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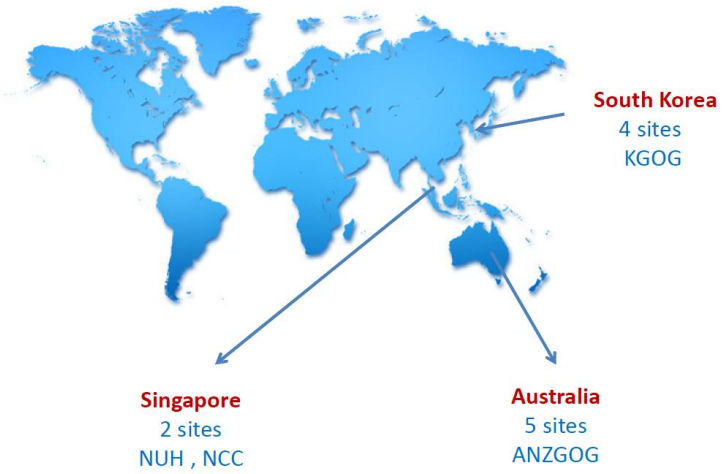
A Multicentre Phase II randomised trial of MEDI4736 (DURVALUMAB) versus physician's choice chemotherapy in recurrent ovarian clear cell adenocarcinomas (MOCCA)



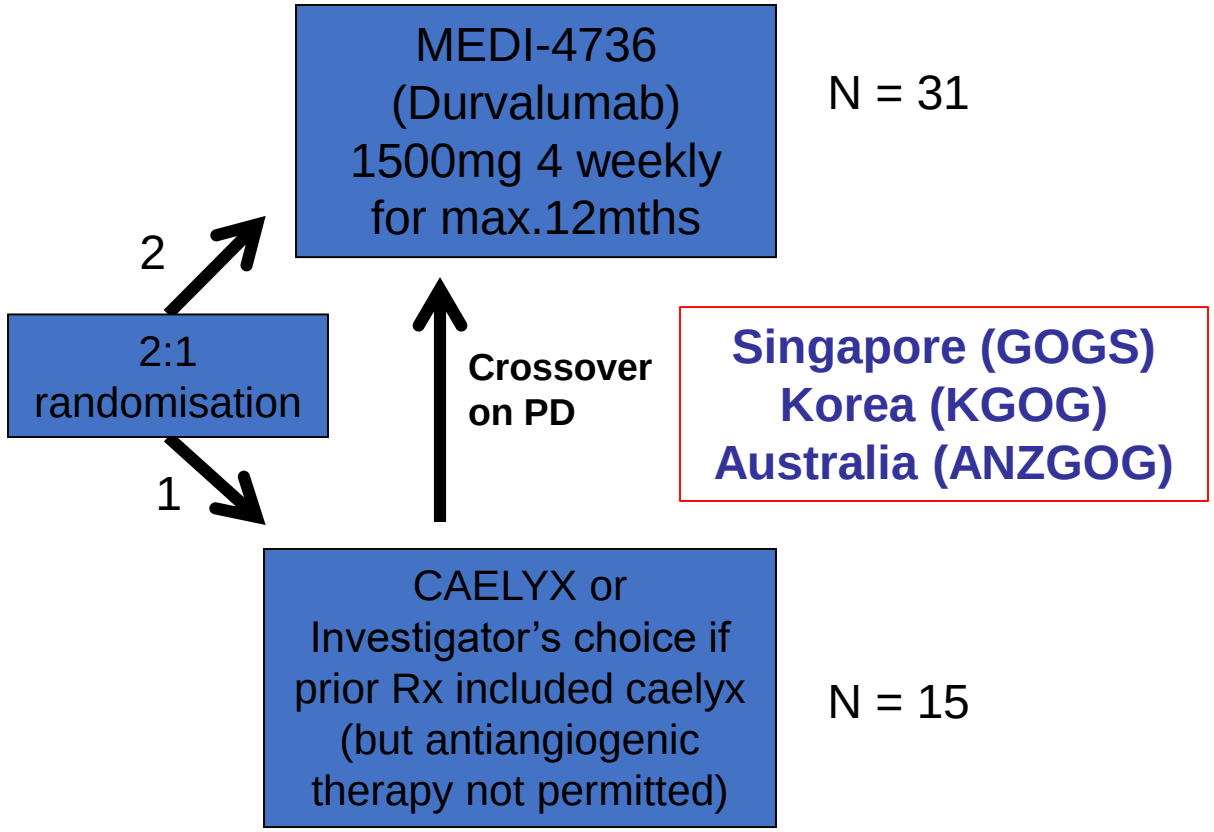
Singapore PI: David Tan NUH GCGS (CI)
Australia PI: Michael Friedlander ANZGOG
Korean PI: Kidong Kim KGOG
Trial Statistician: Prof Tai Bee Choo (NUS)

MOCCA Trial: A Multicentre Phase II randomised trial of MEDI4736 (DURVALUMAB) versus physician's choice chemotherapy in recurrent ovarian clear cell adenocarcinomas (MOCCA)

Relapsed Clear Cell Cancer Ovarian Cancer (>70% clear cell)

Inclusion
-Histologically confirmed
- WT1 negative
-Relapsed after at least 1 line of platinum-based chemotherapy
-Measurable disease by RECIST 1.1
-ECOG 0 / 1

Exclusion
-Concurrent use of experimental anti-cancer agent
-Untreated brain mets



Primary Endpoint:

MOCCA: median PFS improvement from 10 weeks to 20 weeks

Secondary Endpoint:

RECIST/ GCIG response

Trial Objectives

- Primary Objectives:
  - To determine if durvalumab improves progression free survival compared to physician's choice chemotherapy in patients with OCCC

- Secondary Objectives:
  - To determine objective response rate (ORR) in patients with ovarian clear cell carcinoma treated with DURVALUMAB based on RECIST 1.1
  - To assess health related quality of life when patients with ovarian clear cell carcinoma are treated with DURVALUMAB
  - To assess adverse events when patients with ovarian clear cell carcinoma are treated with DURVALUMAB
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Trial Objectives

- Exploratory Objectives:
  - To evaluate the role of the immune-related response criteria (irRC) in determining antitumor responses for OCCC patients on DURVALUMAB
  - To identify predictive novel markers of response to DURVALUMAB (e.g. PTEN loss, *PIK3CA*, *ARID1A* mutations, PD-1 and PDL-1 overexpression)
  - To understand the role of circulating and intratumoral immune regulators (i.e. the tumour microenvironment) in predicting response and the development of resistance to DURVALUMAB

Study design

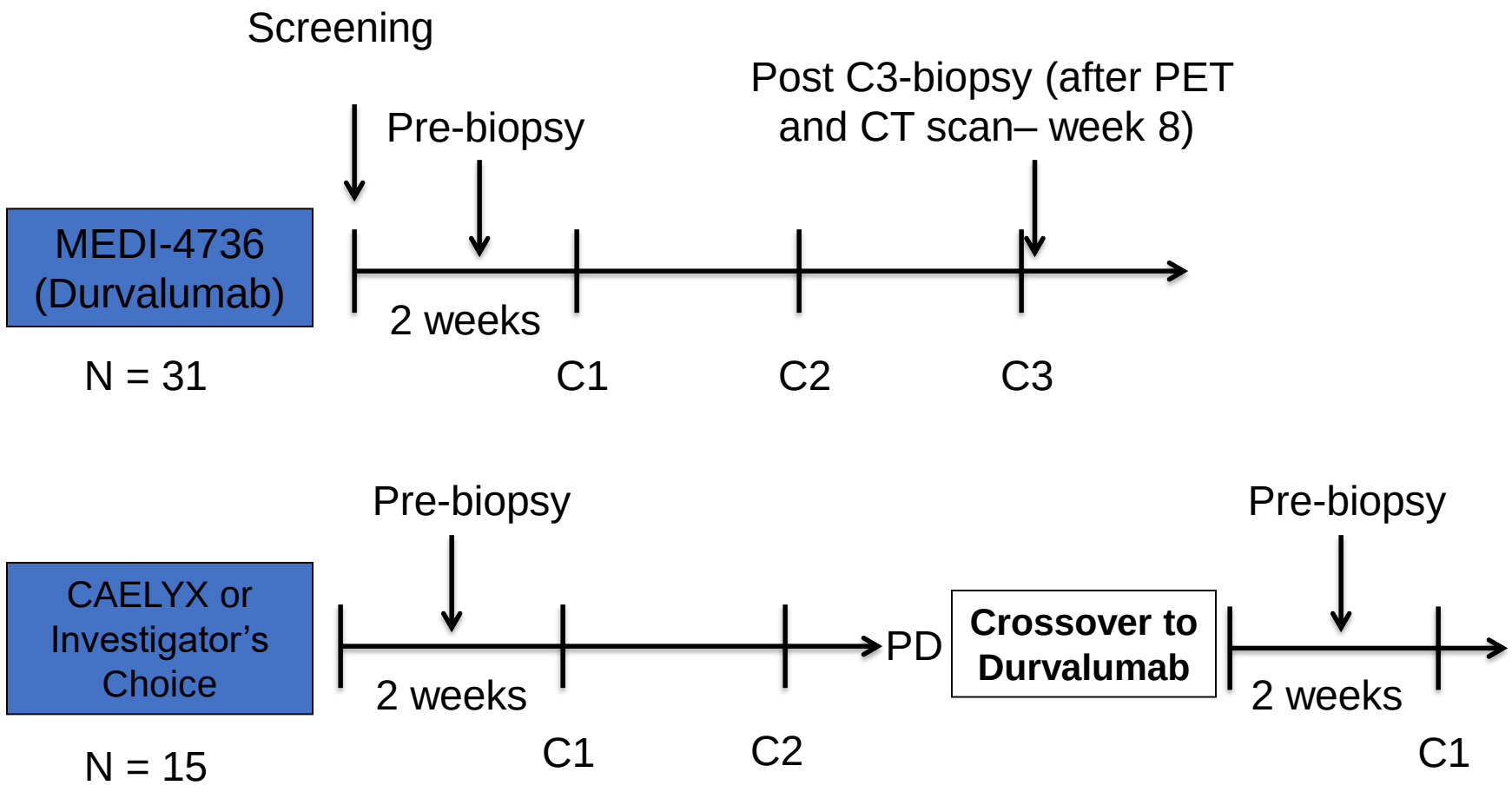
- This study is an open-label trial; patients will be allowed to continue study drug treatment until disease progression or toxicity occurs

- Patients on DURVALUMAB will receive treatment for up to 1 year or disease progression – whichever occurs first.

- Patients on the control arm (investigators' choice chemotherapy) will be allowed to crossover to the DURVALUMAB arm upon disease progression after completing the wash out period of four weeks from previous anti-cancer therapy.

- After discussion with the Principal investigator, patients on DURVALUMAB arm may be allowed to continue on treatment despite disease progression (for up to 2years) if it is felt that they continue to benefit from treatment.

MOCCA Trial: Tissue Biopsies
(where deemed clinically accessible and safe to perform by investigator)



MOCCA translational study

1) Immune Profiling using Luminex Assay on Plasma:

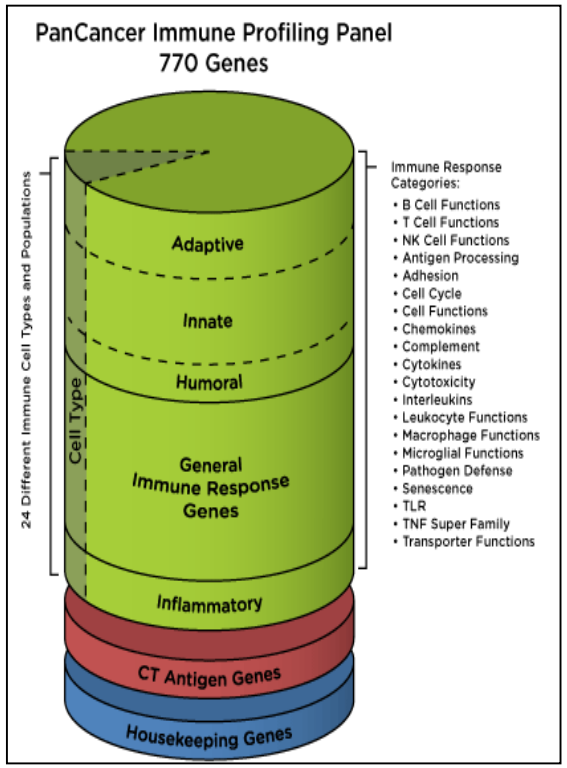
sCD40L, EGF, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, IFN-γ, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, PDGF-AB/BB, RANTES, TGF-α, TNF-α, TNF-β, VEGF,

Eotaxin/CCL11, PDGF-AA

2) Tumor infiltrating leukocytes (TIL) will be isolated from the fresh tumor and stained with the panel to evaluate their activation status

Marker	Population
CD27	Memory
IgM	B-cells
CD15	MDSC
CD86	Activation
CD80	Activation
CD66b	MDSC
CD62L	Activation
CD123	pDC
CD56	NK cells
CD14	Monocytes
CD25	Treg
CD33	MDSC
CD69	Activation
CD28	Memory
CD197 CCR7	T-cells
CD11b	MDSC
CD127	T-cells
HLA-DR	Monocytes
L/D	Live/Dead
CD19	B-cells
CD8	T-cells
IgD	B-cells
CD4	T-cells
CD11c	mDC
CD279 (PD-1)	T-cells

3) nCounter® PanCancer Immune Profiling gene expression analysis



Statistical consideration

- The sample size for this 2:1 randomised trial was based on assumptions concerning the estimated progression free survival in OCCC.
- A retrospective analysis of median PFS in patients with OCCC was 11 weeks (Tan et al J Clin Oncol 32:5s, 2014, suppl; abstr 5548).
- Assuming a median PFS of 10 weeks in the control arm, and a median PFS of ≥ 20weeks in the experimental arm, this translates to a hazard ratio (HR) =0.5.
- Further assuming a 6mth PFS probability of 0.15 in control (Tan et al J Clin Oncol 32:5s, 2014, suppl; abstract 5548), then based on a 2:1 randomisation at 10% significance level (one-sided alpha) and 80% power, a sample size of 31 patients in the experimental arm and 15 patients in the control arm is required (n=46 in total).

Operations and Funding

- Conducted as an investigator initiated clinical trial with AZ and NMRC IAF funding for the study and support for investigational drugs
- NUH will contract with Quintiles and Cenduit for project management and data coordination.
- NUHS will hold separate contracts with the 3 country sites, so that the legal sponsor roles remain with each site / country.
- Any funding from AZ will be directed to NUH/ HORG and channeled to the various sites / countries
- Zuelig will manage drug distribution to the various countries/ sites

Country	Centres	Country-PI	Current recruitment
Singapore	NUH (Coordinating Centre), KKH, NCC	Dr David Tan (Overall PI)	8 – NUH 2 - NCC
Australia	ANZGOG (6 sites)	Prof Michael Friedlander	Awaiting ethics approval
Korea	KGOG (4 sites)	Prof Jae-Weon Kim	planned FPFV 31st Oct