REWENEC: REal World Evidence in NEC generate an external control arm to avoid randomization for second-line clinical trials. A post hoc proof of concept analysis with the randomized phase II BEVANEC study.

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Abstract #3433

Background

Neuroendocrine carcinomas (NECs) are rare and aggressive cancers. After first-line platinum–etoposide, there is no standard second-line treatment. The phase II randomized clinical trial BEVANEC (NCT02820857) compared a randomized treatment arm (RTA) FOLFIRI + bevacizumab to a randomized control arm of FOLFIRI alone which required the enrolment of 125 patients over a long period of 5 years.

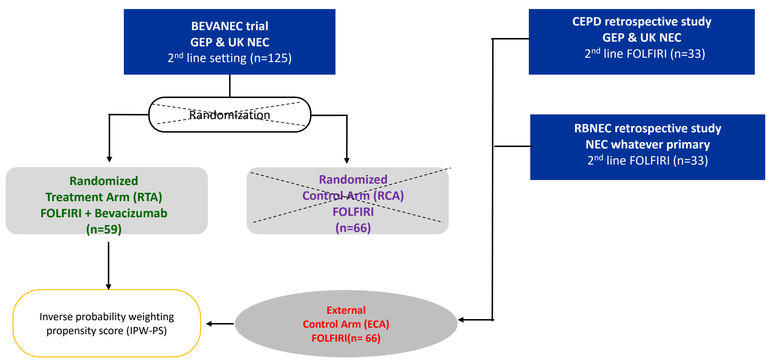
The randomized BEVANEC trial demonstrated no benefit of adding bevacizumab to FOLFIRI as compared to FOLFIRI.

We hypothesized that a single-arm trial of FOLFIRI + bevacizumab compared to an external control arm of FOLFIRI could have demonstrated the same results as the BEVANEC trial

Methods

We compared the patient's characteristics and outcome in the **Randomized control arm (RCA)** of BEVANEC versus an **External Control Arm (ECA)** generated with data from NEC patients from 2 retrospective French cohorts (CEPD and RBNEC) who received second-line FOLFIRI. We emulated a synthetic trial, REWENEC, incorporating an ECA of FOLFIRI in place of the **randomized control Arm (RCA)** and compared the results to that of the BEVANEC trial. An inverse probability weighting propensity score (IPW-PS) approach was used to balance measured confounders in the ECA.

Study design



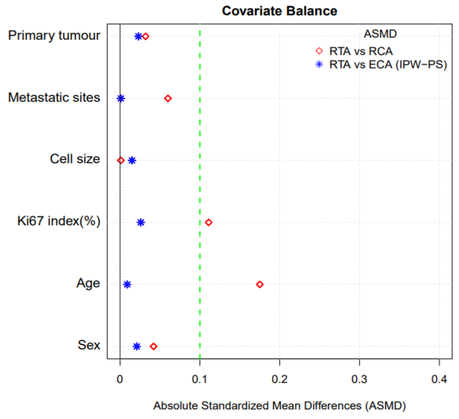
Patient characteristics

		RCA (FOLFIRI)	RTA (FOLFIRI + bev)	ECA (FOLFIRI)
n		66	59	66
Sex	Male	42 (63.6)	40 (67.8)	42 (63.6)
	Female	24 (36.4)	19 (32.2)	24 (36.4)
Age		63.0 (12.2)	65.1 (11.6)	60.5 (12.6)
Ki67 index (%)	≤55	13 (20.3)	5 (9.3)	14 (24.1)
	>55	51 (79.7)	49 (90.7)	44 (75.9)
Cell size	SCNEC	29 (43.9)	26 (44.1)	21 (37.5)
	LCNEC	37 (56.1)	33 (55.9)	35 (62.5)
Metastatic sites	non liver	14 (21.2)	9 (15.3)	17 (26.6)
	liver	52 (78.8)	50 (84.7)	47 (73.4)
Primary tumour	colorectal	18 (27.3)	18 (30.5)	24 (36.4)
	other	48 (72.7)	41 (69.5)	42 (63.6)

Common baseline characteristics in both BEVANEC trial and in CEPD & RBNEC retrospective studies

- available: Age, Sex, poorly differentiated NEC confirmed by experienced pathologist, first line treatment with platinum etoposide, Ki67 index, metastatic sites, primary origin
- Non available: ECOG at the start of 2nd line, LDH and PAL at the start of the 2nd line

Results (1)

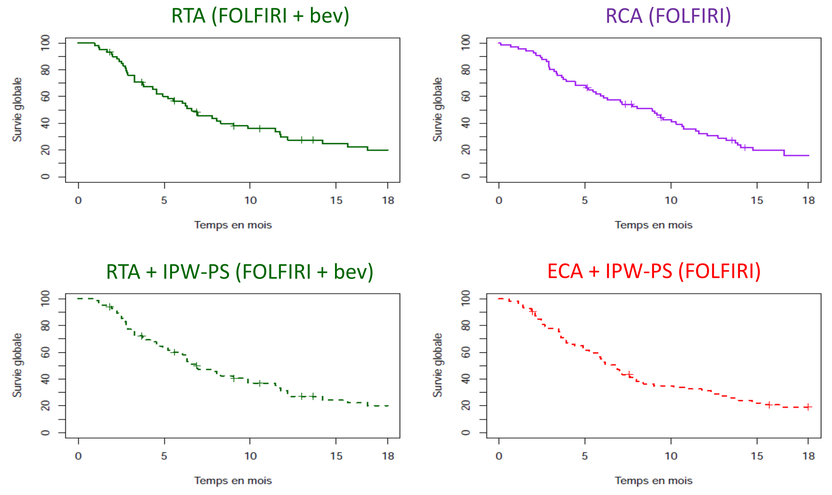


ASMD is a statistical indicator of covariate balance between the treatment arm and the external control arm in the case of using external data.

A covariate is balanced if ASMD ≤ 0.1

→ **Common baseline characteristics were more balanced between the RTA of BEVANEC and the ECA after IPW-PS than between the RTA and the RCA after randomization.**

Results (2)



	RCA	RTA	ECA
	OS [95%CI] (%)		
6 months	**60.5[49.7 ;73.5]**	**56.6[45.1;71.0]**	**55.5[44.6;69.0]**
12 months	**32.4[22.6 ;46.5]**	**29.6[19.5;44.9]**	**30.3[20.9 ;44.0]**
18 months	15.9[8.7;29.0]	20.0[11.3;35.4]	19.0[11.4 ;31.7]
Median	8.9[5.9 ;11.4]	6.6[4.9;11.5]	6.9[5.85 ;9.0]

OS were similar in both ECA and RCA. When substituting the RCA by the ECA and comparing it to the RTA, the synthetic REWENEC trial led to similar outcomes and conclusions as in the BEVANEC trial with no difference in median overall survival between FOLFIRI + bev and FOLFIRI. This suggest that randomization may not have been required in this setting.

Conclusion

Externally controlled trials might be an appropriate compromise between RCT and single-arm trials in NECs. Maintaining a platform of existing good quality data from prospective and retrospective studies would help to design these types of trials and accelerate clinical research in NECs.

References: *Walter et al, Lancet Oncol 2023, Hadoux et al, EJC 2021, Walter et al, EJC 2017, Mishra-Kalyani et al, Annals Oncol 2022, Austin 2009, Greifer 2022, Rosenbaum and Rubin 1983, Quantin 2018*

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