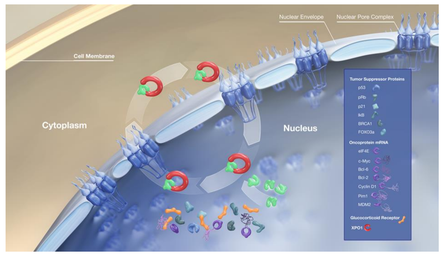
Abstract #313729

Molecular Predictors of Response to Selinexor in Recurrent Glioblastoma (GBM)

Christopher Walker[1], Yao Shen[2], Morten Mau-Soerensen[3], Patrick Y. Wen[4], Martin van den Bent[5], Scott R. Plotkin[6], Annemiek Walenkamp[7], Adam Green[8], Andrea Califano[2], Hua Chang[1], Leah Henegar[1], Sharon Shacham[1], Mariano J. Alvarez[2], Yosef Landesman[1], Andrew B. Lassman[9]

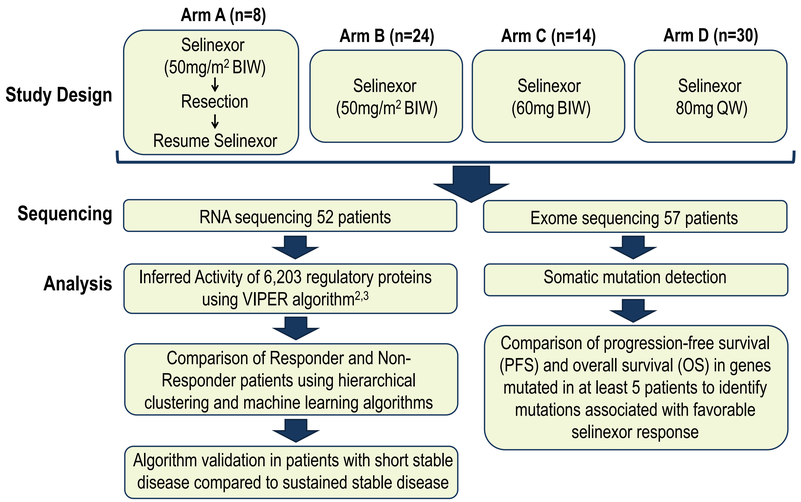
[1]Karyopharm Therapeutics, Inc., Newton, MA; [2]DarwinHealth Inc, New York, NY; [3]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [4]Dana Farber Cancer Institute, Boston, MA; [5]Erasmus MC Cancer Center, Rotterdam, The Netherlands; [6]Massachusetts General Hospital, Boston, MA; [7]University of Groningen, Groningen, The Netherlands; [8]University of Colorado, School of Medicine, Aurora, CO; [9]Columbia University Irving Medical Center, New York, NY

Introduction



- **Selinexor** is an oral Selective Inhibitor of Nuclear Export (SINE) compound that crosses the blood-brain barrier and inhibits the karyopherin protein XPO1.
- Selinexor treatment prevents XPO1 from shuttling its cargo from the nucleus to the cytoplasm resulting in nuclear accumulation of tumor suppressor proteins and oncogene mRNAs.
- Selinexor is approved by the US FDA for the treatment of patients with refractory multiple myeloma and was evaluated as a monotherapy in patients with recurrent GBM, in an open-label multicenter phase 2 study (KING study: NCT01986348).
- The study enrolled 76 heavily-pretreated patients. Patients treated on Arm D (80 mg QW) had an overall response rate of 10%. Notable responses include a patient with unmethylated *MGMT* who achieved a partial response and remains on treatment after > 3 years, and one patient with methylated *MGMT* who achieved a complete response and remains on treatment after > 1 year.[1]
- The most common side effects in patients who received 80mg QW were nausea (60%), leukopenia (43%), fatigue (43%), neutropenia (33%), decreased appetite (27%) and thrombocytopenia (23%).[1]

Methods



References

[1]Lassman, A.B. et al. Efficacy and safety of selinexor in recurrent glioblastoma. ASCO 2019.
[2]Alvarez, M.J. et al. Functional characterization of somatic mutations in cancer using network-based inference of protein activity. *Nat Genet* 2016. 48(8):838-47.
[3]Margolin, A.A. et al., ARACNE: an algorithm for the reconstruction of gene regulatory networks in a mammalian cellular context. *BMC bioinformatics* 2006. 7(Suppl 1):S7.
[4]Wang, X. et al. Point mutations in the PDX1 transactivation domain impair human β-cell development and function. *Mol Metab.* 2019 24:80-97

Results

- We previously reported encouraging results from a phase 2 clinical trial of selinexor for molecularly unselected patients with recurrent GBM.[1]

Table 1. Outcomes from Patients Enrolled and Treated with Selinexor on the Medical Arms of the KING Study

Parameter	Arm B 50 mg/m² (~ 85 mg) BIW (N = 24)	Arm C 60 mg BIW (N = 14)	Arm D 80 mg QW (N = 30)
6 cycle PFS rate (95% CI)	15% (5 – 40)	11% (2 – 68)	30% (17 – 54)
6 mo. PFS (95% CI)	10% (3 – 35)	NE	19% (9 – 41)
Overall Response Rate (95% CI)	8%	7%	10%
Median OS (95% CI)	9.0 mo. (4.9, 16.4)	8.5 mo. (7.8, NE)	9.4 mo. (7.0, NE)

Data presented at ASCO 2019 [1]. BIW, twice weekly; QC, once weekly; CI, confidence interval; mo., months; NE, not evaluable; PFS, progression-free survival; OS, overall survival

Figure 1. Mutations Associated with Improved Survival in Selinexor-Treated Patients

- Patients with adequate selinexor exposure (>21 days and > 3 doses) were exome and RNA sequenced.
- Three genes showed significant correlation between mutation and improved survival with selinexor treatment.
- Notably, the PDX1 transcription factor protein contains an XPO1 nuclear export sequence and the observed mutations have been shown to impact PDX1 mediated transcription of its target genes.[4]

Figure 1. PFS and OS curves shown for mutant (Mut) vs. wild-type (WT) patients for the indicated genes. P-values calculated with log-rank tests. Below each set of curves, lollipop plots show the identified mutations and protein domains (green, missense; orange, in-frame indel; black, nonsense or frameshift).

Figure 2. Clustering Heatmap of Protein Activities in Responder and Non-responder Patients

- Inferred protein activities were determined using the VIPER algorithm[2,3] and compared between responders (partial or complete response) and non-responders (progressive disease).

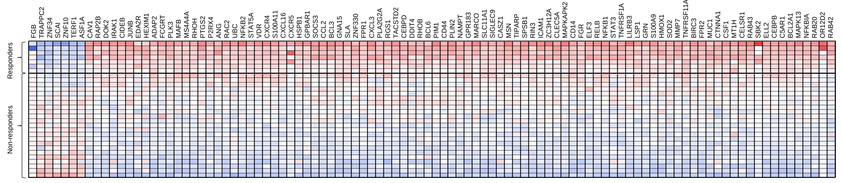


Figure 2. Heatmap shows the relative protein activities of the top 100 most differential active proteins between 7 responder and 23 non-responder patients.

Figure 3. Predictive Machine Learning Model Using Protein Activities

- Five different machine learning approaches were applied to the inferred protein activities to obtain predictive models of response, then combined into an overall integrated model.
- Using only three protein activities yielded maximum accuracy by leave-one-out cross-validation.

Protein	P-value (FDR corrected)	Description
ZC3H12A	6.45×10^{-11}	Zinc finger CCCH-type containing 12A
RAB43	3.81×10^{-10}	RAS-related small GTPase
SOCS3	3.16×10^{-9}	Suppressor of cytokine signaling 3

  - ZC3H12A is an essential RNAse that decays inflammatory genes
  - Rab43 GTPase controls anterograde ER-Golgi transport of nascent G-protein coupled receptors
  - SOCS3 inhibits STAT activation by JAK kinases, and can reduce inflammatory cytokine signaling
- Increased activity of these three proteins was associated with favorable response to selinexor, and together implicate anti-inflammatory signaling in predicting response to selinexor

- The integrated results of the predictive model had an area under the curve of 0.888 ($p < 0.04$, permutation test), a precision score of 0.667 and a recall score of 0.857.
- The model was applied to a separate validation set where patients with long-term stable disease (> 100 days) were considered responders and patients with progressive disease or short stable disease (< 100 days) were considered non-responders.

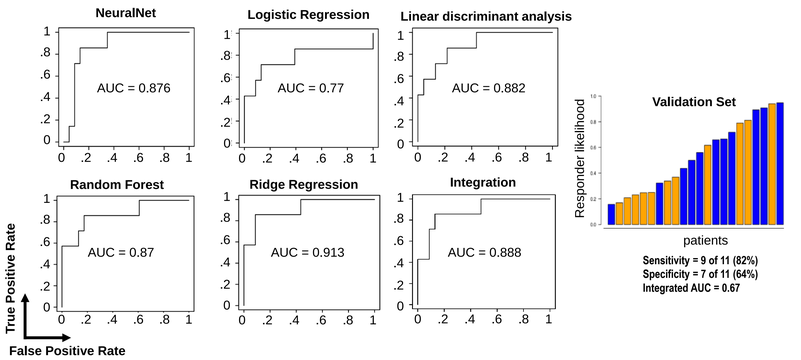


Figure 3. *(left)* Receiver operating characteristic curves illustrate the power of using a three-protein activity score to predict selinexor response, with the indicated machine learning models and an integrated model. (*right*) Bar plots show the predicted probabilities of response using the three protein activity model in a validation set of patients. Responders are indicated by blue bars and non-responders by orange bars.

Conclusions and Future Directions

- Mutations in *DOCK8, EP400, and PDX1* were favorable prognostic markers associated with longer survival times in selinexor treated patients.
- *PDX1* mutations could be cancer drivers associated with increased susceptibility to selinexor, as PDX1 is likely an XPO1 cargo protein and the observed *PDX1* mutations impact protein function.
- Responder and non-responder patients showed distinct signatures of regulatory protein activities that reflect different biologic/transcriptional cell states.
- A machine learning model using only three protein activities predicted clinical benefit from selinexor, and was validated in an independent set of patients.
- Preclinical studies are ongoing to validate these results.
- A phase I/II study of selinexor in combination with multi-agents in newly diagnosed and recurrent glioma is being planned, and will allow further evaluation of this predictive model.

Disclosures: This study was sponsored by Karyopharm Therapeutics.

Christopher.Walker@Karyopharm.com