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Guadecitabine (SGI-110), a novel partner in immunotherapy

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Background

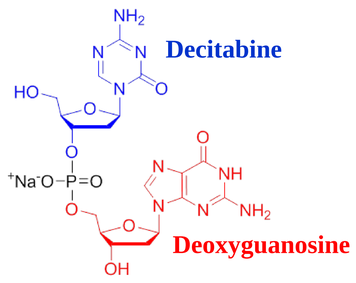
- **Guadecitabine (SGI-110)** is a novel hypomethylating dinucleotide of decitabine (DAC) and deoxyguanosine that is resistant to degradation by cytidine deaminase and results in prolonged *in vivo* exposure to its active metabolite DAC. The differentiated pharmacokinetic profile offers the potential of improved biological and clinical activity and safety over currently available hypomethylating agents (HMA).

- We reported previously results from the Phase 1 dose-escalation study in AML and MDS[1] and the Phase 2 randomized dose-response study in r/r AML patients of SGI-110 given SC at 2 doses (60 and 90 mg/m^2) in a 5-day regimen[2] or at 60 mg/m^2 in a 10-day regimen[3].

- **Rationale for guadecitabine combination with immunomodulating agents**
  - Tumor Associated Antigens (TAAs) including Cancer Testis Antigens (CTAs) e.g. NY-ESO-1 and MAGE-A are often silenced by hypermethylation
  - Guadecitabine demethylates and induces CTA re-expression rendering the tumor more immunogenic
  - Guadecitabine induces better tumor recognition by immune system (cytotoxic CD8+ T lymphocytes)
  - Clinical correlation between hypermethylation and poor survival reported in Melanoma and Liver Cancer
  - Anecdotal clinical data from patients treated with HMA and immunotherapy

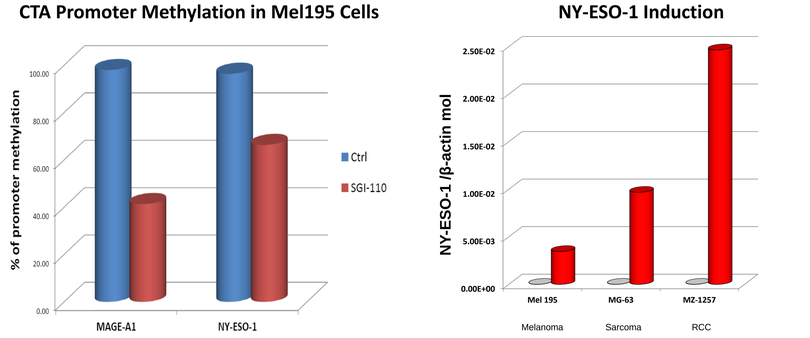
- **Guadecitabine immunomodulatory data**
  - **Preclinical In vitro Data:**
    - ✓ Guadecitabine demethylates the promoters and induces the expression of CTAs MAGE-A3, NY-ESO-1 in cancer cell lines[4]
    - ✓ Guadecitabine induces tumor recognition by cytotoxic T lymphocytes
  - **Preclinical In vivo Data**
    - ✓ Synergy when guadecitabine is combined with CTLA-4 antibody[5]
  - **Clinical Data**
    - ✓ Guadecitabine achieves dose-dependent demethylation and induction of CTAs (NY-ESO-1; MAGE-A1 and A3) in AML and MDS patients [5]

Figure 1: Guadecitabine : next generation HMA



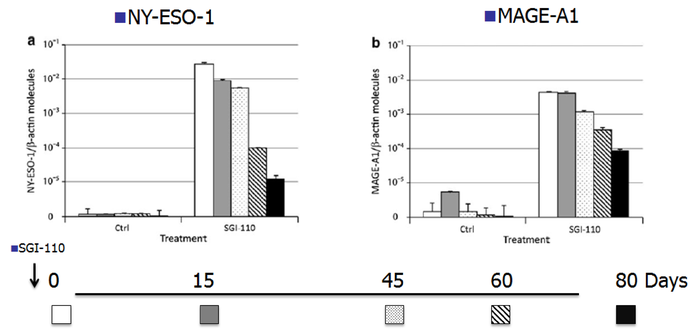
Preclinical Data

Figure 2: Guadecitabine demethylates and induces expression of CTAs



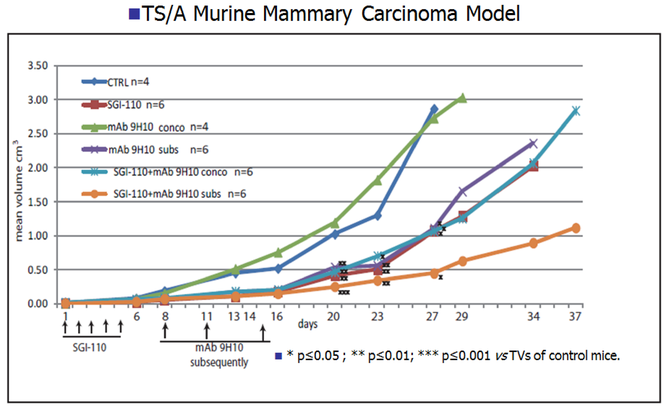
- Increased CTA expression correlates with gene-specific demethylation post-guadecitabine

Figure 3: CTAs expression induced by DNA demethylation persists beyond guadecitabine exposure



Total RNA was extracted from Mel 275 melanoma cells untreated (ctrl) or treated (SGI-110) with 1 uM SGI-110 every 12 h for 2 days and further cultured for 0 (white columns), 15 (gray columns), 45 (dotted columns), 65 (striped columns), and 80(black columns) days after the end of treatment.

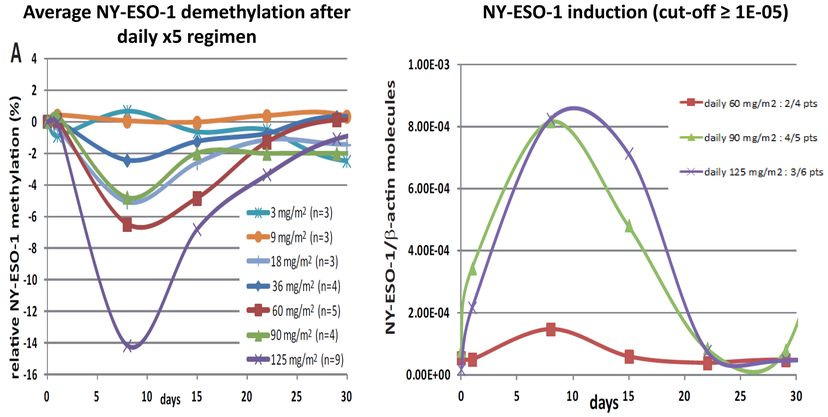
Figure 4: In vivo synergy of guadecitabine and anti-CTLA-4 9H10 mAb immunotherapy



- **Sequential guadecitabine → CTLA-4 Ab better than simultaneous treatment**

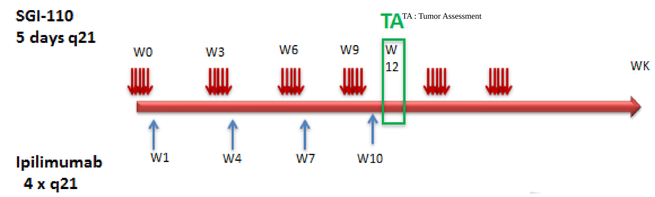
Clinical Data

Figure 5: Guadecitabine demethylates and induces expression of NY-ESO-1 in AML and MDS patients



- Guadecitabine induces a dose-dependent demethylation of NY-ESO-1 promoter
- Similar extent of demethylation observed also for MAGE-A1 promoter
- NY-ESO-1 transcript was induced in 9 of 15 evaluable patients treated at guadecitabine biologically effective doses
- 4 and 5 of the 15 patients also induced MAGE-A1 and -A3 respectively

Figure 6: NIBIT-M4 study, a phase 1b study combining guadecitabine and ipilimumab in metastatic melanoma patients[6]



- The study will enroll from 6 to 19 metastatic melanoma patients . Four pts have been enrolled to date.
- Primary objective : assess MTD and safety of guadecitabine and ipilimumab in 21 day cycles
- Exploratory objective: investigate immune-biologic correlates
- www.clinicaltrials.gov identifier: NCT02608437

Conclusions

- Good scientific rationale for combining guadecitabine with immunotherapy in solid and hematological tumors
- Preclinical and clinical data support use of guadecitabine for potentiation of immunotherapy activity
- Supports ongoing and planned trials of guadecitabine in combination with several immunotherapy agents (CTLA-4, PD-1, and PDL-1 antibodies)

References

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