Background: Cancer cell lines are frequently used in research as in-vitro tumor models. Genomic data and large-scale drug screening have accelerated the right drug selection for cancer patients. Accuracy in drug response prediction is crucial for success. Due to data-type diversity and big data volume, few methods can integrative and efficiently find the principal low-dimensional manifold of the high-dimensional cancer multi-omics data to predict drug response in precision medicine. Method: A novelty k-means Ensemble Support Vector Regression (kESVR) is developed to predict each drug response values for single patient based on cell-line gene expression data. The kESVR is a blend of supervised and unsupervised learning methods and is entirely data driven. It utilizes embedded clustering (Principal Component Analysis and k-means clustering) and local regression (Support Vector Regression) to predict drug response and obtain the global pattern while overcoming missing data and outliers' noise. Results: We compared the efficiency and accuracy of kESVR to 4 standard machine learning regression models: (1) simple linear regression, (2) support vector regression (3) random forest (quantile regression forest) and (4) back propagation neural network. Our results, which based on drug response across 610 cancer cells from Cancer Cell Line Encyclopedia (CCLE) and Cancer Therapeutics Response Portal (CTRP v2), proved to have the highest accuracy (smallest mean squared error (MSE) measure). We next compared kESVR with existing 17 drug response prediction models based a varied range of methods such as regression, Bayesian inference, matrix factorization and deep learning. After ranking the 18 models based on their accuracy of prediction, kESVR ranks first (best performing) in majority (74%) of the time. As for the remaining (26%) cases, kESVR still ranked in the top five performing models. Conclusion: In this paper we introduce a novel model (kESVR) for drug response prediction using high dimensional cell-line gene expression data. This model outperforms current existing prediction models in terms of prediction accuracy and speed and overcomes overfitting. This can be used in future to develop a robust drug response prediction system for cancer patients using the cancer cell-lines guidance and multi-omics data.