# Updated Results of The Phase 3 Randomized Trial Comparing Inolimomab versus Antithymocyte Globulin (ATG) in Adults with Steroid-resistant Acute GVHD

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## Introduction

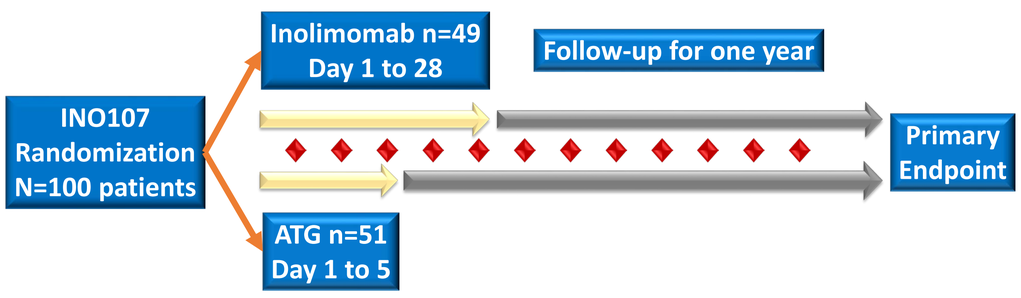
Despite improvements in allogeneic hematopoietic stem cell transplantation (allo-HSCT) settings, graft-versus-host disease (GvHD) remains a significant issue after transplantation and a major cause of non-relapse mortality. Acute GvHD (aGvHD) still develops in about 30% to 80% of patients, for which high dose corticosteroids can be initiated in those with grade ≥II. However, up to 50% of patients fail to obtain a satisfactory response with steroid treatment alone. Treatment of steroid-resistant (SR) aGvHD remains an unmet clinical need. Inolimomab is a monoclonal antibody to CD25 functioning as a selective immunosuppressive agent. More than 1700 patients with aGvHD have been treated with inolimomab in clinical studies or under named patient basis. We recently published results of a phase 3 randomized study comparing inolimomab versus antithymocyte globulin (ATG) in SR-aGvHD in 100 adult patients (Socié et al. Blood 2017). The composite primary objective was to evaluate overall survival (OS) at 1 year without changing baseline allocated therapy. The study concluded that there was no difference between the two arms regarding the primary endpoint ((HR=0,722 in favor of inolimomab, p=0.0941 one sided). The full analysis has been recently completed and we report here the results of the entire safety analysis as well as overall survival update.

## Methods

This randomized multicenter controlled parallel-group phase III study (France / Belgium) included adult patients with grade II-IV SR-aGvHD. Control group was initially set as "usual care" but was changed by the steering committee to ATG (anti-thymocyte globulin), the only registered agent in the indication in France. The study was conducted between years 2009 and 2015. One hundred patients were enrolled in 15 centers and followed for one year.

**Primary endpoint:**
**Composite criteria:** overall survival at 1 year without replacement of the baseline allocated treatment (combination of events of death and change in allocated treatment for any reason)

**Major secondary endpoints:**
- **Safety**
- Survival at D100, 6 months and 1 year
- Remission status at D28
- Relapse/relapse free survival
- Chronic GvHD incidence




**Dosing regimen:**
- **Inolimomab:** IV Perfusion
  - Induction phase: 0.3 mg/kg/day for 1 or 2 weeks
    - Median duration (min, max): 8 (2-8) days
    - Median dose (min, max): 0.3 (0.3-0.3) mg/kg
  - Maintenance phase : 0.4 mg/kg thrice a week until day 28
    - Median duration (min, max): 9 (9-9) days
    - Median dose (min, max): 0.4 (0.4-0.4) mg/kg
- **ATG:** IV Perfusion
  - Dose: 2 and 5 mg/kg/day for 5 days according to SPC
  - Median duration (min, max): 4 (2-9) days
  - Median dose (min, max): 2,5 (2-3) mg/kg

## Results

| *Patients' characteristics* | Inolimomab (n=49) | ATG (n= 51) | P value |
|---|---|---|---|
| Gender, n (%) | | | 0.555 |
| Male | 22 (44.9%) | 26 (51%) | |
| Female | 27 (55.1%) | 25 (49%) | |
| Age, mean (SD) | 46.2 (12.6) | 47.1 (12.96) | 0.727 |
| Disease, n | | | |
| AML / MDS / MPD | 14/4/2 | 10 / 7 / 2 | |
| ALL | 7 | 6 | NS |
| CLL / Lymphoma / Myeloma | 4 / 8 / 4 | 6 / 10 / 7 | |
| Other | 8 | 3 | |
| Complete remission at HSCT, n (%) | 26 (53.1%) | 28 (54.9%) | 0.905 |
| Source of cells, n (%) | | | |
| Peripheral Blood | 40 (81.6%) | 39 (76.5%) | 0.698 |
| Marrow | 9 (18.4%) | 12 (23.5%) | |
| GvHD prophylaxis, n (%) | | | |
| CSA + MTX | 23 (46.9%) | 21 (41.2%) | 0.704 |
| CSA + MMF | 22 (44.8%) | 19 (37.3%) | 0.566 |
| ATG | 13 (26.5%) | 11 (21.5%) | 0.72 |
| Donor type, n (%) | | | |
| Matched sibling | 15 (30.6%) | 20 (39.2%) | 0.489 |
| Matched UD (10/10 allelic) | 31 (63.3%) | 30 (58.8%) | 0.802 |
| 9/10 UD | 3 (6.1%) | 1 (2%) | 0.581 |
| Donor characteristic | | | |
| Age, mean (SD) | 39.3 (12.5) | 37.0( 12.3) | 0.821 |
| Gender (M/F) | 31/18 | 37/14 | 0.435 |
| Conditioning regimen, n (%) | | | |
| Myeloablative | 21 (42.9%) | 19 (37.3%) | 0.713 |
| Reduced intensity | 28 (57.1%) | 32 (62.7%) | 0.713 |
| Irradiation-based, n (%) | 18 (36.7%) | 14 (27.4%) | 0.435 |

**Steroid-refractory aGVHD profile at inclusion**
- 76% of patients with aGVHD grade III/IV
- 51% with gut aGVHD grade III/IV

→ **No difference between the two groups**

### *Safety*

**Number of Adverse Events:** Even if the number of patients experiencing AEs, AEs grade ≥3 or SAEs was similar between the two groups (and close to 100%), **the mean number of events per patient was 20-30% superior in the ATG group (p<0.001).**

**Related Adverse Events**: There was a statistically significant **3 fold reduction in the number of patients experiencing related AEs in the inolimomab group** (14%) vs ATG group (41%) (p=0.004) This statistically significant difference is also apparent if we restrict the analysis only to the most severe related AEs (grade 3, 4 or 5) (12% vs 29% in the inolimomab and ATG group respectively; p<0.04).

**Infectious disorders**: **Statistically significant difference in overall incidence of infectious disorders** is apparent for all infectious related area (p<0.001) with a reduction in potentially life-threatening events like sepsis (14% vs 24%) and septic shock (4% vs 16%).

| | Inolimomab N=49 | ATG N=51 | P value* |
|---|---|---|---|
| Number of AE (% of patients experiencing AEs)* | 1087 (100%) | 1401 (100%) | <0.001 |
| Number of AEs grade ≥3 (% patients experiencing AEs grade ≥3)* | 269 (96%) | 328 (100%) | <0.001 |
| Number of SAE (% of patients experiencing SAEs)* | 116 (98%) | 130.(90%) | NS |
| **Related Adverse Events** | | | |
| Number of patients experiencing related AEs (%) | 7 (14%) | 21 (41%) | 0.004 |
| Number of patients experiencing related AEs grade ≥3 (%) | 6 (12%) | 15 (29%) | <0.04 |

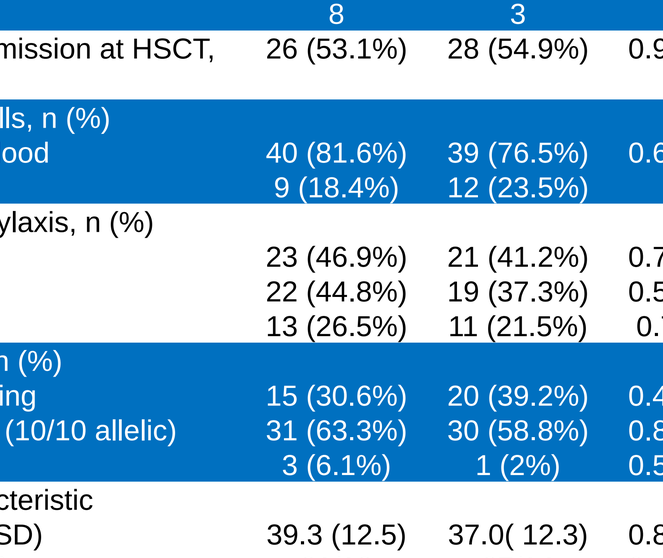
** : Poisson regression analysis*

| | Inolimomab N=49 | | ATG N=51 | | Inolimomab/ATG ratio | | |
|---|---|---|---|---|---|---|---|
| Any infection* | Rate/month | 95% CI | Rate/month | 95% CI | Ratio | 95% CI | P value |
| | 1.38 | [1.25 - 1.52] | 1.79 | [1.64 - 1.96] | 0.77 | [0.67 - 0.88] | <0.001 |

**These results demonstrated that Inolimomab has a significantly better safety profile compared to ATG especially with regard to life-threatening infections**

### *Efficacy*

**Survival analysis:**
While the primary composite criteria was not met, the analysis of each component of this criteria has shown that the major difference in favor of inolimomab was observed for overall survival (HR 0.628, p = 0.055) with no specific difference in the other component (change of baseline allocated treatment for any reason) (HR = 0.767, p = 0.199).




| Analysis | HR (Inolimomab vs ATG) | 90% CI | p-value (1-sided) |
|---|---|---|---|
| Primary endpoint* at 1 year | 0.724 | [0.483, 1.086] | 0.0949 |
| Overall survival* at 1 year | **0.628** | [0.389 , 1.015] | **0.055** |
| Change in allocated treatment* at 1 year | 0.767 | [0.457, 1.286] | 0.1991 |

** : Adjusted by HSCT remission, family link, sex mismatch, gut involvement, skin involvement and liver involvement*

**Borderline significant 37% reduction of death with no significant difference between groups for the second component of the primary endpoint : change in allocated treatment**

## Conclusion

**Given that efficacy on survival appears to be at least equivalent to that of ATG but with a significantly better safety profile, inolimomab may represent a suitable alternative in patients with SR-aGvHD, especially those not candidate for clinical trials evaluating new drugs.**