Hallmarks of pharmacodynamic activity of CDR404, a new antibody-derived T cell engager (TCE) targeted against MAGE-A4+ solid tumors in HLA-A*02:01+ patients

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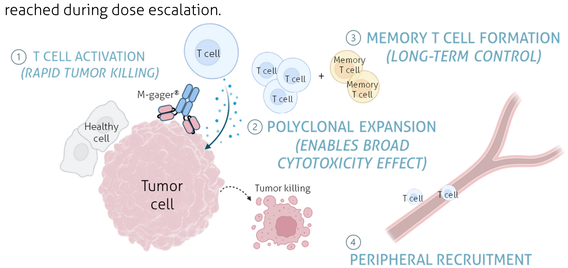
Background

- CDR404 is a novel bispecific & bivalent antibody-based (scFv-FAB-scFv format) TCE targeted against MAGE-A4 for HLA-A*02:01+ patients which is being evaluated in a first-in-human (FIH) trial at multiple sites in US, Europe & U.K. (NCT06402201).
- The trial is enrolling HLA-A*02:01+ solid cancer patients including non-inflamed ("cold") tumors, such as MAGE-A4+ ovarian cancers and soft-tissue sarcomas.
- The mechanism-of-action of CDR404 is "immunological synapse" formation between MAGE-A4$_{230-239}$ peptide presented on HLA-A*02:01 molecules and CD8+ T cells. This is expected to trigger multiple, T cell based, pharmacodynamic (PD) effects which will be essential for sustained cancer cell killing.
- To robustly demonstrate the PD activity of CDR404 in the FIH trial, we developed a quantitative systems pharmacological (QSP) model based on preclinical data to inform the starting dose (100mcg) which was ~10x higher than the MABEL dose.
- CDR404 was administered IV, QW, in 3-weekly cycles. A total of 9 patients were treated at the first two dose levels: 6 pts at 100mcg (DL1) & 3 pts at 200mcg (DL2).
- To confirm the PD effects of CDR404 during the early stages of the FIH trial, we here present 3 patient case studies of the emerging translational data from DL1 & DL2.

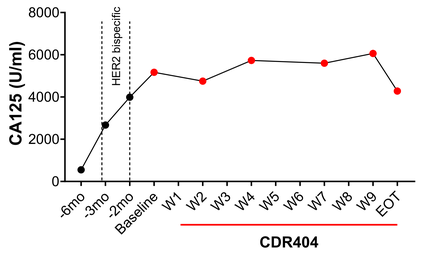
Anticipated PD effects of CDR404 on T cells

TCEs have four canonical, T cell based, hallmarks of pharmacodynamic (PD) activity. CDR404 will need to satisfy each of these 4 PD hallmarks to enable sustained and durable cancer cell killing in patients once pharmacologically effective dose levels are reached during dose escalation.

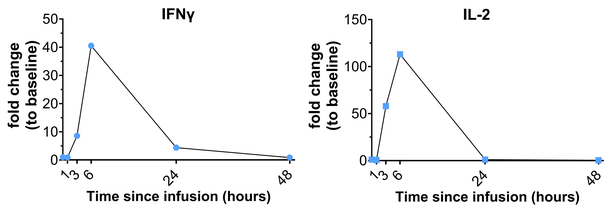


1st PD hallmark – T cell activation: This was confirmed in most patients in DL1 & DL2 by the increase in multiple serum cytokines levels including IFNγ & IL-2 during Cycle 1 infusions.

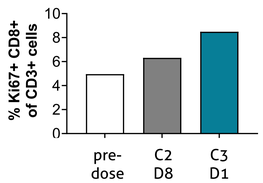
Initial rapid CA125 stabilization followed by 17% reduction after 9 doses



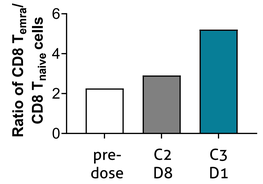
CDR404 triggers increases in serum cytokines indicative of PD Hallmark 1: T cell activation



CDR404 triggers expansion of CD8 T cells indicative of Hallmark 2



CDR404 re-programs CD8 T cells to a memory phenotype indicative of Hallmark 3



① 1st patient treated in the trial with 100mcg in DL1 had clear signals of PD activity & 17% reduction in plasma CA125 levels after 9 doses

- Heavily pre-treated high-grade serous ovarian cancer (7 prior lines)
- High tumor burden liver metastases
- HLA-A*02:01 and HLA-A*01:01; high MAGE-A4 expression
- SAFETY: Grade 1 cytokine release syndrome (CRS) after 1st dose

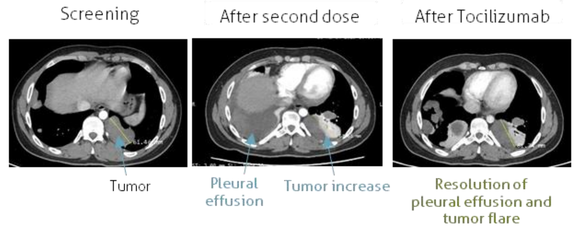
treatment line	7L	8L
months	1.5	2
treatment	*HER2 bispecific*	*CDR404*

② CDR404 at 100mcg in DL1 triggered tumor stabilization for 16 weeks in an 18-year-old with metastatic SS refractory to 1st-line ifosfamide-based chemotherapy

- High-volume metastatic Synovial Sarcoma
- Rapid lung progression, Prior Surgery+RT and doxo/ifo, no standard options available
- HLA*02:01 homozygous; high MAGE-A4 expression
- SAFETY: Grade 2 "tumor flare" in lungs after 2nd dose at 100mcg

treatment line	1L	2L
months	2	4
treatment	*Doxo /Ifo*	*CDR404*

Reversible "TUMOR FLARE" on CT scans of lung metastasis after 2nd dose indicative of T cell activation

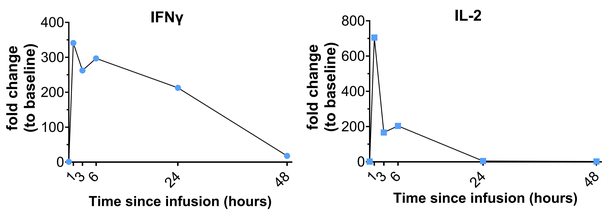


③ CDR404 treatment led to tumor stabilization in a heavily pretreated ovarian carcinosarcoma at 200 mcg after 8 doses

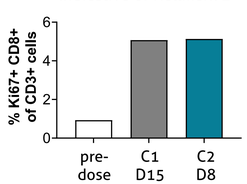
- Aggressive high-volume ovarian carcinosarcoma
- Rapid liver, pelvic and lymphnodal progression
- HLA-A*02:01 homozygous ; intermediate MAGE-A4 expression
- SAFETY: Grade 2 CRS and Grade 2 "tumor flare" (spontaneously reversible inguinal lymphadonopathy) observed during Cycle 1 doses.

treatment line	1L	2L	3L	4L
months	5.5	3	1.5	4
treatment	*ChT +Bev*	*PARPi*	*PARPi*	*CDR404*

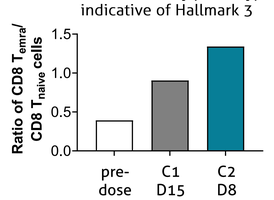
CDR404 triggers increases in serum cytokines indicative of Hallmark 1: T cell activation



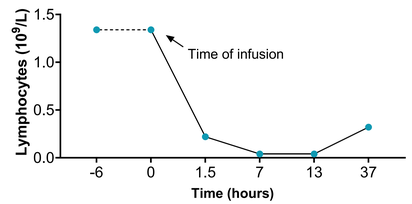
CDR404 triggers expansion of CD8 T cells indicative of Hallmark 2



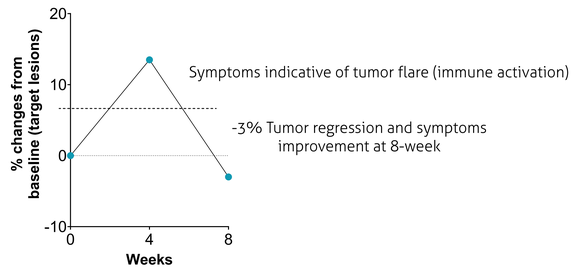
CDR404 re-programs CD8 T cells to a memory phenotype indicative of Hallmark 3



Absolute lymphocyte count (ALC) reduction was indicative of "margination" which fulfills PD Hallmark 4: T cell recruitment from periphery into tumor



CDR404 induced tumor regression on CT scans after 8 doses



Conclusions

- CDR404 triggered anti-tumor control (RECISTv1.1 stable disease) of 8-16 weeks duration in 3 / 9 patients treated at the first two dose levels.
- A higher starting dose enabled by QSP modelling led to all four canonical PD, T cell based, hallmarks being seen in the 1st (ovarian cancer) patient dosed in the trial and included a reduction in plasma CA125 levels after 9 doses.
- All these PD hallmarks were reproducible in other patients with "cold" tumors at the first two dose levels.
- Fully reversible, low grade, episodes of CRS and/or transient tumor flare were reported during Cycle 1 doses in the three presented case studies.
- Dose escalation is ongoing. The QSP model will be serially updated with emerging patient PK and PD data during the trial.

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