Cost-effectiveness of Next Generation Sequencing to Select Microsatellite Stable/Mismatch Repair Proficient Metastatic Colorectal Cancer Patients for Immune Checkpoint Inhibitor Therapy

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Objective: To estimate the incremental cost-effectiveness of alternating two cycles each of fluorouracil/oxaliplatin chemotherapy (FLOX) and immune checkpoint inhibitor therapy (nivolumab) as 1st-line treatment for the major subgroup of metastatic colorectal cancer patients with microsatellite stability/mismatch repair proficiency (MSS/pMMR) selected via next-generation sequencing (NGS), compared with treating all patients with nivolumab and the standard of care (FLOX alone)

Methods:

- Decision-analytic model; extrapolation to lifetime via partitioned survival models
- Separate parametric models fitted for each strategy and endpoint and evaluated via best practices
- Separate health states before and after disease progression using the progression free survival (PFS) endpoint
- Individual patient-level data from the METIMMOX-1 trial (NCT03388190; see **Table 1** for baseline characteristics)

Table 1: Selected Input Parameters including Baseline Characteristics from the Underlying METIMMOX-1 Trial

	Overall	FLOX alone	Alternating nivolumab
n	76	38	38
Median age [years, IQR]:	64.5 [57.8; 72.0]	65.0 [58.5; 72.8]	60.5 [57.0; 72.0]
Female (%):	35 (46.1)	15 (39.5)	20 (52.6)
ECOG status of 0 (%):	44 (57.9)	21 (55.3)	23 (60.5)
RAS/BRAF-mutant (%):	55 (72.4)	29 (76.3)	20 (68.4)
Left-sided (%):	54 (71.1)	27 (71.1)	27 (71.1)
Median TMB [mut/MB, IQR]:	n.a.	n.a.	8.0 [4.1; 10.2]
Cost per FLOX cycle:	€ 427		
Cost per nivolumab cycle:	€ 13,923	(additional costs)	
Cost for NGS (Illumina TSO-500):	€ 1,439	(additional costs)	
Cost for last month of life:	€ 13,803		
Utility *before* PFS is reached (SD):	0.952 ±0.111		
Utility *after* PFS is reached (SD):	0.895 ±0.093		

- Costs expressed in in 2023 Euros and included drugs, tests, 2nd-line treatments, and end-of-life care (**Table 1**)
- EQ-5D-5L surveys collected in-trial before and after PFS endpoint reached **(Table 1)**
- NGS cut-off: tumor mutational burden (TMB) of >8.0 mutations/megabase (median in METIMMOX-1)
- All outcomes discounted at 4% p.a.
- Incremental cost-effectiveness ratios (ICERs) were computed, and deterministic sensitivity analysis was conducted

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Preliminary Results:

- Weibull models selected for both overall survival and PFS based on not all parametric models converging, visual inspection, and Akaike/Bayesian information criteria
- Patients accumulated 1.74 (FLOX alone) to 2.01 (NGS strategy) life years (see **Table 2** for the base case results)

Table 2: Basecase Results

	Costs	Incremental Costs	QALYs	Incremental QALYs	ICER (€/QALY)
FLOX alone	€34,520		1.7374		
Alternating nivolumab for all	€109,577	€ 75,057	1.8610	0.1236	dominated
Selection via NGS	€51,146	€ 16,626	1.9368	0.1994	83,376

- Adding nivolumab for all resulted in an incremental 0.12 QALYs, and selecting via NGS 0.20 QALYs – at an incremental cost of €75,057 and €16,626, respectively
- The treating-all strategy was dominated by the NGS-based strategy, yielding an ICER of €83,376/QALY
- See **Figure** for selected deterministic sensitivity analyses

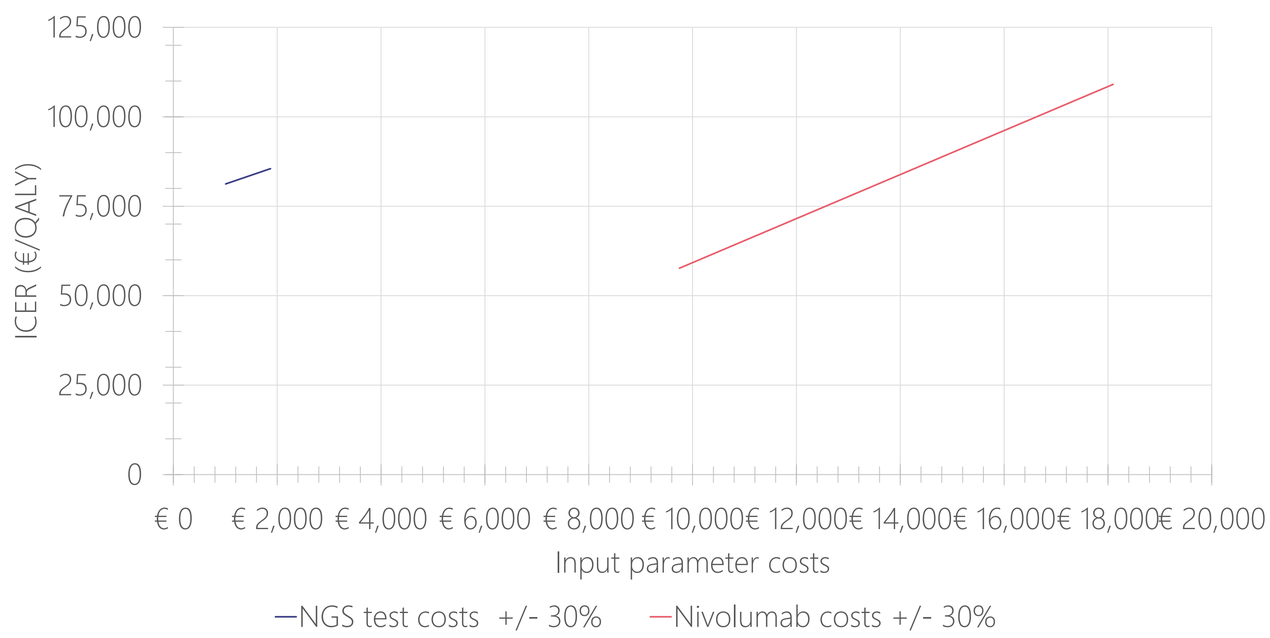

Figure: Selected Deterministic Sensitivity Analyses

Limitations:

- Present calculations based on post-hoc analyses
- TMB data for the control group are missing; pending this, a probabilistic sensitivity analysis is necessary
- Results are only valid in the Norwegian context

Conclusion: Next generation sequencing may be an economically attractive biomarker strategy to select metastatic MSS/pMMR colorectal cancer patients for immunotherapy; however, prospective confirmation is warranted.

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