**POLE** proofreading domain mutation defines a subset of immunogenic colorectal cancers with excellent prognosis

**Authors**
Mark A. Glaire, Enric Domingo, Louis Vermeulen, Tom van Wezel, Gerrit-Jan Leifers, Ragnhild A Lothe, Stine A Danielsen, Arild Nesbakken, Inti Zlobec, Viktor Koelzer, Martin Berger, Sergi Castellvi-Bel, The EPICOLON consortium*, Marco de Bruyn, Marco Novelli, Sabine Tejpar and Mauro Delorenzi on behalf of the PETACC3 Investigators, Rachel Kerr and David Kerr on behalf of the VICTOR and QUASAR2 Investigators, Ian Tomlinson, David N Church

**ABSTRACT**

**Background**
The delivery of precision cancer medicine depends on defining distinct tumour subgroups using biomarkers that may occur at very modest frequencies. One such subgroup comprises patients with exceptionally mutated (ultramutated) tumours caused by mutations that impair DNA polymerase epsilon (**POLE**) proofreading. While these mutations confer enhanced immunogenicity and excellent prognosis in the ~10% of endometrial cancers in which they occur, their consequences in colorectal cancer, where they are less common, are unclear.

**Methods**
We examined the association of **POLE** proofreading domain mutation with clinicopathological variables and immune response in colorectal cancers from the VICTOR, QUASAR2 and PETACC-3 clinical trials, and multiple patient cohorts (LUMC, Oslo, Bern, AMC-AJCC-II, EPICOLON, TCGA). We subsequently investigated its association with prognosis in stage II/III colorectal cancer by Cox regression of pooled individual patient data from these series, comprising more than 4,500 cases.
Results

*POLE* mutations were detected in 66/6,448 (1.0%) colorectal cancers and were significantly associated with young age, male sex, right-sided location, early disease stage, and absence of mismatch repair deficiency (MMR-D) (P≤0.003 for all associations). *POLE*-mutant tumours displayed increased CD8+ lymphocyte infiltration and expression of cytotoxic T cell markers and effector cytokines, similar to immunogenic MMR-D cancers. In multivariable analysis, *POLE* mutation was associated with a greatly reduced risk of cancer recurrence (HR=0.34, 95% CI=0.11–0.76, P=0.006); particularly in stage II disease (HR=0.22, 95% CI=0.02–0.78, P=0.014). This reduction appeared to exceed that associated with MMR-D (HR=0.72 95% CI 0.60–0.87) – an established biomarker of favourable prognosis. Exploratory analysis suggested that the favourable outcome of *POLE*-mutant tumours was independent of chemotherapy.

Conclusions

*POLE* proofreading domain mutations identify a subset of immunogenic colorectal cancers with excellent prognosis. This novel biomarker holds promise to improve patient stratification in colorectal cancer.