PARIS 2022 ESMO congress

#3013
Bevacizumab plus FOLFIRI after failure of platinum-etoposide in patients with advanced neuroendocrine carcinoma: the PRODIGE 41-BEVANEC randomized phase II study

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DECLARATION OF INTERESTS

Thomas Walter

Personal financial interests

Expert board: Ipsen, Novartis, AAA, Terumo

Institutional financial interests

Research grant: Ipsen (principal investigator of LyReMeNET)

Drug supply: Roche (Bevacizumab supply for BEVANEC)

Non-financial interests, Leadership role

Co-coordinator of the scientific group of the French Group of Endocrine Tumors (GTE)

Co-coordinator of the subgroup TNE- PRODIGE

Introduction

- Gastro-entero-pancreatic (GEP) neuroendocrine carcinomas (NEC) are chemosensitive under platinum-etoposide (PE), but almost all patients develop early secondary resistance[1]
- After the failure of PE chemotherapy, there is no standard-of-care in the secondline[1]
- Irinotecan-based regimens showed activity in first line (with cisplatin)[2], and in second line (with 5Fu) allowed ORR of 10-30%, mPFS of 3 months and mOS of 6-9 months after PE in retrospective studies[3,4,5]
- Bevacizumab associated with irinotectan-based chemotherapy is a standard of care in metastatic colorectal cancer [5]
- The efficacy of bevacizumab has also been suggested in patients with GEPNEC[7-10]

[1]Sorbye Cancer 2014; [2]Zhang Cancer 2020; [3]Hentic End Rel Canc 2012; [4]Walter Eur J Cancer 2017; [5]McNamara, ASCO 2022, [6]Heinemann Lancet Oncol 2014 , [7]Welin Cancer 2011, [8]Lindholm Med Oncol 2012, [9]Takeuchi Case Rep Onc 2011, [10]Collot Anticancer Res 2018

PRODIGE 41-BEVANEC trial

Randomized, **non-comparative** phase II trial, with no factor of stratification

- Advanced, refractory GEP and unknown primary NEC (TENpath review)
- PS 0-2
- Progression after first-line PE chemotherapy
- Unresectable locally advanced or metastatic
- Measurable disease (RECIST 1.1)

R 1:1

Folfiri IV every 2 weeks + bevacizumab 5mg/kg IV every 2 weeks

Folfiri IV every 2 weeks

Until progression or unacceptable toxicity (2 years max)

Primary endpoint: >50% of patients alive at 6 months in experimental arm (type I error 10%, power 85% => 59 pts starting CT)

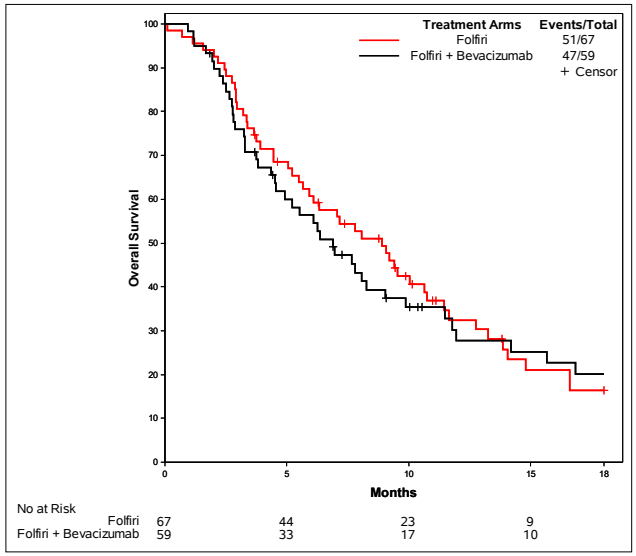
(Folfiri as control arm)

Baseline characteristics

	n	Folfiri-Bev (n=59)	Folfiri (n=67)
Median age in years (IQR)	126	67 (57-75)	66 (58-72)
Male, n (%)	126	40 (67.8)	43 (64.2)
ECOG Performance Status 2, n (%)	125	13 (20.0)	3 (4.5)
Primary tumour location, n (%)	125		
Colorectal		20 (33.9)	18 (27.3)
Pancreas		14 (23.7)	19 (28.8)
Oesogastric		10 (17.0)	12 (18.2)
WHO classification, n (%)	104		
Small-cell NEC		26 (53.1)	29 (52.7)
Large-cell NEC		23 (46.9)	26 (47.3)
Median Ki67 index in % (IQR)	118	80 (70-90)	80 (70-90)
Number of metastatic sites > 2, n (%)	125	16 (27.1)	22 (33.3)
GI-NEC score B (poor prognosis), n (%)	113	25 (46.3)	17 (28.8)
Prior PE chemotherapy in first-line, n (%)	125		
With carboplatin		30 (50.8)	39 (59.1)
With cisplatin		26 (44.1)	19 (28.8)
With both		3 (5.1)	8 (12.1)

Overall survival (primary end point)

Data cutoff of 06 September, 2022



	Folfiri-Bev (n=59)	Folfiri (n=67)
Event : N	31	39
6-months OS in %	**52.5%**	**58.2%**
(80%CI)	**(43.4-61.5)**	**(49.6-66.4)**
Median OS: months (95% CI)	6.9 (4.5-9.0)	8.9 (5.7-10.7)

After multivariate analysis including the treatment arm (exploratory analysis):

Variables		Hazard Ratio [IC 95%] - p-value
Treatment arm	Folfiri	Référence
	Folfiri + Bevacizumab	0.97 [0.63;1.51] - p-value 0.902
GI-NEC score	Good prognosis	Référence
	Poor prognosis	2.42 [1.53;3.82] - p-value <0.001

Secondary endpoints

	n	Folfiri-Bev (n=59)	Folfiri, (n=67)
Clinical response at 3 months from baseline, n (%)			
↘1 point of PS in patients with initial PS ≥1	85	20 (50.0)	17 (37.8)
No ↗of pain meds in patients with initial pain	55	22 (75.9)	18 (69.2)
No weight loss >10%	123	50 (86.2)	58 (89.2)
Best biological response from baseline in patients with elevated level, n (%)			
Chromogranin A		10/33 (30.3)	8/38 (21.1)
NSE		13/34 (38.2)	7/36 (19.4)
Best morphological, n (%)	111	51	60
Objective response		13 (25.5)	11 (18.3)
Stable disease		20 (39.2)	24 (40.0)
Progressive disease		18 (35.3)	25 (41.7)
Median duration of response in months (IQR)	24	7.5 (5.4-12.6)	5.8 (3.8-5.9)
Median PFS: months (95% CI)	126	3.7 (1.9-5.6)	3.5 (1.9-5.1)

Conclusions

- BEVANEC reached its primary endpoint (>50% of 6mo-OS under Folfiri-bevacizumab)
- However, the addition of bevacizumab to Folfiri doesn't seem sufficient to be explored in comparative phase III study
- Folfiri regimen had the highest level of evidence for **unselected** GEPNEC patients after first line PE chemotherapy
  (=> control arm for further comparative studies in second-line post-PE)
- Future directions:

  1/ Move to first-line in combination with oxaliplatin (FOLFIRINEC comparing PE with Folfirinox), maybe more relevant in GEPNEC with a molecular « adenocarcinoma-like » profile?

  2/ To combine chemotherapy with immunotherapy to maintain the response duration?

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PRODIGE 41-BEVANEC trial : Back-up slides for the Discutant

Thomas Walter

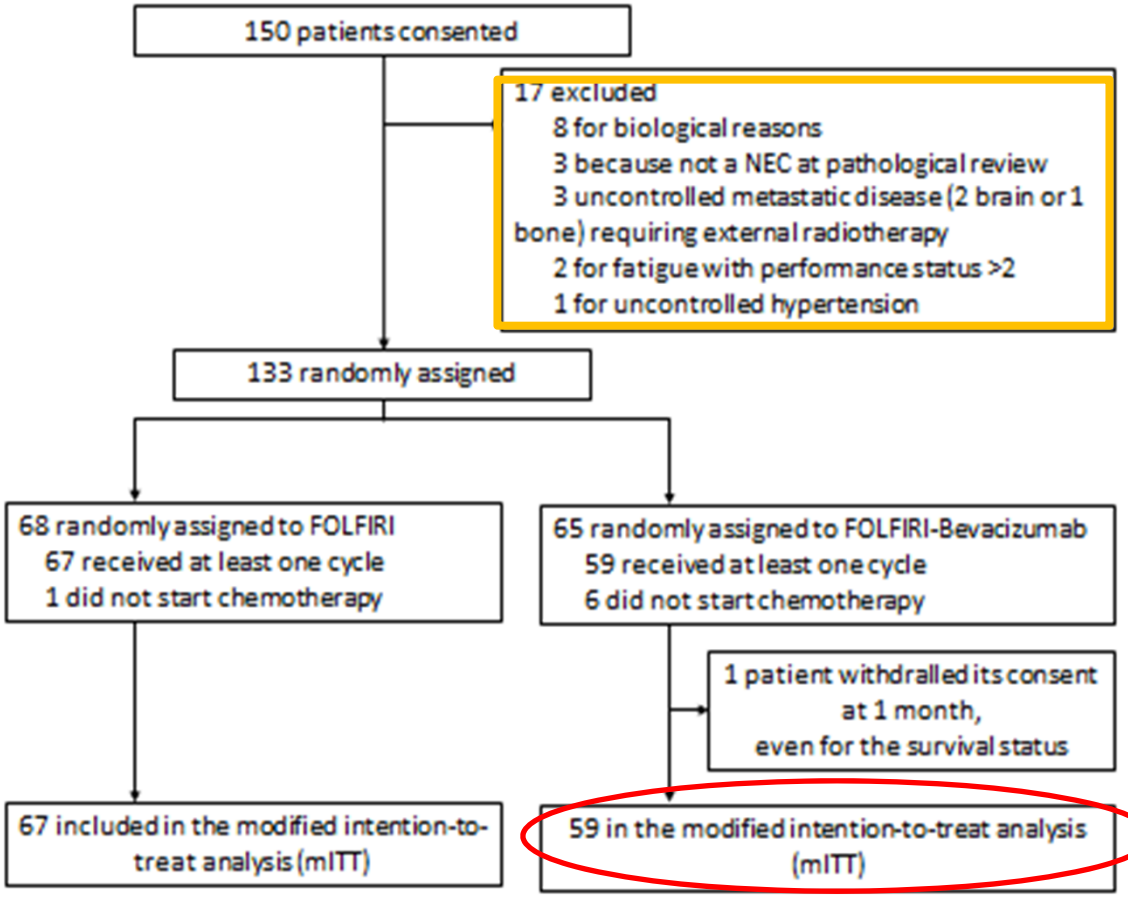
PRODIGE 41-BEVANEC trial: Endpoints and statistical plan

Endpoints	Statistical plan
• Primary endpoint: percentage of patients alive at 6 months after randomization • Secondary endpoints: ORR assessed every 8 weeks, progression-free survival, overall survival, clinical and biological (CgA, NSE, LDH) responses, and safety	• The hypothesis for the control arm (35% of patients alive at 6 months) • The clinical hypothesis was to expect an OS rate at 6 months from 35% to 50% with the addition of bevacizumab • The type I error is 10%, the power 85% • Planned Sample: 59 patients starting chemotherapy (mITT)

PRODIGE 41-BEVANEC trial: Patient disposition

Included in 26 centers from September 6, 2017 to February 8, 2022.
Data cut-off: July 15th, 2022

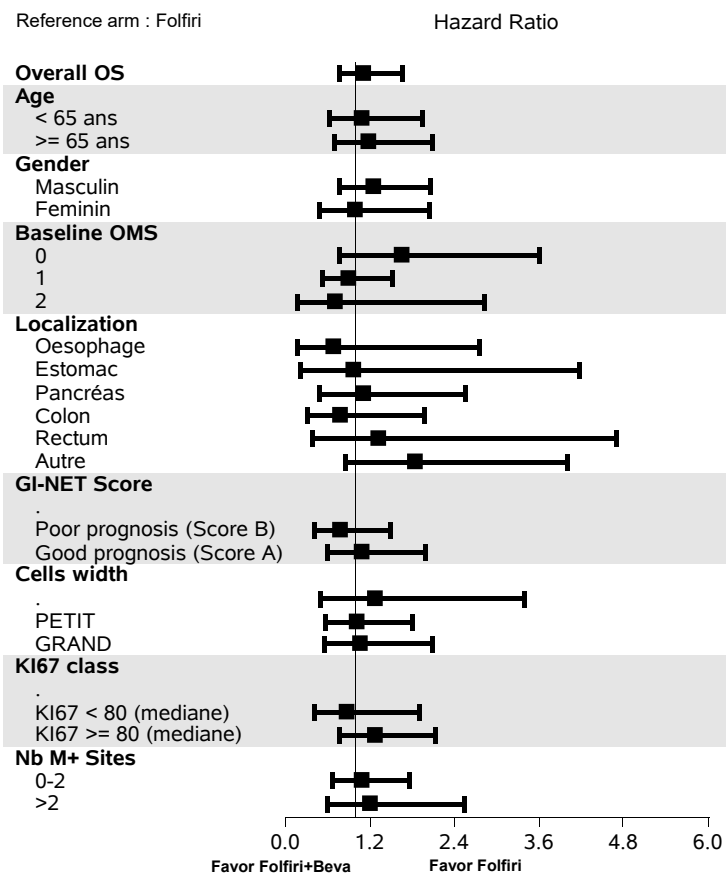
Median FU (KM reverse): 23.4 months (95%CI, 19.7-38.2)



PRODIGE 41-BEVANEC trial: description of chemotherapy

	n	Folfiri-Bev (n=59)	Folfiri, (n=67)
Mean number of cycles (IQR)		10.1 (3.0-16.0)	7.9 (4.0-12.0)
Mean chemotherapy duration in months (IQR)	126	5.0 (1.4-7.2)	3.7 (1.5-5.2)
Mean ratio in % of the dose (IQR) of:			
5FU bolus		77 (75-100)	59 (?? -100)
5FU Continuous		92 (96-100)	92 (96-100)
Irinotecan		88 (84-100)	98 (83-100)
Bevacizumab		95 (99-100)	-
Patients given GCSF, n (%)	126	20 (33.9)	24 (35.8)
Reasons for Folfiri discontinuation, n (%)	126		
Disease progression		40 (71.4)	55 (88.7)
Investigator decision		7 (12.5)	3 (4.8)
Toxicity		1 (1.8)	0 (0)
Patient decision		4 (7.1)	1 (1.6)
Death		2 (3.6)	2 (3.2)

PRODIGE 41-BEVANEC trial: forrest plots analysis (OS)



	Events/Total	Hazard Ratio (95% CI)	P-value [1]
Overall OS	97/126	1.12 (0.75-1.67)	0.58
Age			
< 65 ans	47/60	1.09 (0.61-1.95)	0.76
>= 65 ans	50/66	1.20 (0.68-2.09)	0.53
Gender			
Masculin	64/83	1.25 (0.76-2.06)	0.38
Feminin	33/43	0.99 (0.48-2.05)	0.98
Baseline OMS			
0	27/39	1.65 (0.76-3.60)	0.20
1	58/73	0.89 (0.52-1.51)	0.67
2	12/13	0.70 (0.17-2.83)	0.62
Localization			
Oesophage	9/12	0.68 (0.17-2.75)	0.59
Estomac	9/10	0.96 (0.22-4.18)	0.96
Pancréas	23/33	1.11 (0.49-2.55)	0.80
Colon	19/22	0.77 (0.30-1.98)	0.59
Rectum	11/16	1.32 (0.37-4.69)	0.66
Autre	26/32	1.84 (0.85-4.00)	0.12
GI-NET Score			
.			
Poor prognosis (Score B)	40/42	0.77 (0.40-1.48)	0.44
Good prognosis (Score A)	45/71	1.09 (0.60-1.99)	0.77
Cells width			
.	17/22	1.29 (0.49-3.38)	0.60
PETIT	46/55	1.01 (0.56-1.81)	0.98
GRAND	34/49	1.07 (0.54-2.10)	0.85
KI67 class			
.			
KI67 < 80 (mediane)	31/45	0.89 (0.41-1.90)	0.75
KI67 >= 80 (mediane)	60/73	1.28 (0.77-2.14)	0.34
Nb M+ Sites			
0-2	67/87	1.09 (0.67-1.76)	0.74
>2	30/38	1.21 (0.58-2.53)	0.60

[1]Covariate Wald p-value;

PRODIGE 41-BEVANEC trial: factors associated with OS (univariate)

Variables		N event	% Event	HR [IC 95%]	p-value
Treatment arm	Folfiri	51/67	76.12	Reference	
	Folfiri + B	46/59	77.97	1.12 [0.75;1.67]	0.583
Age in years	< 65	47/60	78.33	1.28 [0.86;1.92]	0.227
	≥ 65	50/66	75.76	Reference	
Sex	Female	33/43	76.74	Reference	
	Male	64/83	77.11	1.06 [0.69;1.61]	0.794
Performance Status*	0	27/39	69.23	Reference	
	1	58/73	79.45	1.61 [1.01;2.55]	0.044
	2	12/13	92.31	2.56 [1.28;5.12]	0.008
Primary tumour location	Other	26/32	81.25	Reference	
	Colon	19/22	86.36	1.53 [0.84;2.78]	0.165
	Estomac	9/10	90.00	0.58 [0.27;1.24]	0.160
	Oesophagus	9/12	75.00	1.11 [0.52;2.38]	0.796
	Pancreas	23/33	69.70	0.66 [0.37;1.16]	0.150
	Rectum	11/16	68.75	0.96 [0.47;1.95]	0.901
GI-NEC score	A	45/71	63.38	Reference	
	B	40/42	95.24	2.40 [1.54;3.75]	<0.001
WHO classification	Large cell	34/49	69.39	Reference	
	Small cell	46/55	83.64	1.15 [0.74;1.81]	0.530
KI67 (median: 80%)	< 80	31/45	68.89	Reference	
	≥ 80	60/73	82.19	1.13 [0.73;1.75]	0.596
Number of metastatic sites	0-2	67/87	77.01	Reference	
	> 2	30/38	78.95	1.14 [0.74;1.76]	0.564

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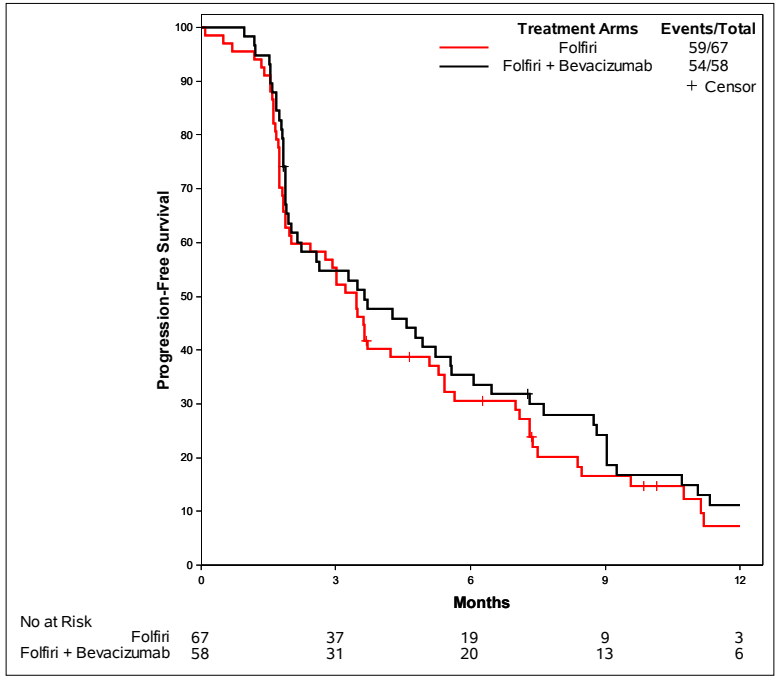
PRODIGE 41-BEVANEC trial : Progression-free Survival



	Folfiri-Bev (n=59)	Folfiri (n=67)
Median PFS: months [95% CI]	3.7 (1.9-5.6)	3.5 months (1.9-5.1)

GCO-001 NIPINEC trial: Safety (>10% in frequency)

	Folfiri-Bev		Folfiri	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Total treatment-related adverse events	48 (81.4)	25 (42.4)	46 (68.7)	13 (19.4)
Gastrointestinals disorders				
Nausea	29 (49.2)	2 (3.4)	30 (44.8)	1 (1.5)
Vomiting	14 (23.7)	0 (0)	7 (10.4)	0 (0)
Diarrhoea	20 (33.9)	6 (10.2)	17 (25.4)	3 (4.5)
Abdominal pain	11 (18.6)	0 (0)	7 (10.4)	0 (0)
Constipation	7 (11.9)	0 (0)	6 (9.0)	0 (0)
Mucositis	7 (11.9)	1 (1.7)	9 (13.4)	0 (0)
Asthenia	20 (33.9)	6 (10.2)	24 (35.8)	0 (0)
Anorexia	10 (16.9)	0 (0)	8 (11.9)	0 (0)
Hemathological adverse events				
Neutropenia	9 (15.3)	7 (11.9)	10 (14.9)	7 (10.4)
Anemia	11 (18.6)	1 (1.7)	9 (13.4)	0 (0)
Thrombocytopenia	8 (13.6)	1 (1.7)	8 (11.9)	0 (0)
Toxicity of specific interest for bevacizumab				
Hypertension	5 (8.5)	1 (1.7)	0 (0)	0 (0)
Digestive haemorrhage	2 (3.4)	0 (0)	1 (1.5)	0 (0)
Gastrointestinal perforation	0 (0)	0 (0)	0 (0)	0 (0)
Epistaxis	8 (13.6)	0 (0)	2 (3.0)	0 (0)
Deep vein thrombosis	1 (1.7)	0 (0)	1 (1.5)	0 (0)