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Another IND Cleared To Commence Clinical Trials

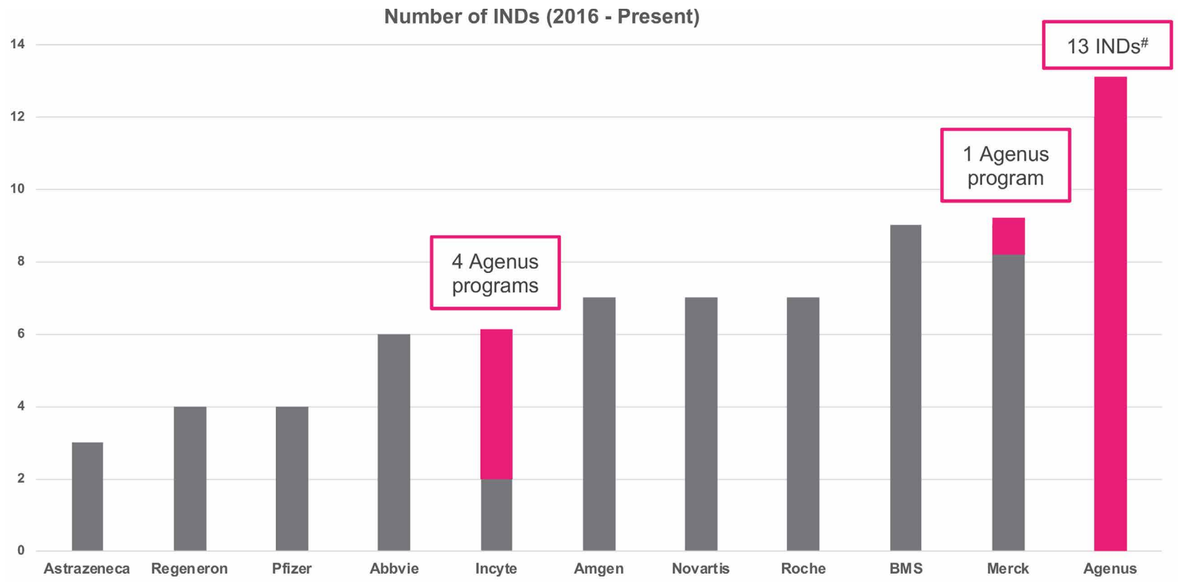
CD137 agonist is among 13 Agenus inventions to be filed as IND in the last 3.5 years

AGEN2373 is Agenus' CD137 agonist antibody which has been specifically designed to overcome the shortcomings of earlier generation CD137 agonists, which have demonstrated toxicity or lack of optimal activity. CD137 is a member of the tumor necrosis factor (TNF) receptor family. Its alternative names include **4-1BB**. The receptor plays a key role in memory response, which is critical for achieving durable (not transient) immune responses.

Using our biological and structural engineering expertise we produced an antibody designed to achieve optimal memory response without the toxicities associated with other candidates. We believe our antibody has the potential to bring an important therapeutic advancement to patients with cancer. **Why?** *Because AGEN2373 can stimulate two key immunological pathways. Both are important in generating effective and durable responses against cancer. We expect to dose our first patient shortly.*

While the field of immuno-oncology seems to have hit a wall after the successes of antibodies binding to immune receptor targets, PD-1 and CTLA-4, our discovery engine and expertise has advanced a substantial number of first and best in class candidates to address the limitations of these first-generation antibodies. Our recent collaboration with Gilead, with $120M in an upfront payment and $30M in an equity investment, is yet another testament of our achievements. This year we already triggered two cash milestones from the Gilead collaboration.

The advancement of AGEN2373 can potentially mean another lifesaving medicine will be available for some patients with cancer and mark an important milestone for our business as one that fuels innovation. The sheer number of therapies advanced by Agenus into the clinic in the past 3.5 years is simply unprecedented.



Analysis as of July 2019
INDs include programs partnered with Incyte, Merck and Gilead

Why Is CD137 Agonism Important?

CD137 is a highly attractive target for cancer immunotherapy because it represents a potent pathway that regulates cancer fighting T and NK cell responses. In addition to the potential to target both arms of immunity: innate (through NK cells) and adaptive (through T cells), CD137 agonist antibodies can restore the tumor fighting capabilities of T cells and NK cells. In addition, molecules targeting the CD137 ligand may promote maturation of antigen presenting cells that are important in educating the immune system to seek out cancer. At the same time, these molecules can eliminate regulatory T cells which protect cancer cells. Furthermore, this important pathway (CD137 agonism) can improve the efficacy of a range of other therapeutic approaches including anti-PD1 & anti-CTLA-4 checkpoint inhibitors, cancer vaccine, chemotherapy, radiotherapy, and adoptive cell therapies.

AGEN2373 Is Designed To Perform Better Than Other Antibodies In This Class

The first CD137 agonist antibody to enter the clinic, Urelumab (BMS), showed promising signals of efficacy as a single-agent in early Phase 1 trials but encountered difficulties in Phase 2 studies due to severe liver toxicity. Whereas, Utomilumab (Pfizer), showed a clean safety profile, but has not shown optimal clinical activity.

At Agenus, we have recognized the importance of this target for some time, and we have had the capabilities to engineer the molecule in a way that addresses the shortcomings encountered by the other molecules; resulting in our AGEN2373 optimally designed to achieve favorable features of safety and clinical activity.

AGEN2373 is a fully human monoclonal antibody that boosts the immune response to cancer cells by enhancing CD137 co-stimulatory signaling in activated immune cells – both adaptive (T cells) and innate (NK cells). The unique binding properties of AGEN2373 are expected to optimize its specificity for the tumor site and mitigate toxicities that may be associated with systemic activation of CD137 in humans. AGEN2373 deliberately stimulates CD137 only upon antibody cross-linking, and therefore, CD137 agonism is not activated in the absence of this cross-linking. This selective or conditional agonist activity is anticipated to minimize on-target, off-site toxicities observed with other molecules in this class.

Therefore, we believe AGEN2373 presents a unique, potential best-in-class opportunity to target this pathway in our fight to combat cancer using best in class immunological tools.

In 2018, we presented data at SITC showing that AGEN2373 is well-tolerated in non-human primates and may be combined with other checkpoint antibodies to enhance T cell activity. Based on these results, Agenus plans to develop AGEN2373 as a monotherapy and in combination with standard-of-care and other I-O treatments.

AGEN2373 is an investigational agent that has not been approved for any uses. Efficacy and safety have not been established.