# Supplementary table

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| **Supplementary Box 1. Eligibility criteria for a Phase 1 study of NKTR-255 as monotherapy, or in combination with daratumumab or rituximab, in hematologic malignancies** |
| **Inclusion criteria for patients with all tumor types** * Age ≥18 years
* Written informed consent
* Relapsed/refractory MM or NHL with documented progressive disease on or after their last regimen, with no available therapies that would confer clinical benefit for primary disease
* WOCBP must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening and a serum/urine pregnancy test within 24 hours prior to dosing
	+ WOCBP and men who are sexually active with WOCBP must commit to either abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously for the duration of study treatment and for 1 month after the last dose of NKTR-255 or 3 months after the last dose of daratumumab or rituximab
		- Contraception must begin 4 weeks prior to dosing
		- Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy
* ECOG PS ≤2
* Response (PR or better) to ≥1 prior regimen
* eGFR ≥40 mL/min/1.73 m2 calculated using the CKD-EPI collaboration creatinine equation [Levey AS, et al]
* Life expectancy of >3 months with treatment
* The following laboratory test results during screening:
	+ ANC or AGC ≥1000/μL
	+ Platelets ≥30,000/μL
	+ Hemoglobin ≥8 g/dL
	+ Absolute lymphocytes ≥500/μL
	+ Leukocytes ≥3000/μL

**Inclusion criteria for patients with MM*** Measurable relapsed/refractory MM as defined by the IMWG criteria[Kumar S, et al] following treatment with ≥3 lines of therapy with no other available treatment that would confer benefit for primary disease
* Measurable disease within ≥1 of the following:
	+ Serum M-protein level ≥0.5 g/dL
	+ Urine M-protein level ≥200 mg/24 hours
	+ Serum FLC assay: involved FLC level ≥10 g/dL (100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
	+ Extramedullary plasmacytoma (measured within 28 days of screening) can be used to adjudicate response assessments with any of the 3 other markers
* **Dose-expansion cohort only:**
	+ Relapsed or refractory disease defined as disease progression (defined by IMWG criteria [Kumar S, et al]) while on therapy or within 60 days of therapy
	+ Previous exposure to proteasome inhibitor, immunomodulatory, and anti-CD38 therapy
	+ Prior daratumumab (or other anti-CD38 therapies), with ≥3 months’ washout
	+ Responded at least once to prior daratumumab treatment

**Inclusion criteria for patients with NHL*** Histologically confirmed CD19-/CD20-positive NHL (including large B cell lymphoma, high-grade B cell lymphoma, primary mediastinal large B cell lymphoma, or diffuse large B cell lymphoma, arising from follicular lymphoma) confirmed by archived tumor biopsy tissue from last relapse or fresh biopsy at the time of inclusion
* Measurable or detectable disease according to the Lugano classification [Cheson BD, et al] and/or extranodal disease that is measurable by 18F-FDG-PET imaging only
* Evidence of disease progression (according to Lugano classification [Cheson BD, et al]) on or after the last regimen
* **Dose-expansion cohort only:**
	+ Disease progression on a commercially approved CD19 CAR-T product, with the first dose of NKTR-255 administered within 30 days of progression

**Inclusion criteria for patients with iNHL*** Histologically confirmed CD19-/CD20-positive iNHL (follicular lymphoma Grade 1, 2, 3a; marginal zone lymphoma; small lymphocytic lymphoma or lymphoplasmacytic lymphoma) confirmed by archived tumor biopsy tissue from last relapse or fresh biopsy at the time of inclusion
* Anti-CD20 mAb-refractory disease, defined as progressive disease while on or within 6 months of taking rituximab (or another anti-CD20 mAb)
* Anti-CD20 mAb-sensitive disease, defined as a response to a prior rituximab-containing (or another anti-CD20 mAb) regimen, and relapse >6 months from the last administration of rituximab-containing (or another anti-CD20 mAb) therapy
* Patients with cutaneous-only disease with clearly measurable skin lesions are permitted
* **Dose-expansion cohort only:**
	+ Relapsed/refractory iNHL that has progressed during or following ≥1 prior systemic rituximab-containing (or another anti-CD20 mAb-containing) regimen for lymphoma

**Exclusion criteria*** Any treatment-related neurotoxicity or cytokine-release syndrome prior to enrollment that does not return to baseline prior to NKTR-255 treatment
* Use of an investigational agent or device within 28 days before administration of first dose of study drug(s) (except for investigational antimyeloma agents, which cannot be taken within 14 days prior to study treatment)
* Active, known, or suspected autoimmune disease
	+ Patients requiring systemic treatment within the past 3 months or with a documented history of clinically severe autoimmune disease that requires systemic corticosteroids or immunosuppressive agents
	+ Exceptions include any patient on ≤10 mg of prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, type 1 diabetes, Graves’ disease, Hashimoto's disease, alopecia areata, eczema, psoriasis, or with medical monitor approval
* History of allergy or hypersensitivity to study drug components
* History of organ transplant that requires ongoing use of immune suppressive agents
* Prior IL-2 or IL-15 therapy
* Previous daratumumab or other anti-CD38 therapies without a 3-month washout
* Use of warfarin within 14 days of initiating study drug(s)
	+ Low molecular weight heparin is allowed on the study
* Unresolved toxicity from previous anticancer therapy, unless resolved to Grade ≤1; or resolved to Grade 2 (with the exceptions outlined in the inclusion criteria or deemed clinically not significant, and approved by the sponsor); or resulting from incomplete recovery from surgery
* Prior surgery or radiotherapy within 14 days of initiating study drug(s)
	+ Patients must have recovered from all radiation-related toxicities, not required corticosteroids, and not had radiation pneumonitis
* Patients participating in observational studies should be discussed with the medical monitor to confirm eligibility
* Patients who have had <28 days of anticancer treatment, chemotherapy, or biologic therapy or <14 days from approved anti-myeloma agent, or systemic or inhaled steroid therapy at doses >10 mg of prednisone or equivalent before administration of the first dose of study drug(s)
* Approved tyrosine kinase inhibitor therapy (sunitinib, sorafenib, vemurafenib, dabrafenib, cobimetinib), or systemic or inhaled steroid therapy at doses >10 mg of prednisone or equivalent <14 days before administration of the first dose of study drug(s)
	+ Patients in Cohort A may receive bridging chemotherapy within the 30-day window following progression on CAR-T therapy and before starting study drug
* Active infection requiring systemic therapy within 7 days prior to dosing
* Known immunodeficiency or active human immunodeficiency virus (antibodies to HIV-1 or HIV-2)
* Known to be seropositive or active for hepatitis B or hepatitis C
	+ Subjects who had hepatitis B but have received an antiviral treatment and show non-detectable virus for 3 months are eligible
	+ Subjects who are seropositive because of hepatitis B virus vaccine are eligible
* Prolonged Fridericia’s corrected QT interval (QTcF) >450 ms for men and >470 ms for women at screening
* History of unstable or deteriorating cardiac disease within the previous 6 months prior to screening including but not limited to the following:
	+ Unstable angina or myocardial infarction
	+ Congestive heart failure (New York Heart Association Class III or IV)
	+ Uncontrolled clinically significant arrhythmias
* Known current drug or alcohol abuse
* History of malignancy (other than MM or NHL) within 3 years before the date of screening
	+ Exceptions are squamous and basal cell carcinomas of the skin and carcinoma *in situ* of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years
* Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the investigator, would preclude the patient from adhering to the protocol
* Any concurrent medical condition or disease (e.g., active systemic infection) that is likely to interfere with study procedures or results, or that, in the opinion of the investigator, would constitute a hazard for participating in this study
* Patient has any of the following laboratory test results during screening:
	+ AST and ALT level ≥2.5 × ULN
	+ Alkaline phosphatase level ≥2.5 × ULN
	+ Total bilirubin level ≥2 × ULN (except for Gilbert syndrome: direct bilirubin 2 × ULN)
	+ Potassium level <3.0 mEq/L
	+ Corrected serum calcium >14.0 mg/dL (3.5 mmol/L)
* Plasma cell leukemia (>2.0 × 109/L circulating plasma cells by standard differential), Waldenström’s macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis
* Pregnant or breastfeeding women or women planning to become pregnant while enrolled in this study or within 4 weeks after the last dose of NKTR-255 or within 3 months after the last dose of daratumumab or rituximab
* Contraindication to or unable to receive daratumumab (Cohort B only)
* Patients with hypertension must be receiving a stable antihypertensive regimen for the 14 days prior to study treatment
	+ Screening blood pressure must be <150 mm Hg for systolic blood pressure and <90 mm Hg for diastolic blood pressure (by ≥1 and ≤3 observations taken during the screening period)
* Active brain metastases or leptomeningeal metastases
	+ Patients with brain metastases are eligible if they have been treated and there is no radiographic evidence of progression for ≥4 weeks after treatment is complete (confirmed by head imaging obtained within 28 days prior to study treatment)
	+ There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalents) for ≥4 weeks prior to study treatment
	+ A stable dose of anticonvulsants is required within 14 days prior to study treatment
	+ Treatment for CNS metastases may include stereotactic radiosurgery (e.g., GammaKnife, CyberKnife, or equivalent) or neurosurgical resection
	+ Patients who received whole brain radiation therapy are not eligible
* T cell-/histiocyte- or NK cell-rich NHL and other variants not otherwise specified that contain high numbers of T or NK cells
* Active CNS involvement (NHL)
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| **Abbreviations:**AGC, absolute granulocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor T cell; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; 18F-FDG-PET, 18F-fluorodeoxyglucose–positron emission tomography; FLC, free light chain; HCG, human chorionic gonadotropin; IL, interleukin; IMWG, International Myeloma Working Group; iNHL, indolent non-Hodgkin lymphoma; mAb, monoclonal antibody; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PR, partial response; ULN, upper limit of normal; WOCBP, women of childbearing potential.**References:**Cheson BD, Fisher RI, Barrington SF, *et al*. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J. Clin. Oncol.* 32(27), 3059–3067 (2014).Kumar S, Paiva B, Anderson KC, *et al*. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 17(8), e328–e346 (2016).Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* 150(9), 604 (2009). |