress level (quality of life)

End point title	SE | Part 2: Psychological distress level (quality of life)

End point description:

The Rotterdam Symptom Checklist (RSCL) was used to measure symptom-related physical and psychological distress covering four domains: (1) Psychological Distress Level (PDL), (2) Physical Symptom Distress Level (PSDL), (3) Activity Level (AL), (4) Overall Evaluation of Life (OV).
The scores of the items for the physical symptom distress and psychological distress scales were reversed so that lower scores refer to a worse condition and higher scores to a better condition. All scores were standardized according to the manual of RSCL to a % percentage ranging from 0% to 100%. Then, the change scores of each RSCL domain from baseline was calculated for each patient and for each time point. Positive changes indicate that the condition became better compared to baseline. Mean changes of 8 points or more in these indicators are considered as clinically relevant.

End point type	Secondary

End point timeframe:

At week 4, 8, 14, 20

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[5]	21[6]		
Units: Score				
number (confidence interval 95%)				
PDL (4w)	9.5 (0.0 to 19.1)	0.0 (-4.8 to 14.3)		
PDL (8w)	4.8 (0.0 to 14.3)	0.0 (-9.5 to 19.1)		
PDL (14w)	9.5 (0.0 to 14.3)	4.8 (0.0 to 14.3)		
PDL (20w)	14.3 (-4.8 to 19.1)	0.0 (-4.8 to 19.1)		
PSDL (4w)	3.6 (-1.5 to 7.8)	0.0 (-11.1 to 1.5)		
PSDL (8w)	4.3 (0.0 to 10.2)	-1.4 (-7.3 to 4.4)		
PSDL (14w)	4.3 (-10.2 to 11.6)	4.3 (-3.0 to 8.7)		
PSDL (20w)	5.8 (0.0 to 15.9)	4.3 (0.0 to 13.0)		
AL (4w)	8.3 (0.0 to 12.5)	-6.2 (-20.8 to 12.5)		
AL (8w)	8.3 (-4.2 to 25.0)	0.0 (-8.3 to 33.3)		
AL (14w)	4.2 (-7.1 to 16.7)	0.0 (0.0 to 20.0)		
AL (20w)	12.5 (-4.2 to 29.2)	4.2 (0.0 to 20.8)		
OV (4w)	0.0 (0.0 to 16.7)	0.0 (-16.7 to 0.0)		
OV (8w)	0.0 (0.0 to 16.7)	0.0 (-33.3 to 16.7)		
OV (14w)	0.0 (-16.7 to 16.7)	0.0 (0.0 to 16.7)		

OV (20w)	16.7 (0.0 to 33.3)	0.0 (0.0 to 33.3)		

Notes:

[5] - PDL/PSDL/AL: n(4w)=18; n(8w)=17; n(14w)=20; n(20w)=13 | OV: n(4w)=18; n(8w)=17; n (14w)=19; n(20w)=12

[6] - PDL/PSDL/OV: n(4w)=21; n(8w)=15; n(14w)=17; n(20w)=13 | AL: n(4w)=20; n(8w)=14; n (14w)=16; n(20w)=13

Attachments (see zip file)	SAKK17/04_QoL/1704_QoL.png

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Overall survival

End point title	SE | Part 1: Overall survival

End point description:

Overall survival (OS) was calculated from registration until death for all registered patients. In total, 135 deaths were observed (Tumor: [87.4%]; Toxicity: [3.0%]; Other: [6.7%]; Unknown: [3.0%]).

End point type	Secondary

End point timeframe:

From registration until death.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: OS (months)				
median (confidence interval 95%)	14.9 (11.9 to 18.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 1: Overall survival rate at year 1 to 5

End point title	SE | Part 1: Overall survival rate at year 1 to 5

End point description:

OS rate for all registered patients.

End point type	Secondary

End point timeframe:

At year one, two, three, four and five.

End point values	Part A: Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	151			
Units: Patients (%)				
number (confidence interval 95%)				
1-year OS	57.7 (49.4 to 65.2)			
2-year OS	30.6 (23.4 to 38.2)			
3-year OS	20.2 (14.1 to 27.0)			
4-year OS	11.8 (7.2 to 17.7)			
5-year OS	9.1 (5.0 to 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 2: Overall survival

End point title	SE | Part 2: Overall survival

End point description:

Overall survival (OS) was calculated from randomization until death for all randomized patients. In total, 51 events were observed, 26 events in Arm A (Tumor: [88.5%]; Other: [11.5%]) and 25 events in Arm B (Tumor: [88.0%]; Other: [8.0%]; Unknown: [4.0%]).

End point type	Secondary

End point timeframe:

From randomization until death.

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: OS (months)				
median (confidence interval 95%)	16.9 (10.7 to 22.2)	14.9 (7.0 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Part 2: Overall survival rate at year 1 to 3

End point title	SE | Part 2: Overall survival rate at year 1 to 3

End point description:

OS rate for all randomized patients.

End point type	Secondary

End point timeframe:

At year one, two and three.

End point values	Part B: Arm A - No radiotherapy	Part B: Arm B - Hemithoracic radiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Patients (%)				
number (confidence interval 95%)				
1-year OS	63.0 (42.1 to 78.1)	51.8 (31.9 to 68.5)		
2-year OS	27.9 (12.5 to 45.6)	25.9 (11.4 to 43.1)		
3-year OS	12.0 (3.0 to 27.5)	11.1 (2.8 to 25.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From registration until end of study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	SAF - Non-randomized patients
Reporting group description: Adverse events for all non-randomized patients.	
Reporting group title	SAF - Arm A
Reporting group description: Adverse events for all patients allocated to Arm A.	
Reporting group title	SAF - Arm B
Reporting group description: Adverse events for all patients allocated to Arm B.	

Serious adverse events	SAF - Non-randomized patients	SAF - Arm A	SAF - Arm B
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 97 (31.96%)	5 / 27 (18.52%)	15 / 27 (55.56%)
number of deaths (all causes)	84	26	25
number of deaths resulting from adverse events	8	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion	Additional description: Recurrent pleural effusion related to malignant pleural mesothelioma (not regarded as progression)		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposarcoma			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage	Additional description: Hemorrhage Grade 4 with surgery		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic	Additional description: Hemorrhagic shock due to hemothorax right after re-thoracotomy		
subjects affected / exposed	0 / 97 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia	Additional description: Acute ischemia of both legs due to arterial occlusive disease. Phimosis.		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hernia repair	Additional description: Surgery for herniation, right heart failure.		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Haematoma evacuation	Additional description: Postoperative hemothorax, re-surgery for hemostasis and drainage		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial repair	Additional description: Heart luxation post extrapleural pneumonectomy,		

	diaphragm- and pericardium reconstruction		
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension	Additional description: Pulmonary hypertension in context of extrapleural pneumonectomy and hypoxia Grade 4		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Haemothorax	Additional description: Hematothorax and atrial fibrillation		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary air leakage			
subjects affected / exposed	0 / 97 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopleural fistula	Additional description: Broncho-pleural fistula requiring re-thoracotomy		
subjects affected / exposed	0 / 97 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chylothorax	Additional description: Chylothorax Grade 3 requiring re-thoracotomy		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure	Additional description: Non-random.: Respiratory failure Grade 4 due to progressive post-surgical pulmonary edema | Arm B: Respiratory insufficiency (hypoxia Grade 4), atrial fibrillation (supraventricular arrhythmia Grade 3)		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pulmonary embolism	Additional description: Non-random. - One Patient: Pulmonary embolism, ischemic cerebrovascular insult with hemiplegia right.		
subjects affected / exposed	2 / 97 (2.06%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Seroma	Additional description: Mediastinal shift and wound seroma post extrapleural pneumonectomy		
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis	Additional description: Radiation pneumonitis with respiratory decompensation		
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction	Additional description: Subacute myocardial infarction, subtotale arterial occlusive disease		
subjects affected / exposed	0 / 97 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute right ventricular failure	Additional description: Arrhythmia with hyperacute right ventricular heart failure		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac arrest	Additional description: Cardio-vascular arrest (ventricular arrhythmia Grade 4)		

subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction	Additional description: Myocardial infarction, cerebrovascular infarction		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting	Additional description: Two patients (non-random.): Nausea and vomiting		
subjects affected / exposed	2 / 97 (2.06%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pylorospasm	Additional description: Pylorospasm Grade 3 requiring pyloroplasty		
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea	Additional description: Vomiting Grade 3, diarrhea Grade 3 and hypokalemia Grade 3.		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic hernia	Additional description: Diaphragmatic herniation (post pneumonectomy) requiring re-sugery		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal haemorrhage			
subjects affected / exposed	0 / 97 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infectious pleural effusion			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema	Additional description: Non-random.: [1] Post-pleuropneumonectomy empyema (PPPE) with Bronchial stump insufficiency (BSI); [2] Severe PPPE; [3] BSI and empyema, post-OP multiorgan fail.; [4] Fever due to suspected post-OP Empyema | Arm A: [1] Bronchopleural fistula and PPPE		

subjects affected / exposed	4 / 97 (4.12%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia	Additional description: Non-random. - One patient: Pneumonia left and renal insufficiency		
subjects affected / exposed	3 / 97 (3.09%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Sepsis	Additional description: Sepsis with multiorgan failure		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration	Additional description: One patient (Arm B): Dehydration Grade 3, dysphagia Grade 3, anorexia Grade 3, nausea Grade 2, vomiting Grade 2 during radiotherapy; one patient (non-random.): Polyuria, dehydration		
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SAF - Non-randomized patients	SAF - Arm A	SAF - Arm B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 97 (93.81%)	27 / 27 (100.00%)	27 / 27 (100.00%)
Vascular disorders			
Thrombosis			
subjects affected / exposed	8 / 97 (8.25%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences (all)	8	1	0
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	46 / 97 (47.42%)	12 / 27 (44.44%)	15 / 27 (55.56%)
occurrences (all)	56	14	29
Pyrexia			
subjects affected / exposed	8 / 97 (8.25%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	8	2	1
Mucosal inflammation			
subjects affected / exposed	5 / 97 (5.15%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	5	0	2
Chest pain			
subjects affected / exposed	43 / 97 (44.33%)	9 / 27 (33.33%)	13 / 27 (48.15%)
occurrences (all)	51	12	18
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 97 (27.84%)	8 / 27 (29.63%)	9 / 27 (33.33%)
occurrences (all)	34	9	12
Dyspnoea			
subjects affected / exposed	41 / 97 (42.27%)	10 / 27 (37.04%)	19 / 27 (70.37%)
occurrences (all)	51	11	37
Dysphonia			
subjects affected / exposed	8 / 97 (8.25%)	1 / 27 (3.70%)	1 / 27 (3.70%)
occurrences (all)	10	1	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 97 (9.28%)	2 / 27 (7.41%)	3 / 27 (11.11%)
occurrences (all)	9	2	3
Mood altered			
subjects affected / exposed	5 / 97 (5.15%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences (all)	5	0	1
Investigations			
Neutrophil count			
subjects affected / exposed	0 / 97 (0.00%)	1 / 27 (3.70%)	3 / 27 (11.11%)
occurrences (all)	0	1	3
Weight increased			
subjects affected / exposed	0 / 97 (0.00%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	0	2	1
Weight decreased			

subjects affected / exposed	12 / 97 (12.37%)	2 / 27 (7.41%)	7 / 27 (25.93%)
occurrences (all)	13	2	10
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	7 / 27 (25.93%)
occurrences (all)	1	0	8
Nervous system disorders			
Taste disorder			
subjects affected / exposed	4 / 97 (4.12%)	5 / 27 (18.52%)	2 / 27 (7.41%)
occurrences (all)	4	5	2
Dizziness			
subjects affected / exposed	5 / 97 (5.15%)	2 / 27 (7.41%)	4 / 27 (14.81%)
occurrences (all)	5	2	5
Neuropathy peripheral			
subjects affected / exposed	8 / 97 (8.25%)	2 / 27 (7.41%)	2 / 27 (7.41%)
occurrences (all)	8	2	2
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 97 (1.03%)	1 / 27 (3.70%)	5 / 27 (18.52%)
occurrences (all)	1	1	7
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 27 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	3
Ear and labyrinth disorders			
Auditory disorder			
subjects affected / exposed	11 / 97 (11.34%)	1 / 27 (3.70%)	6 / 27 (22.22%)
occurrences (all)	12	1	9
Tinnitus			
subjects affected / exposed	25 / 97 (25.77%)	4 / 27 (14.81%)	6 / 27 (22.22%)
occurrences (all)	26	4	6
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	34 / 97 (35.05%)	6 / 27 (22.22%)	6 / 27 (22.22%)
occurrences (all)	39	6	8
Diarrhoea			

subjects affected / exposed	11 / 97 (11.34%)	2 / 27 (7.41%)	8 / 27 (29.63%)
occurrences (all)	12	2	10
Dysphagia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 27 (3.70%)	4 / 27 (14.81%)
occurrences (all)	1	1	4
Oesophagitis			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	8 / 27 (29.63%)
occurrences (all)	0	0	11
Dyspepsia			
subjects affected / exposed	3 / 97 (3.09%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	3	2	1
Nausea			
subjects affected / exposed	60 / 97 (61.86%)	16 / 27 (59.26%)	21 / 27 (77.78%)
occurrences (all)	72	17	39
Vomiting			
subjects affected / exposed	20 / 97 (20.62%)	3 / 27 (11.11%)	11 / 27 (40.74%)
occurrences (all)	24	3	16
Abdominal pain			
subjects affected / exposed	5 / 97 (5.15%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences (all)	5	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	6 / 97 (6.19%)	1 / 27 (3.70%)	3 / 27 (11.11%)
occurrences (all)	6	1	3
Erythema			
subjects affected / exposed	2 / 97 (2.06%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 97 (0.00%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 97 (21.65%)	6 / 27 (22.22%)	12 / 27 (44.44%)
occurrences (all)	22	6	22

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2007	Amendment 1: Changes in the ordering of Pemetrexed by Eli Lilly (Suisse) for the Swiss centers participating only, as it was paid by the health insurances since 1st February 2007. Also some administrative items were changed and exclusion criteria were completed.
06 June 2008	Amendment 2: Changes in the feasibility control in order to check the feasibility of randomization alone. Also some administrative changes were made regarding trial medication and SAE reporting, so as to allow more foreign centers to participate in this trial. There was a new release of particular CRFs.
11 February 2010	Amendment 3: Recently published clinical data from the University Hospital Zurich and other centers that mostly reflect single institution experiences suggested improved dose constraints for the contralateral lung when postoperative hemithoracic. Second, according to the last SAKK safety report (Sept. 2008) one patient treated with IMRT at the University Hospital Zurich suffered from grade 4 pneumonitis. Replanning of the physics plan in this patient suggested that there was room for improvement if the novel lung constraints were used for treatment planning. Also, the shipment for blocks on dry ice was adapted according to guidelines from Swiss Post.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26538423