PROREPAIR-B: A prospective cohort study of DNA repair defects in mCRPC

David Olmos[1,2], N.Romero-Laorden[1], R.Lozano[1,2], Y.Cendón[1], L.Magraner[1], A.Medina[3], L.Rivera[1,2], G.Grau[1,2], C.Pritchard[4], E.Castro[1] on behalf of PROCURE network.

1. Spanish National Cancer Research Centre (CNIO), Madrid-Spain
2. Institute of Biomedical Research in Malaga (IBIMA), Málaga-Spain
3. Centro Oncológico de Galicia, La Coruña-Spain
4. University of Washington, Seattle-US

Background
Germline mutations in DNA repair genes have been associated with poor prostate cancer outcomes and progression to metastatic disease, but no conclusive data are available regarding survival from mCRPC and response to currently approved survival-prolonging therapies (SPT).

Methods
Prospective multicentre observational study of newly diagnosed mCRPC patients with unknown germline mutation status at study entry. Patients were treated at physician choice's with currently approved SPTs. Primary endpoint was to assess the impact or *BRCA1, BRCA2, ATM* and *PALB2* germline mutations on cause-specific survival (CSS) from diagnosis of mCRPC. Secondary endpoints included the association of those mutations to the response to SPT.

Results
From Jan-2013 to Apr-2016, 419 eligible patients were enrolled. Identified C were 14 *BRCA2*, 8 *ATM* and 4 *BRCA1* (6.2%). Median time from ADT initiation to mCRPC in C and NC was 23.7 vs 26.7 m (p=0.22); in the *BRCA2* subgroup was 18 m (p=0.24). Other baseline characteristics were also NS different between C and NC at 1st SPT initiation: ECOG 0-1 (92% vs 88%), median PSA (27.9 vs 31.0), bone (96% vs 86%), nodal (48% vs 52%) and visceral (12% vs 16%) metastasis.

After a median follow-up of 36 m, 207 prostate-cancer deaths were observed. Median CSS from mCRPC was 28.5 m in C vs 36.0 m in NC (p=0.5), and 17.4 m in the *BRCA2* subgroup (p=0.02). Median CSS and PFS from 1st taxane in C and NC were 17.3 vs 24.5 m, p=0.6 (*BRCA2* 12.8 m, p<0.01) and 7.8 vs 7.1 m, p=0.4 (BRCA2 5.7 m, p=0.3), respectively. CSS and PFS from 1st ART in C and NC were 25.4 vs 26.6 m, p=0.9 (*BRCA2* 27.6 m, p=0.5) and 8.2 vs 9.4 m, p=0.8 (*BRCA2* 5.8 m, p=0.4), respectively.

Conclusions
When all C considered, non-significant trends to worse CSS from mCRPC, from 1st taxane and from 1st ART were observed. Nonetheless, pre-planned subgroup analyses suggest that *BRCA2* mutations are associated with significantly worse outcomes.

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Conflict of interests
None