

Rationale and design of three ongoing phase 1/2 trials of modakafusp alfa, an innate immunity enhancer, in patients with multiple myeloma: The iinnovate clinical development program

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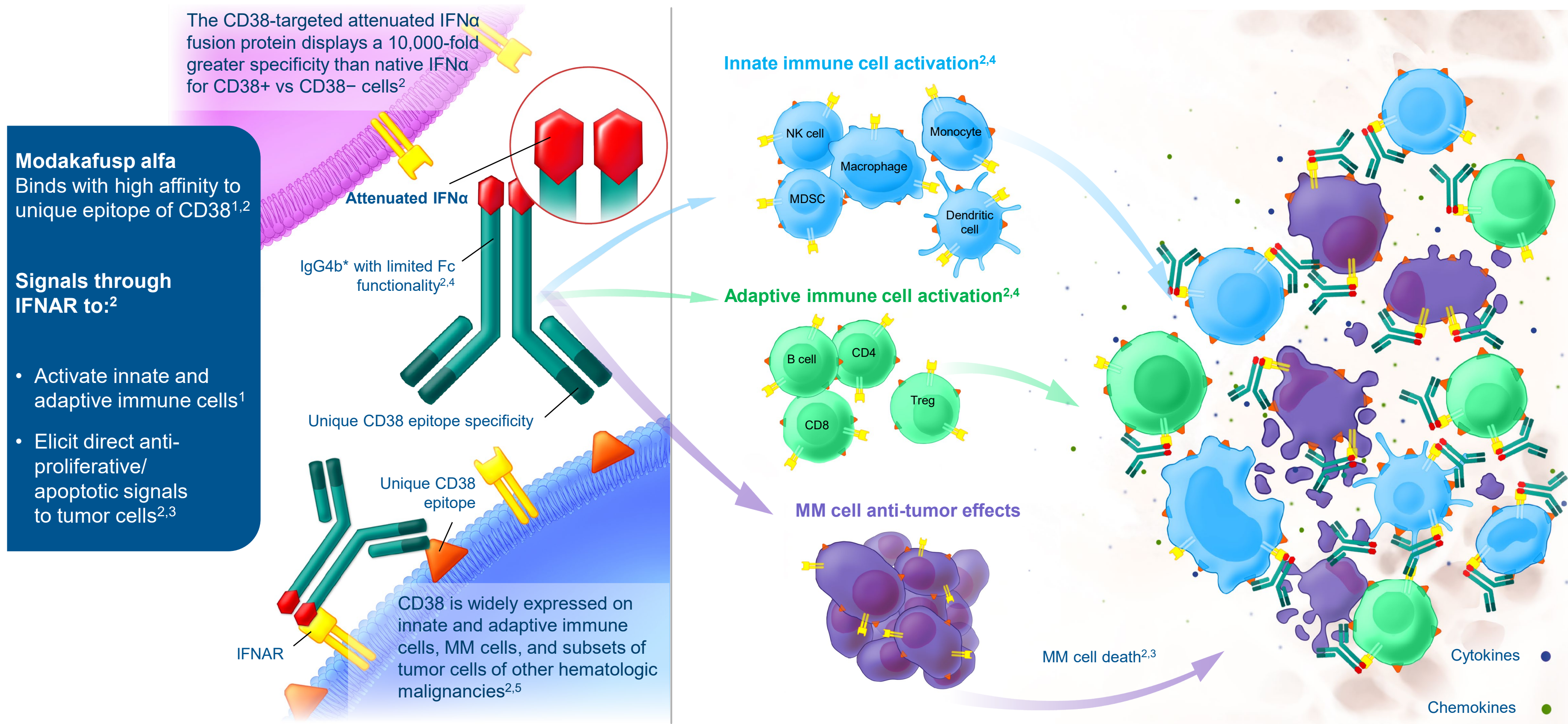
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Background

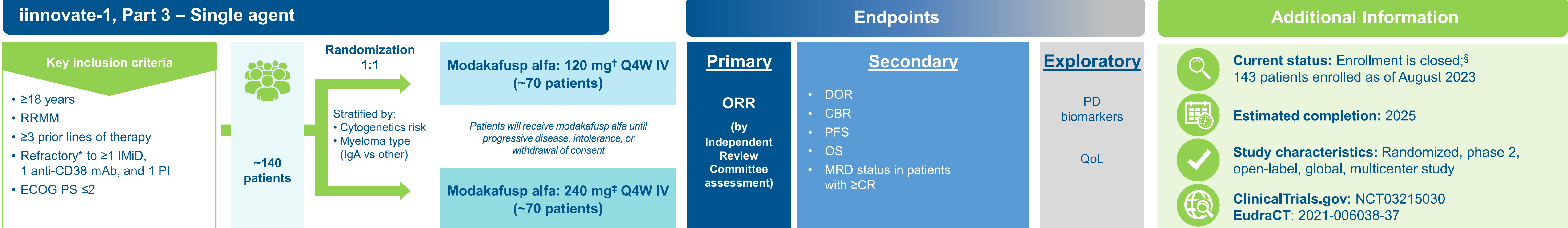
- Novel targeted therapies for multiple myeloma (MM) are highly warranted, particularly for patients with relapsed/refractory disease and/or with resistance to multiple drugs
- Modakafusp alfa is a first-in-class, innate immunity enhancer designed to deliver attenuated interferon (IFN) to innate and adaptive immune cells, as well as myeloma cells (**Figure 1**)^{1,2}
- Modakafusp alfa comprises two attenuated IFNα2b molecules genetically fused to the Fc portion of a humanized IgG4 mAb, which binds to a unique epitope on CD38
- The attenuation of the IFN molecules results in reduced IFN receptor binding affinity, which drives targeted IFN signaling in immune and myeloma cells²
- The IgG4 backbone has limited effector function, in contrast to the IgG1 backbones of currently approved anti-CD38 mAbs^{6,7}
- Preclinical studies have shown prolonged tumor growth delays when modakafusp alfa is combined with SOC agents, such as IMiDs, PIs, and anti-CD38 mAbs^{8,9}
- In the first-in-human study in patients with heavily pre-treated RRMM (iinnovate-1, Parts 1 and 2; NCT03215030), modakafusp alfa given at 1.5 mg/kg Q4W resulted in a manageable safety profile and single-agent activity with an ORR of 43%; the maximum tolerated dose was 3 mg/kg Q4W¹⁰
- We present the design and status of the iinnovate-1-2-3 studies
 - These studies plan to determine the optimal dose of modakafusp alfa as a single agent and in doublet and triplet combinations with SOC agents for different MM patient populations, including patients with the highest unmet medical needs

Figure 1: Modakafusp alfa mode of action



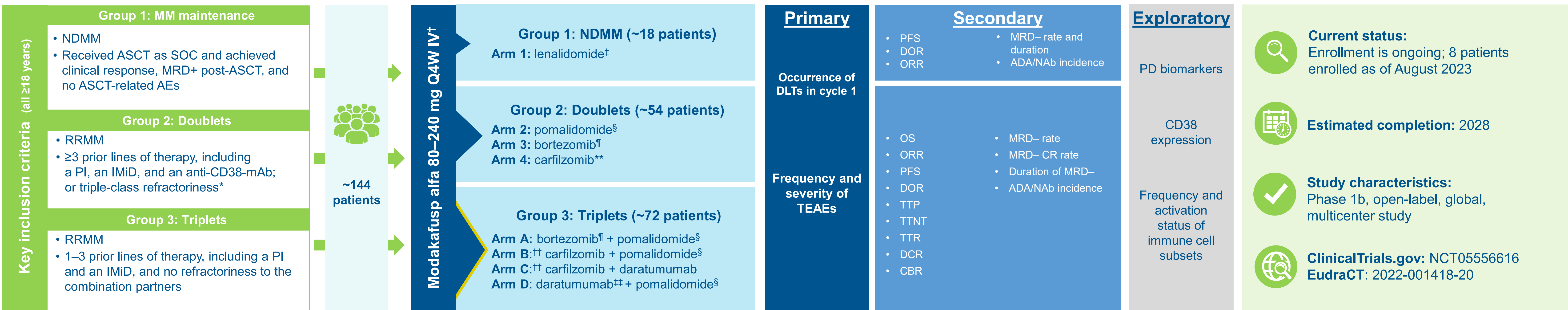
*IgG4 is a poor inducer of Fc-mediated effector functions, such as antibody-dependent cellular cytotoxicity and phagocytosis.⁴

Study Designs



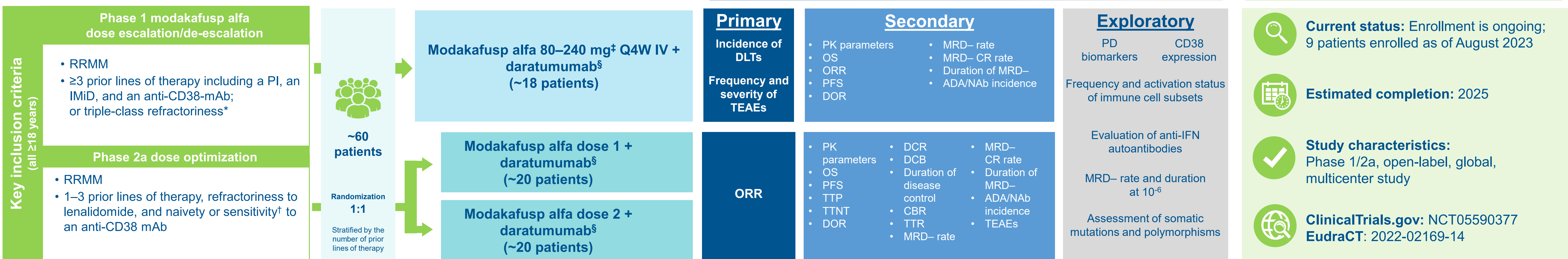
*Defined as <25% reduction in M-protein or progression of disease during treatment or ≤60 days after cessation of treatment. †Fixed-dose equivalent of 1.5 mg/kg. ‡Fixed-dose equivalent of 3 mg/kg. §Except in mainland China.

iinnovate-2 – Doublet and triplet combinations



*Regardless of the number of prior line(s) of therapy. †Group 1 (NDMM) and group 2 (RRMM, doublets) have a starting dose of modakafusp alfa of 80 mg with escalating (to 120 and 240 mg) / de-escalating (to 60 mg) dosing regimens, depending on the safety observed. Group 3 (RRMM, triplets) has a starting dose of modakafusp alfa based on the RP2D determined in group 2 and in the iinnovate-3 study (yellow arrow). ‡Oral lenalidomide 10 mg once daily. §Oral pomalidomide 4 mg on days 1–21 of each 28-day cycle. ¶SC bortezomib 1.3 mg/m² on days 8, 15, and 22 of cycles 1–8, and on days 8 and 22 thereafter. **IV carfilzomib on days 1, 8, and 15, 20 mg/m² on cycle 1 day 1 only, then 70 mg/m² on cycle 1 day 8 thereafter; closed due to two events of thrombotic microangiopathy. ††To be removed from the study. ‡‡SC daratumumab 1800 mg (QW in cycles 1–2, Q2W in cycles 3–6, and Q4W thereafter).

iinnovate-3 – Combination with daratumumab SC



*Regardless of the number of prior line(s) of therapy. †Defined as non-refractoriness to a prior anti-CD38 mAb according to IMWG. ‡Escalation/de-escalation from the starting dose of 80 mg (to either 120 and 240 or 60 mg) based on the safety observed. Two dose levels of modakafusp alfa in combination with daratumumab SC will be selected and further explored in the phase 2a dose optimization part of the study. §SC daratumumab 1800 mg (QW in cycles 1–2, Q2W in cycles 3–6, and Q4W thereafter).