It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the MDACC IND office guidelines, and Institutional Review Board policy.

11.4.3 Investigator Communication with Supporting Companies

To protect human subjects, entities that provide the IMGN901 drug to or receive the IMGN901 drug from other entities will share safety information with each other. To that end, the PI and the research team will provide copies of IND Safety Reports within 24 hours of submission to ImmunoGen, Inc. Pharmacovigilance and, upon request, the Safety Officer of other IMGN901 entities. In turn, the MD Anderson IND office (or study Principal Investigator) will receive IND Safety Reports originating from other entities using IMGN901. Each entity will provide notification when their study is closed and no further safety data will be forthcoming

12 STATISTICAL CONSIDERATIONS

The primary objectives of the study are to evaluate the overall response rate to IMGN901 in patients with CD56 expressing hematological malignancies including but not limited to relapsed/refractory leukemia, myelofibrosis refractory to ruxolitinib or JAK-inhibitor therapy, and BPDCN. A response and toxicity summary for each treatment cohort (1, 2 and 3) will be submitted to the IND Medical Monitor per the guidelines found in the statistical section 12.0.

Cohort 1 (Relapsed/refractory leukemia)

The primary objective of cohort 1 is to assess the efficacy of treatment of IMGN901 in CD56 expressing hematological malignancies including but not limited to AML, high-risk MDS, natural-killer leukemia, acute lymphoblastic leukemia, accelerated and blast-phase CML who have failed prior therapy or for which no standard therapy exists. We anticipate that the majority of the patients in this cohort will be relapsed/refractor AML. The efficacy of IMGN901 will be measured by the ORR, defined as CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) within 3 cycles of therapy with IMGN901 in patients with CD56 expressing leukemia's (defined in section 10.0) who have failed prior therapy or for which no standard therapy exists.

We anticipate that the majority of patients in this cohort will be relapsed/refractory AML. The historical data suggested the ORR to current standard salvage treatment is 30%. The target ORR with the experimental treatment is 50%. The regimen of the IMGN901 will be considered worthy of

further investigation if it elicits an increase in ORR to 50% with acceptable toxicity. A >30% therapy related non-hematological grade 3/4 toxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions above, were constructed that meet the following two conditions,

1) Stop if Prob[p(ORR,E) > 0.50 | data] < 0.05, or
2) Stop if Prob[p(TOX,E)>0.30 | data]>0.95,

where P(ORR, E) and P(TOX, E) are the true ORR and toxicity rates for the IMGN901. The first rule provides for stopping the study if the data suggest that it is unlikely (i.e., probability < 5%) that ORR rate of the IMGN901 is greater than the ORR rate of standard treatment by 20%. The second condition will stop the study early if excessive therapy-related non-hematological grade 3/4 toxicity (>30%) is highly probable (i.e., probability >95%) for the IMGN901. Monitoring for toxicity and futility will not begin until 5 patients have been evaluated, and cohort size for future evaluations is 5.

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in Table 4. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients.

Table 4. Stop accrual if the number of drug-related non-hematological grade 3/4 toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated

# patients evaluated	5	10	15	20
# patients with toxicities	4-5	6-10	8-15	Always stop with this many patients

Monitoring the ORR rate, based on the above assumptions and monitoring conditions is found in Table 5. For example, accrual will cease if less than 1 patient experience an overall response within 3 cycles of IMGN901 in the first 15 patients treated. If <1/15 of the initially treated patients achieve response we will consider alternate dosing schedule with IMGN901 administered on days 1,8,15 of a 21-day cycle. This will be done in discussion with the MDACC IND office, FDA and the IRB. Rules for dose-interruption and dose-adjustment will remain as defined in the protocol.

Table 5. Stop accrual if the number with overall response is less than or equal to indicated (i.e., # patients with overall response) among the number of patients evaluated

# patients evaluated	5	10	15	20
# patients with overall response	0	0-2	0-4	Always stop with this many patients

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 6). In order to utilize the software for the design, a response constant rate of 0.30 and beta (0.6, 1.4) priors and delta of 20% were assumed for the standard treatment response distribution and experimental treatment response prior distribution, respectively. In addition, a 30% toxicity constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity constant rate and experimental treatment toxicity prior distribution, respectively.

The probability of stopping the study early if the true ORR of the IMGN901 was 50% and the true toxicity rate was 30% was 11.3%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 63.7% when the true ORR was 30% and 57.3% when true ORR rate was 50%.

Table 6. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with IMGN901 treatment

True Toxicity Rate	True ORR	Prob(stop the trial early)
0.10	0.30	0.5725
	0.40	0.2778
	0.50	0.0972
	0.60	0.0244
	0.70	0.0045
0.20	0.30	0.5779
	0.40	0.2870
	0.50	0.1086
	0.60	0.0367
	0.70	0.0171
0.30	0.30	0.6083
	0.40	0.3384
	0.50	0.1730
	0.60	0.1062
	0.70	0.0881
0.40	0.30	0.6892
	0.40	0.4751
	0.50	0.3438
	0.60	0.2908
	0.70	0.2764
0.50	0.30	0.8113
	0.40	0.6812
	0.50	0.6014
	0.60	0.5693
	0.70	0.5605

Cohort 2 (Myelofibrosis refractory to JAK-inhibitor therapy)

The primary objective of the cohort 2 is to assess the efficacy of IMGN901 in MF patients who are refractory to JAK-inhibitor therapy. No standard of care exists for such patients. The efficacy of IMGN901 will be measured by the overall response rate, defined as a 50% shrinkage in spleen size on manual palpation (or 35% shrinkage in spleen size on imaging examination) and/or a 50% reduction in the total symptom score within 3 cycles of IMGN901 therapy.

Futility Monitoring

Historical data on similar patients shows an ORR of 20%. The target response rate is 35%. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

$\Pr(p(ORR, E) > 0.35|data) < 0.025$

where P(ORR, E) s the overall response rate (ORR) for the treatment. That is, if at any time during the study we determine that there is a less than 2.5% chance that ORR rate of the IMGN901 is greater than the ORR rate of standard treatment by 15% we will stop enrollment to this cohort. P(ORR, E) is assumed to follow a prior of Beta (0.4, 1.6). The stopping boundaries for ORR, based on these assumptions and monitoring conditions are found in Table 7. We will apply these stopping boundaries continuously starting from the first patient in cohorts of 10. For example, accrual will cease if 0 patients experiences overall response among the first 10 patients treated within 3 cycles of therapy with IMGN901. The operating characteristics are summarized in Table 8.

Table 7. Stopping boundaries for ORR

Number of patients evaluated for overall response	10	20
Number of patients with overall response (i.e., CR, CRp or CRi) is less than or equal to	0 – 1	2-4

Table 8. Operating characteristics for monitoring ORR

True overall Response Rate	Early Stopping Probability	Average number of patients treated
0.20	0.3758	16
0.25	0.2440	18
0.30	0.1493	19
0.35	0.0860	19
0.40	0.0464	20
0.45	0.0233	20

Toxicity Monitoring

In addition, we will monitor toxicities. The probability of toxicity is denoted by P(TOX, E). We assume P(TOX, E) ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement: Pr(P(TOX, E) > 0.30 | data)>0.85. That is, we will stop the study if, at any time during the study, we determine that there is more than 90% chance that the toxicity is more than 30%. The stopping boundaries for toxicities, based on these assumptions and monitoring conditions is found in Table 9. We will apply the toxicity monitoring rule in cohort size of 5, starting from the 1st patient. For example, accrual will cease if all 3 patients experience toxicities among the first 5 patients treated. The operating characteristics are summarized in Table 10.

Table 9. Stopping boundaries for toxicity monitoring

The number of patients evaluated for toxicities	5	10	15	20
The number of patients with toxicities is greater than or equal to	3	5	7	9

Table 10. Operating characteristics for toxicity monitoring

True overall Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.10	0.0089	20
0.20	0.0787	19
0.30	0.2607	17
0.40	0.5173	14
0.50	0.7846	10

Cohort 3 (BPDCN)

The primary objective of the cohort 3 is to assess the efficacy of IMGN901 in patients with a confirmed pathological diagnosis of BPDCN. The efficacy of IMGN901 will be measured by the ORR, defined as CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) (as specified in section 10.0) within 3 cycles of therapy with IMGN901.

Futility Monitoring

Historical data on similar patients show a ORR of 20%. The target response rate is 35%. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

Pr (p(TOX,E)> 0.35|data) < 0.025

where p(ORR,E) is the overall response rate (ORR) for the treatment. That is, if at any time during the study we determine that there is a less than 2.5% chance that ORR rate of the IMGN901 is greater than the ORR rate of standard treatment by 15% we will stop enrollment to this cohort. P(ORR,E) is assumed to follow a prior of Beta (0.4, 1.6). The stopping boundaries for ORR, based on these assumptions and monitoring conditions are found in Table 11. We will apply these stopping boundaries continuously starting from the first patient and in cohorts of 10. For example, accrual will cease if less than 1 patients experiences overall response among the first 10 patients treated within 3 cycles of therapy with IMGN901. The operating characteristics are summarized in Table 12.

Table 11. Stopping boundaries for ORR

Number of patients evaluated for overall response	10	20
Number of patients with overall response (i.e., CR, CRp or CRi) is less than or equal to	0-1	2-4

Table 12. Operating characteristics for monitoring ORR

True overall Response Rate	Early Stopping Probability	Average number of patients treated
0.20	0.3758	16
0.25	0.2440	18
0.30	0.1493	19
0.35	0.0860	19
0.40	0.0464	20
0.45	0.0233	20

Toxicity Monitoring

In addition, we will monitor toxicities. The probability of toxicity is denoted by P(TOX, E). We assume P(TOX, E) ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement: Pr(P(TOX, E) > 0.30 | data)>0.85. That is, we will stop the study if, at any time during the study, we determine that there is more than 90% chance that the toxicity is more than 30%. The stopping boundaries for toxicities, based on these assumptions and monitoring conditions is found in Table 13. We will apply the toxicity monitoring rule in cohort size of 5, starting from the 1st patient. For example, accrual will cease if all 3 patients experience toxicities among the first 5 patients treated. The operating characteristics are summarized in Table 14.

Table 13. Stopping boundaries for toxicity monitoring

The number of patients evaluated for toxicities	5	10	15	20
The number of patients with toxicities is greater than or equal to	3	5	7	9

Table 14. Operating characteristics for toxicity monitoring

True overall Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.10	0.0089	20
0.20	0.0787	19
0.30	0.2607	17
0.40	0.5173	14
0.50	0.7846	10

Statistical Analysis Plan

All patients who received any dose of the study agent will be included in the analysis for efficacy and safety. Demographic/clinical characteristics (including duration of response) and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. For the primary efficacy analysis, we will estimate the ORR for the IMGN901, along with the 95% confidence interval. Patients who drop out of the study before completing all the cycles will be treated as "failures" for the primary analysis. Overall response rate (ORR) during the study period will also be presented with the 95% confidence interval. The association between ORR and patient's clinical characteristics will be examined by Wilcoxon's rank sum test or Fisher's exact test, as appropriate. Toxicity type, severity and attribution will be summarized for each patient using frequency tables. The distribution of time-to-event endpoints including duration of response, overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. Correlation analysis (such as logistic regression analysis) will be conducted to determine the relationship between IMGN901 and other gene expression and clinical response.

13.0 REFERENCES:

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63: 11-30.