177Lutethium - Peptide Receptor Radionuclide Therapy (Lu-PRRT) plus Capecitabine versus Lu-PRRT in FDG positive, gastro-entero-pancreatic neuroendocrine tumors: a randomized phase II study. (Lu-Ca-S)

This is a randomized, open label, phase II study. Patients with gastro-entero-pancreatic neuroendocrine tumors (GEP-NET) well differentiated G1 – G2 (ki67 ≤20%) and G3 (ki67 ≤55%), SSR and 18-FDG PET positive will be enrolled in the study and will be randomly assigned to the 2 different arms with the aim to evaluate the PFS of the Lu-PRRT (total activity of 25.9 GBq in both arm) in well differentiated G1 – G2 (ki67 ≤20%) and G3 (ki67 ≤55%), SSRs and FDG PET positive patients with or without capecitabine as radiosensitizer.

CLINICAL STUDY REPORT

06/11/2024

Study Activated:	10/05/2016
First Patient Enrolled:	13/10/2016
Accrual:	35 pts (09/05/2024)

Study Chair:
Dr. Stefano Severi

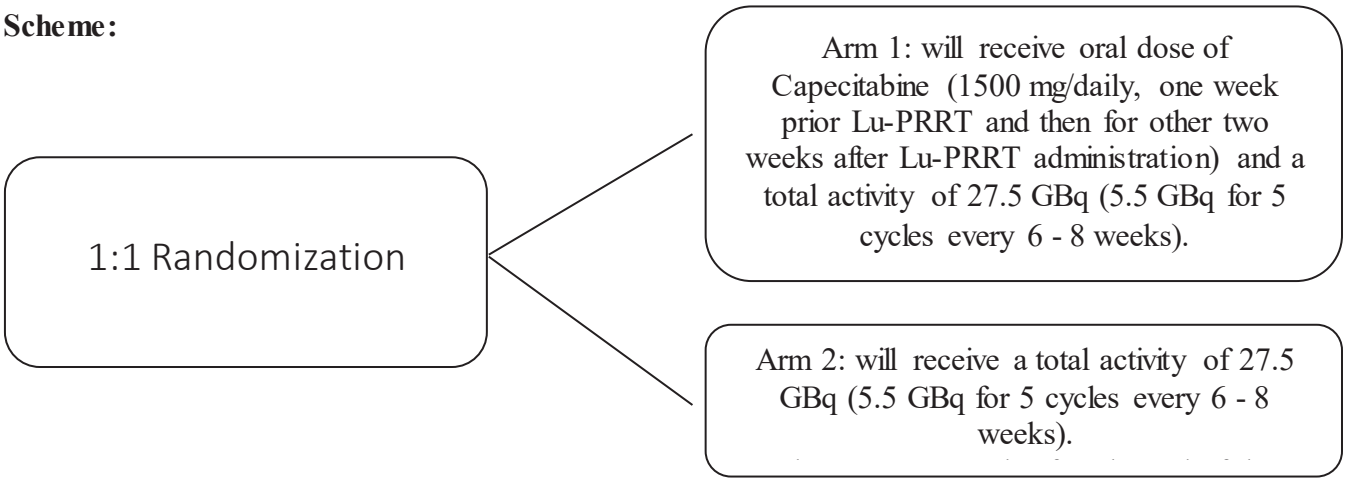
Prepared by:
Dr. Oriana Nanni

STUDY IRST100.17 CLINICAL STUDY REPORT

Project Title:	177Lutethium - Peptide Receptor Radionuclide Therapy (Lu-PRRT) plus Capecitabine versus Lu-PRRT in FDG positive, gastro-entero-pancreatic neuroendocrine tumors: a randomized phase II study. (Lu-Ca-S)
Patient Population:	Patients with documented histopathological diagnosis of gastro-entero-pancreatic neuroendocrine tumor, will be admitted to therapeutic phase only if the diagnostic receptor imaging (OctreoScan) demonstrate a significant uptake in the tumor (grade 2 or 3, according to Rotterdam scale) and/or PET/CT68Ga-peptide images with a tumor uptake at least equal t liver background. Patients with 18FDG PET/CT positive disease and with a SUV >2.5 at least in one documented lesion. Documented progression after standard therapy such as long acting octreotide or lanreotide (SS-LAR), Everolimus in P-NETs or platinum based therapy in G3 patients. Main inclusion criteria: 1. Histopathologic diagnosis of gastro-entero-pancreatic neuroendocrine tumor, well differentiated G1 – G2 (ki67 ≤20%) and G3 (ki67 ≤55%) 2. Male or Female, aged >18 years 3. Measurable disease according to RECIST 1.1 criteria 4. Patients with documented disease will be admitted to therapeutic phase only if the diagnostic receptor imaging, OctreoScan, with a significant uptake in the tumor (grade 2 or 3, according to Rotterdam scale) and/or PET/CT 68Ga-peptide images with a tumor uptake at least equal to liver background 5. Patients with documented disease will be admitted to therapeutic phase only if the 18FDG PET/CT is positive with a SUV >2.5 at least in one documented lesion. 6. Non operable advanced disease 7. Documented progression after standard therapy such as long acting octreotide or lanreotide (SS-LAR), Everolimus in P-NETs or platinum-based therapy in G3 patients. 8. Patients have to finish prior standard chemotherapy or therapeutical radiotherapy (less than 25% body surface) at least 6 weeks. Main exclusion criteria: 1. Ki67 index >50% 2. FDG PET negative 3. Patients treated with chemotherapy and therapeutic radiotherapy within 6 weeks 4. More than 25% body surface radiotherapy 5. Patients treated with previous radiometabolic therapy with an adsorbed dose to the kidney more than 23 Gy and 1.2 Gy for the bone marrow or as surrogate of dosimetry, a Total Cumulative Activity (TCA) of >250 mCi of 90Y dotatoc or >800 mCi of 177Lu dotatate 6. All acute toxic effects of any prior therapy (including surgery radiation therapy, chemotherapy) must have resolved to a grade ≤1 according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) 7. Life expectancy minor than 6 months. 8. ECOG performance status >2

Sample Size:	Sample size is calculated using PFS as endpoint and assuming a median PFS for PRRT of 20 months. Assuming a recruitment period of 36 months and further 36 months of follow-up, an exponential maximum likelihood test of equality of survival curves with a 0.1 two-sided significance level will have 80% power to detect a constant HR=0.65 when 133 events occur. A total of 176 patients are needed (88 patients for each arm).

Scheme:



Randomization is stratified according to:

- pancreas vs gastrointestinal;
- G1-G2 vs G3;
- syndromic vs non-syndromic.

Treatment Schedule:

Treatment Arm 1 (experimental treatment):
ARM 1: patients will receive radiosensitising Capecitabine, commercially available package, at dosage of 1500 mg/die divided in three 500 mg administrations. They will start 7 days prior to each cycle of 177Lu-dotatate and will continue for 14 consecutive days starting from the day of the discharge. Patients will be treated with 177Lu-dotatate intravenously up to a total cumulative dose of 27.5 GBq, divided in 5 cycles of 5.5 GBq each, with treatment intervals of 6 - 8 weeks. One month after the end of the 5 cycles of Lu-PRRT patients will receive somatostatine analogues i.m. (any analogues) according to the standard dosage, until the date of first observation of documented disease progression or death due to any cause.

Treatment Arm 2 (standard treatment):
ARM 2: patients will be treated with 177Lu-dotatate intravenously up to a total cumulative dose of 27.5 GBq, divided in 5 cycles of 5.5 GBq each, with treatment intervals of 6 - 8 weeks. One month after the end of the 5 cycles of Lu-PRRT patients will receive somatostatine analogues i.m. (any analogues) according to the standard dosage, until the date of first observation of documented disease progression or death due to any cause.

Amendment/Notification Summary:

The protocol was amended from Version 1.0 (dated 02.02.16) to version Eme1.0 (dated 27/07/2017), with changes to the schedule, modifying the dose from 3.7 GBq per cycle for 7 cycles to 5.5 GBq per cycle for 5 cycles. The document was approved by AIFA on 12/01/2018 and by the EC on 20/10/2017.

SUMMARY

The primary objective of this study is to evaluate the PFS of the Lu-PRRT (total activity of 25.9 GBq in both arm) in well differentiated G1 – G2 (ki67 ≤20%) and G3 (ki67 ≤55%), SSRs and FDG PET positive patients with or without capecitabine as radiosensitizer.
The secondary objectives are disease control rate (DCR), the acute and late toxicity and the OS estimated separately for each arm.

The following Biostatisticians' Report was generated using data retrieved on 05/11/2024, unless otherwise indicated.

Outline of Report
Section 1: Accrual
Section 2: Patient characteristics
Section 3: Adverse events
Section 4: Treatment summary
Section 5 and further: Outcomes

1. ACCRUAL

The study was activated on 10/05/2016, and the first patient was enrolled on 13/10/2016. Last patient was enrolled on 27/08/2019. As study closure, the accrual is 35 patients. Only one center in Italy was activated and participated in the trial.
The study initially included a 7-week arm 1 schedule (Arm 1a) and 9 patients were enrolled. Following the amendment (January 2018), the arm 1 schedule became 5 weeks (Arm 1b) and 8 patients were enrolled.

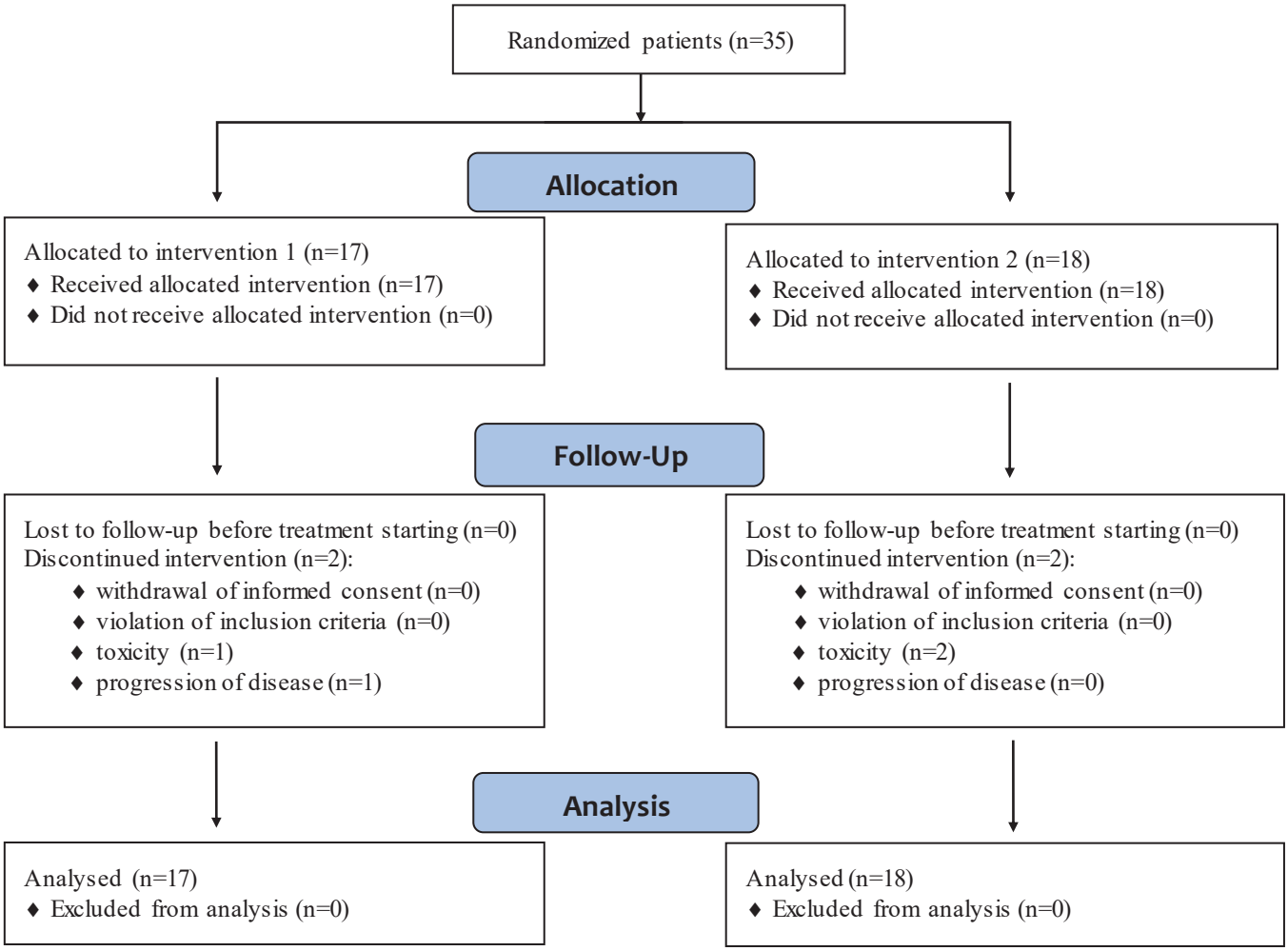
Table 1.1: Detailed accrual information.

Center	Center activation	Enrolled patients	Enrollment date of first patient	Enrollment date of last patient
IRST	10/05/2016	35	13/10/2016	27/08/2019
TOTAL	**-**	**35**	13/10/2016	27/08/2019

	Arm 1a*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR	Arm 1b*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR	Arm 2: Lu-PRRT followed by SS-LAR	Overall
1) Randomized patients	**9**	**8**	**18**	**35**
2) Patients for baseline characteristics	**9**	**8**	**18**	**35**
3) Safety population for toxicity	**9**	**8**	**18**	**35**
4) Efficacy population for OS/PFS	**9**	**8**	**18**	**35**
5) Patients with measurable disease	**9**	**8**	**18**	**35**
6) Other analysis	**NA**	**NA**	**NA**	**NA**

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

Consort 2010 Flow diagram



2. PATIENT CHARACTERISTICS

As of the data retrieval date **35 patients** were **enrolled** in Lu-Ca-S study (9 patients before amendment and 8 patients post-amendment). Table 2.1 gives the distribution of randomized patients according to treatment. Stratification factors at randomization were histological type (pancreas vs gastrointestinal), grade (G1-G2 vs G3) and syndromic disease (syndromic vs non-syndromic). Table 2.2 gives the distribution of **randomized patients with evaluable data (n=35) according to treatment**.

Table 2.1 Patient randomization assignment and strata

Variable	Arm 1a*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=9 (%)	Arm 1b*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=8 (%)	Arm 2: Lu-PRRT followed by SS-LAR n=18 (%)	Overall n=35 (%)
Age (years)				
18-64	6 (66.7)	6 (75.0)	14 (77.8)	26 (74.3)
65-84	3 (33.3)	2 (25.0)	4 (22.2)	9 (25.7)
≥85	0	0	0	0
Age (years)				
Median value (range)	54 (34-71)	61 (45-76)	49 (24-78)	57 (24-78)
Sex				
Female	4 (44.4)	5 (62.5)	11 (61.1)	20 (57.1)
Male	5 (55.6)	3 (37.5)	7 (38.9)	15 (42.9)
Histology				
gastrointestinal	3 (33.3)	1 (12.5)	4 (22.2)	8 (22.9)
pancreatic	6 (66.7)	7 (87.5)	14 (77.8)	27 (77.1)
Grade				
G1-G2	9 (100)	8 (100)	16 (88.9)	33 (94.3)
G3	0	0	2 (11.1)	2 (5.7)

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

Table 2.2 Randomized patients with evaluable data (n=35) according to treatment

Variable	Arm 1a*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=9 (%)	Arm 1b*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=8 (%)	Arm 2: Lu-PRRT followed by SS-LAR n=18 (%)	Overall n=35 (%)
Age (years)				
18-64	6 (66.7)	6 (75.0)	14 (77.8)	26 (74.3)
65-84	3 (33.3)	2 (25.0)	4 (22.2)	9 (25.7)
≥85	0	0	0	0
Age (years)				
Median value (range)	54 (34-71)	61 (45-76)	49 (24-78)	57 (24-78)
Sex				
Female	4 (44.4)	5 (62.5)	11 (61.1)	20 (57.1)
Male	5 (55.6)	3 (37.5)	7 (38.9)	15 (42.9)
Histology				
gastrointestinal	3 (33.3)	1 (12.5)	4 (22.2)	8 (22.9)
pancreatic	6 (66.7)	7 (87.5)	14 (77.8)	27 (77.1)
Grade				
G1-G2	9 (100)	8 (100)	16 (88.9)	33 (94.3)
G3	0	0	2 (11.1)	2 (5.7)

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

3. ADVERSE EVENTS (AE)

15 (6 in Arm 1a, 1 in Arm 1b and 8 in Arm 2) of the 35 patients with at least 1 cycle of treatment have at least one selected G2-G4 AE form.
Table 3.1 summarizes the targeted AEs reported by AE type and maximum grade separated by the two treatment arms. The maximum grade consolidates the reports of a given type of AE for a patient over time by taking the maximum across time (i.e., a patient appears only once for a given type of AE). Patients with reports of multiple AEs of different types are reported multiple times under the relevant AE categories.

Table 3.1. Targeted AEs reported among patients with at least 1 cycle of treatment

	Arm 1a: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR (n=17) (%)			Arm 1b: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR (n=17) (%)			Arm 2: Lu-PRRT followed by SS-LAR (n=18) (%)		
	G2	**G3**	**G4**	**G2**	**G3**	**G4**	**G2**	**G3**	**G4**
WBC	2 (22.2)	0	0	0	0	0	4 (22.2)	2 (11.1)	0
Neutropenia	2 (22.2)	0	0	0	0	0	1 (5.6)	2 (11.1)	0
Asthenia	1 (11.1)	0	0	0	0	0	1 (5.6)	0	0
Thrombocytopenia	0	1 (11.1)	0	0	0	0	0	1 (5.6)	0
Hemoglobin	0	0	0	0	0	0	1 (5.6)	0	0
Vomiting	0	0	0	1 (12.5)	0	0	0	0	0
Nausea	1 (11.1)	0	0	1 (12.5)	0	0	0	0	0
Itching	1 (11.1)	0	0	0	0	0	0	0	0
Dyspnea	1 (11.1)	0	0	0	0	0	0	0	0
Pain	0	0	0	0	0	0	0	1 (5.6)	0
Hand-foot syndrome	1 (11.1)	0	0	0	0	0	0	0	0
Tingling hands	1 (11.1)	0	0	0	0	0	0	0	0
Skin reaction	1 (11.1)	0	0	0	0	0	0	0	0
Pneumonia	0	0	0	1 (12.5)	0	0	0	0	0

*Maximum grade consolidates the reports *of a given type of AE* for a patient over time by taking the maximum across time;
**Patients' maximum AE grade consolidates the reports of all AE types for a patient over time;

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

Results for EudraCT database

- quanti pazienti sono affetti da un determinato SAE o non SAE
- quanti pazienti in tutto sono esposti
- quante volte ricorre quell'evento
- quante volte quell'evento è associato al trattamento
- il numero dei decessi
- numero dei decessi associati al trattamento

Table 3.2. Values for Serious Adverse Events per reporting group

Reporting group	Subjects affected number	Subjects exposed number	Occurrences all number	Occurrences causally related to treatment number	Fatalities number	Fatalities causally related to treatment number
Enrolled patients: Overall	2	35	2	0	1	0
Enrolled patients: Arm 1a	0	9	0	0	0	0
Enrolled patients: Arm 1b	0	8	0	0	0	0
Enrolled patients: Arm 2	2	18	2	0	1	0

Table 3.3. Values for non-Serious Adverse Events per reporting group

Reporting group	Subjects affected number	Subjects exposed number	Occurrences all number
Enrolled patients: Overall	26	35	123
Enrolled patients: Arm 1a	9	9	48
Enrolled patients: Arm 1b	4	8	16
Enrolled patients: Arm 2	13	18	59

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

4. TREATMENT SUMMARY

As of the data retrieval date, 35 of the 35 randomized patients have at least one treatment form submitted. Table 4.1 summarizes reason for end of chemotherapy by arm. Table 4.2 summarizes the treatment information for the two arm of treatment.

Table 4.1 Reason for treatment discontinuation

Variable	Arm 1a*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=9 (%)	Arm 1b*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=8 (%)	Arm 2: Lu-PRRT followed by SS-LAR n=18 (%)	Overall (n=35) (%)
Chemotherapy completed according to protocol	8 (88.9)	7 (87.5)	16 (88.8)	31 (88.5)
Progressive disease or clinical progressive disease	0	1 (12.5)	0	1 (2.9)
Investigator's decision	0	0	0	0
Unacceptable toxicity	1 (11.1)	0	2 (11.1)	3 (8.6)
Death	0	0	0	0

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

Table 4.2. Treatment compliance (n. of patients)

	Arm 1a*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=9	Arm 1b*: oral low dose of capecitabine in association with Lu-PRRT followed by SS-LAR n=8	Arm 2: Lu-PRRT followed by SS-LAR n=18	Overall (n=35)
Total number of patients with treatment data available	9	8	18	35
Number of cycles				
1	0	1	0	1
2	1	0	0	1
3	0	0	0	0
4	0	1	2	3
5	1	6	9	16
6	0	0	1	1
7	7	0	6	13
Median number of cycles (range, interquartile range)	7 (2-7, 7-7)	5 (1-7, 5-5)	5 (4-7, 5-7)	-
Treatment compliance:				
Treatment omitted, hematological toxicity	2	0	1	3
Treatment omitted, non hematological toxicity	0	0	0	0
Treatment omitted, other causes	2	0	0	2
Treatment delayed, hematological toxicity	4	0	6	10
Treatment delayed, non hematological toxicity	5	2	4	11
Treatment delayed, other causes	0	0	0	0
Dose reduction, hematological toxicity	1	0	0	1
Dose reduction, non hematological toxicity	3	0	0	3
Dose reduction, other causes	0	1	0	1

Patients are counted once time.

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

5. OUTCOMES

As of the data retrieval date, of the 35 evaluable patients:

- Median follow up (range): 12.4 months (8.2 – 67.0)
- 10 patients have died

Overall survival

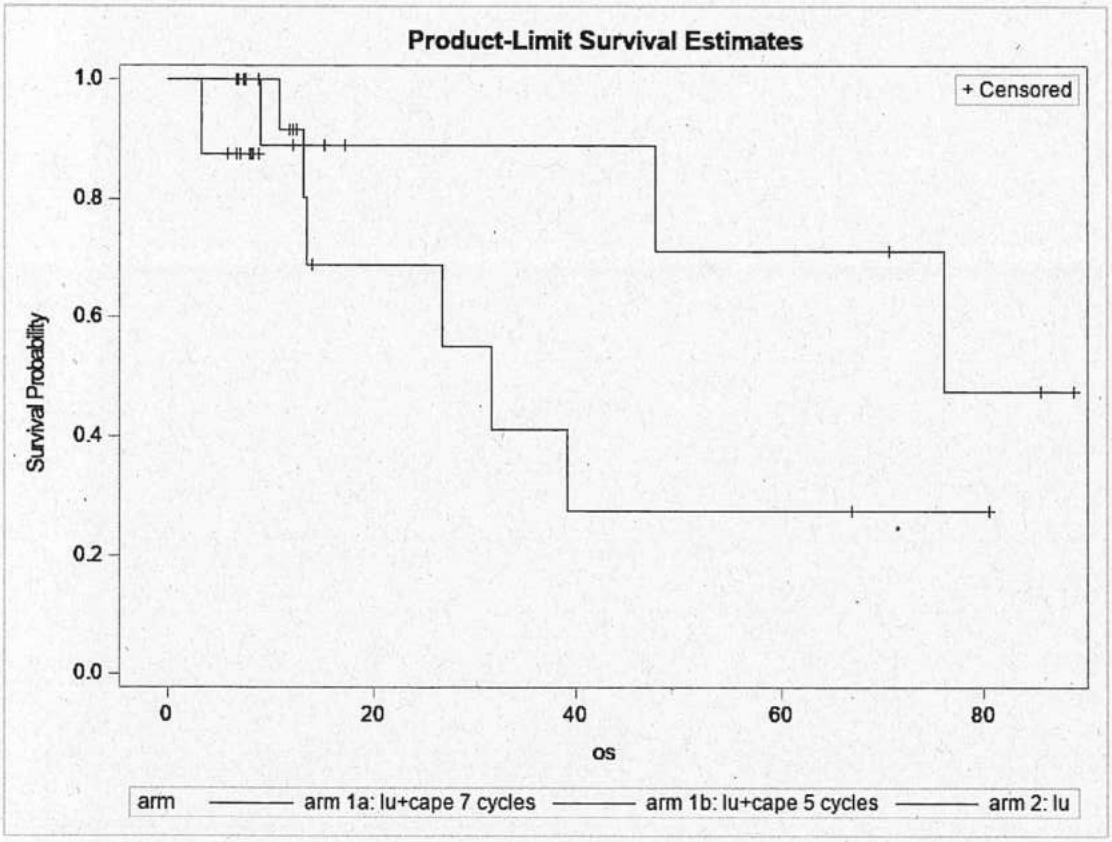
Table 5.1. Overall survival

	Number of patients	Number of events	Median OS (months) (95% CI)
All cases	35	10	47.7 (26.7-nr)
Arm 1a*	9	3	76.2 (8.8-nr)
Arm 1b*	8	1	nr
Arm 2	18	6	31.6 (13.0-nr)

nr=not reached

*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

Kaplan-Meier curves of Overall Survival by arm



*Arm 1a: patients enrolled in arm 1 before amendment
*Arm 1b: patients enrolled in arm 1 post amendment

Forlì, 06/11/24

Oriana Nanni