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CUP-ONE Trial: A prospective double-blind validation of molecular classifiers in the diagnosis of Cancer of Unknown Primary and clinical outcomes

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Background

Cancer of unknown primary remains a major challenge with poor prognoses, protracted pathways and limitations of site-determination by immunohistochemistry. Gene expression signatures (GEP) show promise as molecular cancer classifiers, but their utility in diagnosis and prognosis warrants study. The CUP-ONE Trial prospectively compared a 92-gene assay GEP versus centralized IHC (C-IHC; 10 markers)

Methods

641 consented patients (36 UK sites; 54 mths) had local pathology & MDT outputs classified as a Reference diagnosis (RD). Tissue was allocated, double-blind, randomized to 3 arms (N): C-IHC (329); CTID (418) CancerTYPE ID, Biotheranostics & Healthscope (418; became unviable). Outputs mandated classification to 14 cancer types. The Intention to diagnose (ITD N=392) set had at least 1 available classifier output. Primary Endpoint was %match of a classifier to RD-site of origin (ratio: total number Match results and total number in ITD dataset with a confirmed or suspected RD (C/S; N=131)). Secondary endpoints included overall classifier accuracy in evaluables with a C/S site of origin, concordance of classifiers & a pre-specified diagnostic score

Results

Investigators final classifications (N) were CUP (451), 'Suspected' (72) and revised 118 to 'known' sites. In the ITD set: median 67yrs, 50% male, 92% stage IV. 418 (65%) samples were sufficient for 1 classifier output. Sample inadequacy (C-IHC 7.3%; CTID 13.4%) lead to 306 C-IHC & 362 CTID classifications. In Pair-wise comparisons CTID correctly classified 17.2% [1.9%-29.6%; p=0.0243] more than C-IHC; Agreement of 2 classifiers was 97%. Secondary analysis comparisons showed point estimates favouring CTID but not all statistically significant. Both classified Lung, Colorectal, Breast and Ovary well but CTID did particularly well with Cholangiocarcinoma /gall bladder (60% accuracy) but not in pancreas (9.1%) versus C-HIC (27.2%). Median OS (mths) was poor across all 3 groups CUP: 5.3 (4.6-6.4); Suspected: 9.0 (8.3-11.9); Confirmed: 7.8 (5-13)

Conclusions

CUP-ONE assessed accuracy of CTID Vs C-IHC with comparable outcomes but a higher assignment of Cholangiocarcinoma in CUP. Survival was better in the C/S subset but remains poor overall

Clinical trial identification

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