#781 - First-in-human evaluation of CDR404, a MAGE-A4–targeted T cell engager, in ovarian cancer: pharmacodynamic and clinical activity findings from early dose cohorts

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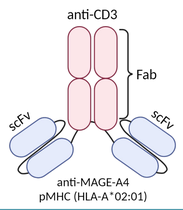
1 Background

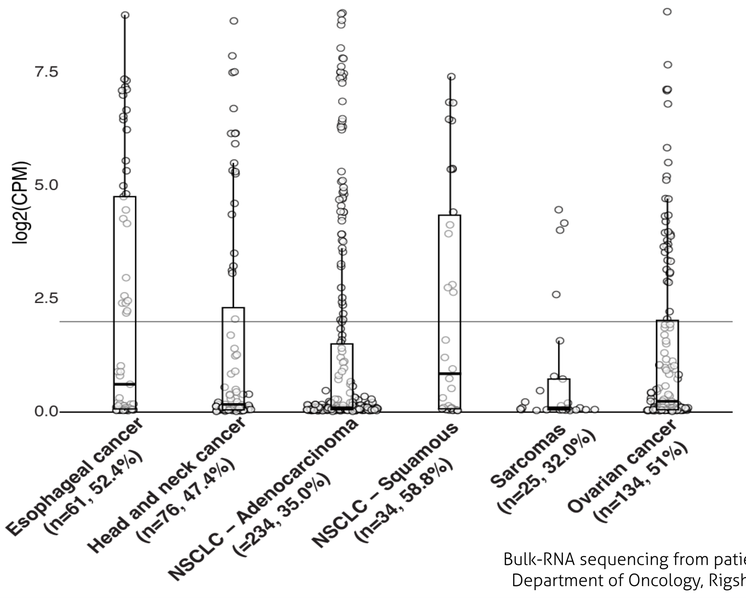
- T cell engagers are emerging as a chemo-free, orthogonal immunotherapy to treat solid tumors, including those with limited response to immune checkpoint inhibitors.
- CDR404 is a bispecific, bivalent antibody-based TCE targeting MAGE-A4$_{230-239}$ in HLA-A*02:01+ patients designed to enable antigen-specific T cell-mediated antitumor killing.
- A first-in-human trial (NCT06402201) is ongoing in the US, UK and EU, enrolling HLA-A*02:01+ solid cancer patients including ovarian cancer (OC), head and neck, squamous lung cancer and soft-tissue sarcomas.
- Here we present initial pharmacodynamic (PD) and clinical data from OC patients treated at dose levels 1-4 (DL1-DL4), prior to reaching the pharmacologically effective dose range (PEDR).



Representation of the molecular structure of CDR404

Molecular weight 100 kDa

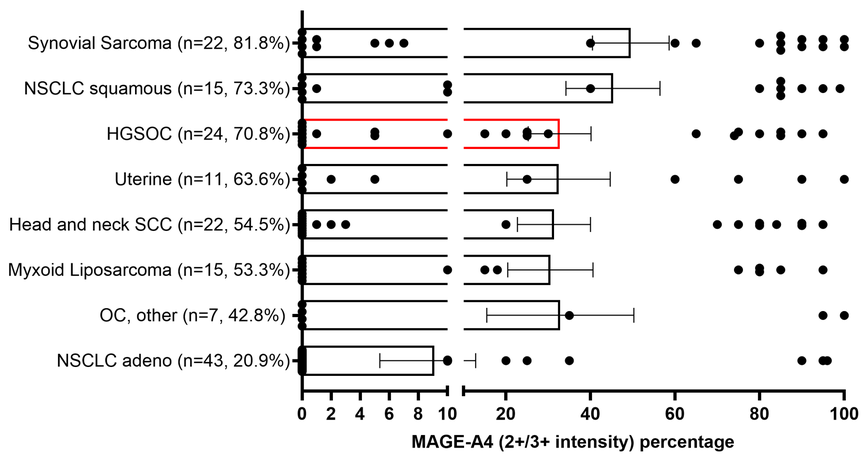
2 *MAGE-A4 mRNA* expression in a large cohort of Phase I patients at Rigshospitalet, Denmark



- *MAGE-A4 mRNA* is highly expressed in a substantial proportion of heavily pretreated patients.
- *MAGE-A4* expression is particularly elevated in squamous tumors (head and neck, lung) as well as ovarian cancer.

Bulk-RNA sequencing from patients with advanced solid tumors at the Phase I Unit, Department of Oncology, Rigshospitalet, Copenhagen, Denmark (NCT02290522).

3 Variety of solid tumors express MAGE-A4



Immunohistochemistry staining results using the E7O1U MAGE-A4 antibody on 159 selected solid tumor samples in the CDR404-001 trial. MAGE-A4 positivity was defined as ≥1% tumor cells with 2+/3+ intensity. HGSOC: high-grade serous ovarian cancer; NSCLC: non-small cell lung cancer; SCC: squamous cell carcinoma.

Both high-grade serous ovarian cancer (HGSOC) and other OC subtypes demonstrate relevant levels of MAGE-A4 protein expression.

4 CDR404-001 Phase 1 trial

Key inclusion criteria:

- Age ≥ 18 years
- Advanced/metastatic solid tumors refractory to SOC
- ECOG 0-1
- HLA-A*02:01+ (central/local testing)
- Tumor MAGE-A4+ by IHC
- Measurable disease (RECIST 1.1)

PART A - Dose exploration

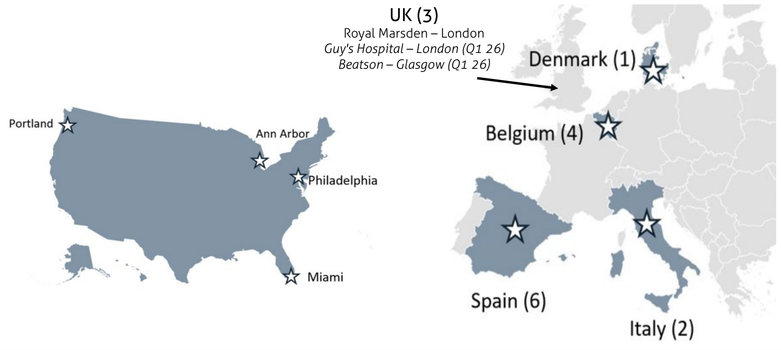
Ovarian, squamous lung, head and neck and sarcoma tumors
Initially weekly iv infusion
QSP-informed starting dose
BOIN12-assisted 3+3 escalation

PART B - Dose Expansion

Monotherapy in platinum-resistant high-grade serous ovarian cancer (HGSOC)

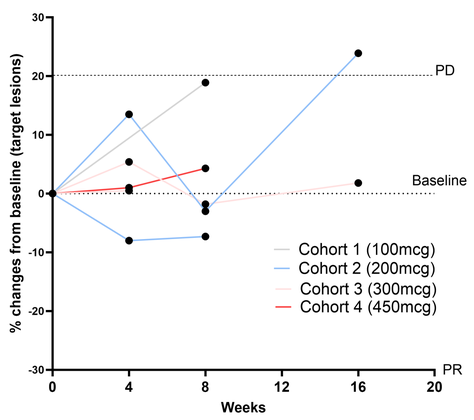
Maintenance therapy in 2L platinum-sensitive HGSOC

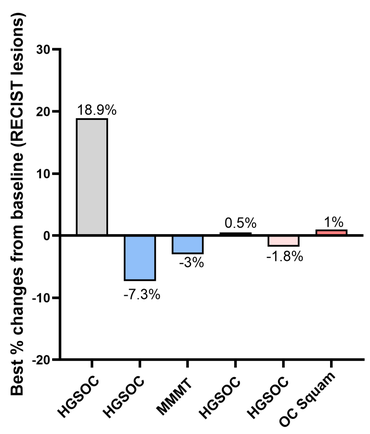
BOIN12: Bayesian Optimal Interval Phase I/II; ECOG, Eastern Cooperative Oncology Group; IHC: Immunohistochemistry; HLA, human leukocyte antigens; IV, intravenous; QSP Quantitative system pharmacology; RECIST, Response Evaluation Criteria in Solid Tumors; SOC: Standard-of-care.



Sites actively enrolling across multiple regions for dose escalation; dose expansion to open thereafter.

5 Initial signs of anti-tumor activity across early dose cohorts in heavily pretreated OC patients

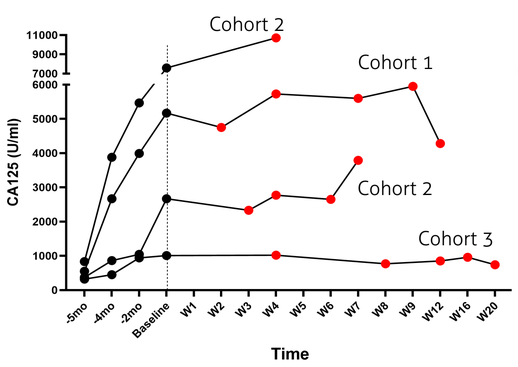


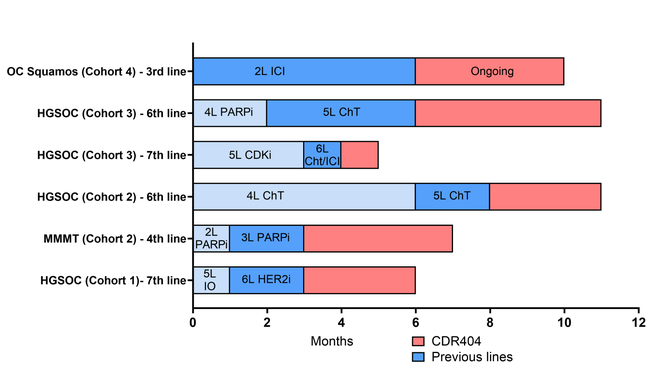


Key terms: HGSOC: High-grade serous ovarian cancer; MMMT: Mixed Mullerian tumour; PR: Partial response,, PD: Progressive disease RECIST: Response Evaluation Criteria in Solid Tumors; SQ: Squamous. The target dose was reached using a two step-up regimen starting from Cohort 3 (100→ 200→ target dose). Dexamethasone premedication was introduced from Cohort 3.

Modest tumor reductions and disease stabilization observed before entering pharmacologically effective dose range (PEDR).

6 Early CA125 stabilization and emerging clinical durability at early dose levels of CDR404

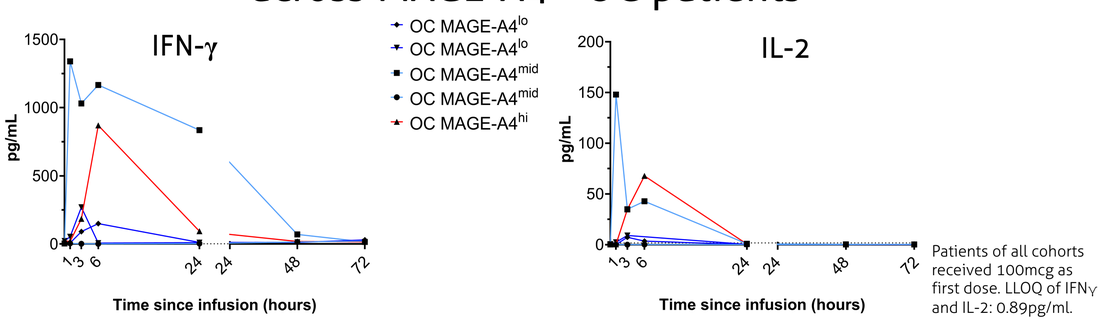




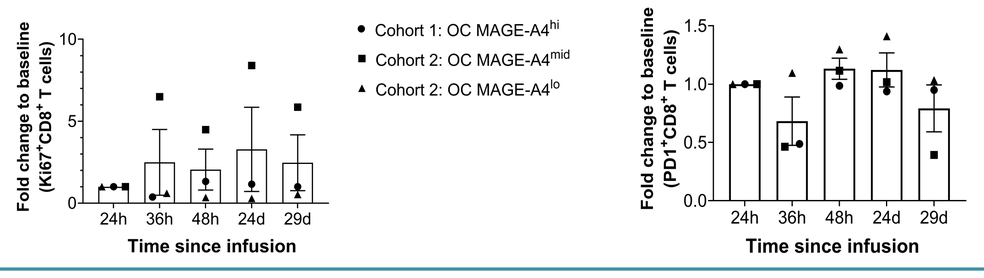
Cohort 1: 100mcg flat dose; Cohort 2: 100-200mcg; Cohort 3: 100-200-300mcg, Cohort 4: 100-200-450 mcg of CDR404; CA125: Cancer antigen 125; HGSOC: High-grade serous ovarian cancer; MMMT: Mixed Mullerian Tumour.

CA125 stabilization and encouraging durability signals across OC histologies in Cohorts 1-4 indicating emerging pharmacodynamic activity at early dose levels.

7 CDR404 induces T-cell activation and proliferation across MAGE-A4+ OC patients



Patients of all cohorts received 100mcg as first dose. LLOQ of IFNγ and IL-2: 0.89pg/ml.



8 Conclusions

- MAGE-A4 is broadly expressed across multiple solid tumors, including high-grade serous ovarian cancer (HGSOC), supporting patient selection for CDR404.
- At early, dose levels, CDR404 induces controlled T-cell activation and proliferation irrespective of MAGE-A4 level in a subset of ovarian cancer patients.
- Early PD activity is accompanied by initial clinical signals, including CA125 and tumour stabilization in a subset of heavily pretreated HGSOC, a typically immunologically cold tumor type with limited treatment options.
- Dose escalation is ongoing with planned expansion in HGSOC to further characterize activity, durability and safety.

For more information, contact CDR-Life at cdr404-001_study@cdr-life.com or visit:
- Clinicaltrials.gov: https://clinicaltrials.gov/study/NCT06402201
- EudraCT: 2023-508808-38-00

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