DEKA-1: a dose-finding Phase 1 trial evaluating safety and biomarkers using DK2[10] (EGFR) for inoperable locally advanced and/or metastatic EGFR+ tumors with progressive disease failing systemic therapy.

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Abstract

Background: Both interleukin-2 (IL-2) and interleukin-10 (IL-10) have been extensively studied for their stimulatory function on T cells and their potential to obtain sustainable tumor control in RCC, melanoma, lung, and pancreatic cancer as monotherapy, as well as combination with PD-1 blockers, radiation, and chemotherapy. While approved, IL-2 alone remains significantly toxic, which prevents its widespread use. The significant efforts undertaken to uncouple IL-2 toxicity from its anti-tumor function have been unsuccessful and early phase clinical safety observed with PEGylated IL-10 was not met in a blinded Phase 3 trial. Deka Biosciences has engineered a novel molecule coupling wild-type IL-2 to a high affinity variant of Epstein Barr Viral (EBV) IL-10 via a scaffold (scFv) that binds to epidermal growth factor receptors (EGFR). This patented molecule, termed DK2[10] (EGFR), is retained at high levels within the tumor microenvironment (TME) for days after dosing. In addition to overlapping and non-redundant anti-tumor function, IL-10 reduces IL-2 mediated cytokine release syndrome risks and inhibits IL-2 mediated T regulatory cell proliferation.

Coupled cytokines exhibit and reduced toxicity

IL-2

20-30% Overall Response Rate (ORR)
Stimulates CD8+, CD4+ T and NK cell anti-tumor function
Induces toxic Cytokine Release Syndrome (CRS)
Induces proliferation of efficacy limiting CD4+ T regs

Anti-EGFR scFv

Targets Diakine™ to accumulate in the TME

IL-10

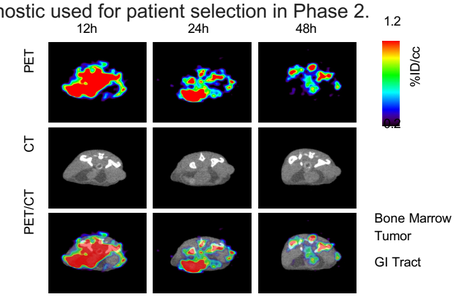
20-30% Overall Response Rate (ORR)
Stimulates CD8+ T cell anti-tumor function
Blocks Cytokine Release Syndrome (CRS)
Blocks CD4+ T reg proliferation

Tumor targeting further enhances potency and further reduces toxicity

Methods: DK2[10] (EGFR) is being evaluated for safety, pharmacokinetics and biomarker profiles in an open-label, dose-escalation (Phase 1) study with 5 (0.025-0.3 mg/kg) monotherapy dose levels, and (expansion cohorts) in combination with (i) PD-1 blockers, (ii) radiation or (iii) chemotherapy in patients with advanced solid tumors overexpressing EGFR. Plasma and tissue samples will be investigated for pharmacodynamic and predictive biomarkers and genetic signatures associated with IFN-gamma secretion, aiming to select subjects for treatment in Phase 2.Final aim will be correlation of IFN secretion pattern into a genetic signature companion diagnostic used for patient selection in Phase 2.

Targeting Diakines™ to the tumor

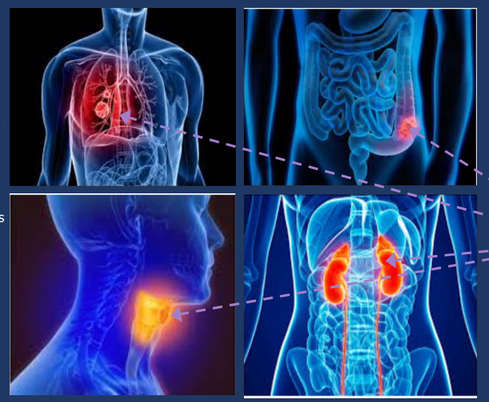
- Targeting DK2[10] (EGFR) to bind to tumor associated antigens expressed on tumor cells (EGFR) leads to accumulation in the tumor microenvironment.
- ~2% of the initial dose is present in the tumor after 48 hours, representing an intratumoral concentration of ~ 400 ng/mL (tumor volume)



RATIONALE

IL-2 and IL-10 both exhibit immune-driven anti-tumoral effects
EGFR is expressed in many advanced solid cancers

IL-10 TAMES IL-2
IL-10 limits IL-2 related CRS risks and blocks Tregs expansion

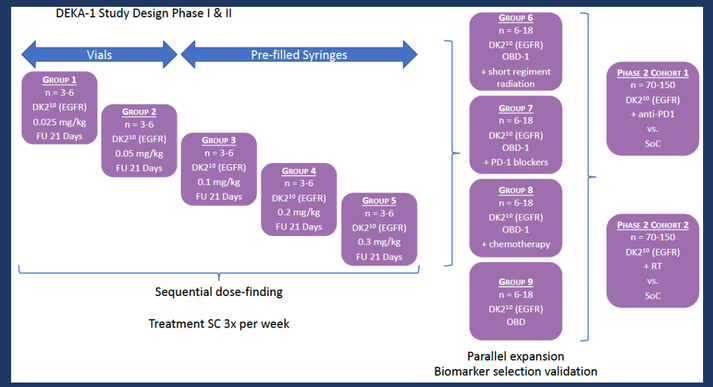


TARGETED
Any tumor target:
Capable of targeting any cell surface protein and delivering
to any tumormicroenvironment

Conclusion: Through successful coupling of wild-type IL-2 with a high affinity IL-10 and targeting directly to the tumor microenvironment, DK2[10] (EGFR) has the potential to harness IL-2 and IL-10's known anti-cancer promise while reducing immunogenicity and toxicity risks enabling safe concomitant cytokine treatment with other anti-cancer modalities.

Trial design

- ✓ Phase 1-1b, multi-center open label dose-escalation-expansion trial
- ✓ ~60 patients will be enrolled at ~ 5 sites
- ✓ selecting squamous cell carcinoma or other histology's overexpressing EGFR receptors
- ✓ Home-based subcutaneous dosing 3x/week cup till clinical progression,
- ✓ Patients reaching complete remission can stop dosing



Key Inclusion criteria

- ECOG performance status of 0-1
- Solid tumors known for high expression of EGFR or proven EGFR amplification documented in histology report based on protein expression, protein activation, gene copy number, polymorphisms, mutation, or EGFR ligand expression (>50%). Most common solid cancers meeting this histological profile are tumors of the e.g., colon, kidney, pancreas, skin, urinary tract, gynecologic, head and neck, triple negative breast cancers or NSCLC
- Measurable disease, defined as at least one (non-irradiated) lesion measurable on CT/MRI or bone scan as defined by RECIST 1.1.
- Progressive disease (PD) at study entry defined by local standard
- Laboratory values at screening:
  - Neutrophil >1000 cells/mm3, platelet >75 cells/mm3, Hb >8 g/dL
  - Creatinine clearance (Cockcroft Gault equation, using ideal body weight in weights over 80kg) > 50ml/min
  - Coagulation: INR and aPTT <1.5xULN
  - AST and ALT <2xULN, bilirubin<2.5xULN or <5xULN in presence of liver metastases
- Life expectancy of >3 months according to the investigator's judgment
- Subjects have failed one or more lines of systemic therapy

Key exclusion criteria

- Subjects with documented diffuse peritoneal disease or persistent abundant ascites
- Subjects with baseline QT prolongation (e.g., exclusion of patients with QTc > 480 msec)
- Concomitant or recent (<4 weeks or 5 half-lives of the last treatment, whichever is shorter) treatment with agents with anti-tumor activity, including immune therapies, chemotherapy or experimental therapies. Bone treatments and supportive care can be continued
- Major surgery within 4 weeks, Radiation therapy for the treatment of target lesions within less than 3 weeks (if single fraction of radiotherapy, then within 2 weeks) and radionuclide therapy for the treatment of metastases within 4 weeks prior to screening
- Uncontrolled intercurrent illness including, but not limited to, ongoing and uncontrolled infection (TBC, COVID or HIV patients treated with at least two anti-retroviral drugs and control of their infection with at least 500 /mm3 CD4+ T-cells in their blood and patients cured from Hepatitis B or C (i.e negativity of PCR) and liver function compatible with eligibility criteria are allowed to participate), multiple myeloma, multiple sclerosis, myasthenia gravis, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirement
- Any other conditions that, in the investigator's opinion, might indicate the subject to be unsuitable for the study

End points

Primary Outcome Measures:

1. Incidence of Adverse Events (AEs) with DK2[10] (EGFR);
2. Identify recommended dose of DK2[10] (EGFR) based on toxicities observed

Secondary Outcome Measures:

1. Serum concentrations of DK2[10] (EGFR) and presence of anti-DK210 (EGFR) antibodies will be determined at various time points;
2. Overall and Best (9 weeks) response rate based on clinical examination and investigator review of radiographic images

Correlative Outcome Measures:

1. Circulating DNA will be measured before and during dosing;
2. Immunophenotyping of peripheral blood mononuclear cells will be performed by flow cytometry summarized by dose level;
3. Serum concentrations of proinflammatory cytokines such as IL-6, IL-10, TNF-alpha, IL-1 beta, and interferon (IFN)-gamma will be assessed at various time points and summarized by dose level

This trial (NCT05704985) is now enrolling

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