Nal-IRI/LV5-FU versus paclitaxel as second-line therapy in patients with metastatic esophageal squamous cell carcinoma (OESIRI-PRODIGE 62): A FFCD multicenter, randomized, phase II study.

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Background

- **50% of patients diagnosed with esophagus squamous cell cancer (ESCC) has a metastatic ESCC (mESCC).**
- 50% of patients with initially local/loco-regional disease present disease recurrence after surgery or definitive chemoradiation.
- First-line palliative treatment combines fluoropyrimidine with platinum salt +/- immune checkpoint inhibitor.
- Patients with intolerance/progression after first-line treatment and good performance status may benefit from a second-line chemotherapy but up until now, **there is no randomized trial available comparing second-line chemotherapies in mESCC**.
- Based on phase I/II trials and retrospective studies, the most commonly used regimens in second-line setting of mESCC are **paclitaxel monotherapy or irinotecan monotherapy or combined with 5FU (FOLFIRI)**.

Methods

- **Multicenter, open-label, randomized phase II trial.**
- **To evaluate efficacy and safety of nanoliposomal irinotecan (Nal-IRI) plus 5FU versus paclitaxel as second-line therapy in mESCC.**
- **Primary endpoint: percentage of patients alive 9 months (OS) after randomization** (H0=40% and H1=60%).
- With α 5%, power 85% and 5% of patients lost to follow-up, **53 patients per arm (n=106)** will be randomized.
- Secondary endpoints: progression-free survival (PFS), overall response rate (ORR), safety (NCI CTCAE v.4.0) and quality of life (QoL).

Inclusion criteria

Main inclusion criteria:

- **Histologically proven mESCC**
- **Failure after first-line platinum-based chemotherapy or metastatic recurrence within 6 months after the end of treatment of localized disease**
- **WHO performance status ≤2**
- Good blood and liver parameters
- Albumin ≥25 g/l
- Creatinine clearance ≥50 ml/min (MDRD formula)

Non-inclusion criteria:

- **Peripheral neuropathy ≥ grade 2**
- **Gilbert's syndrome or any known counter indication to irinotecan**
- **Complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency (uracilemia ≥16 ng/ml)**

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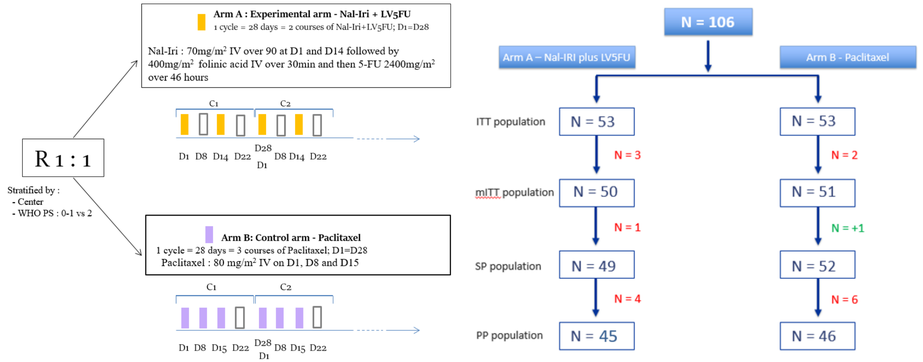
Study design and flowchart



Results: population

Table 1. Patient and tumor characteristics according to treatment arm

		Arm A - Nal-IRI plus LV5FU2 N=50	Arm B – Paclitaxel N=51	All patients N=101
Patients characteristics				
Age (Mean, SD)		65,8 (+/- 8.5)	65.0 (+/- 8.1)	65.4 (+/- 8.3)
Gender : Female		7 (14.0%)	11 (21.6%)	**18 (17.8%)**
WHO PS	0	20 (40.0%)	10 (19.6%)	30 (29.7%)
	1	24 (48.0%)	35 (68.6%)	**59 (58.4%)**
	2	6 (12.0%)	6 (11.8%)	12 (11.9%)
Previous treatments				
Chemotherapy (CT) alone		21 (42.9%)	19 (37.3%)	**40 (40.0%)**
Chemoradiation alone		22 (44.9%)	24 (47.1%)	**46 (46.0%)**
CT + immunotherapy (ICI)		6 (12.2%)	8 (15.6%)	14 (14.0%)
Metastatic location			N=51	
Liver metastases		15 (30.6%)	10 (19.6%)	25 (25.0%)
Lung metastases		25 (51.0%)	29 (56.9%)	**54 (54.0%)**
Lymph node metastases		39 (73.5%)	32 (62.7%)	**68 (68.0%)**
Peritoneal metastases		1 (2.0%)	4 (7.8%)	5 (5.0%)
No. of metastatic sites	1	21 (42.9%)	24 (47.1%)	**45 (45.0%)**
	2	17 (34.7%)	19 (37.3%)	**36 (36.0%)**
	≥ 3	11 (22.4%)	8 (15.7%)	19 (19.0%)

Conclusion

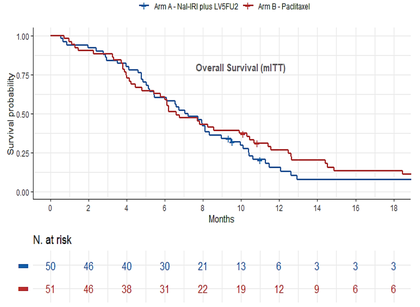
- **Low efficacy of paclitaxel and irinotecan-based chemotherapy in 2nd line treatment for mESCC patients.**
- **Paclitaxel alone provides better safety profile as compared to 5FU Nal-IRI combined.**

Results: outcome and safety

- **Primary endpoint was not met**: only 17 patients were still alive at 9 months in the experimental arm (Nal-IRI plus LV5FU2).
- Median follow-up was 21.8 months.

Table 2. Overall survival and progression-free survival

	Arm A - Nal-IRI plus LV5FU2 N=50	Arm B – Paclitaxel N=51
Overall survival		
Alive	5 (10.0%)	3 (5.9%)
Median OS	**7.1 [5.2 – 8.3] months**	**6.6 [4.8- 10.3] months**
OS at 9 months	34.0% [90%CI: 22.9-46.5]	39.2% [90%CI: 27.7-51.7]
Median PFS	2.4 [95%CI: 2.1-3.6]	2.1 [95%CI: 1.9-3.3]
Disease control rate	47.8%	40.4%



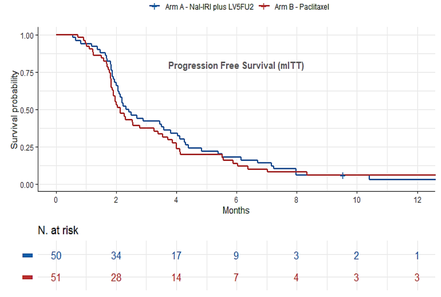


Table 3. Safety and quality of life

	Arm A - Nal-IRI plus LV5FU2 N=50	Arm B – Paclitaxel N=51
Safety		
Grade 3-4 adverse events related to the treatment	**51.0%**	**38.5%**
Toxic deaths	2 (14.0%)	0
Neuropathy	23 (2.0%)	21 (7.7%)
Leucopenia	23 (6.1%)	24 (15.4%)
Diarrhea	**6 (16.3%)**	**0**
Vomiting	**(10.2%)**	**0**
Treatment stop for toxicity	**10.4%**	**3.9%**
Dose reduction for toxicity	77.8%	83.3%
Quality of life		
Deterioration in QoL (loss of more than 5 points of the EORTC-QLQC30 Global Health score)	63.0%	48.3%