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#2418 – A comparative of NVP-AUY-922 (AUY) and Geldenamycin (G) in human tumor primary culture microspheroids. Robert A. Nagourney, Paula Bernard, Federico Francisco, Meghan Cule, Ryan Wexler, Steven S. Evans. *Rational Therapeutics, Long Beach, CA; Univ. of California at Irvine, Irvine, CA; Todd Cancer Institute, Long Beach, CA.*

Abstract

Introduction: Molecular chaperone heat shock protein 90 (HSP90) maintains the stability and function of client proteins essential for malignant transformation. The ansamycin Geldenamycin (G) and its derivate 17-AAG are potent HSP90 inhibitors with activity observed in human tumors. The resorcinol-based HSP90 inhibitor AUY offers advantages with regard to solubility & DT-diaphorase independence. To evaluate and compare the activity of AUY & G we conducted ex vivo analysis of programmed cell death (EVA-PCD®) on microspheroids isolated from fresh human tumor specimens.

Method: The EVA-PCD® method as previously reported (Nagourney, RA Anticancer Res. 2012) isolates microspheroids of desired size by mechanical and enzymatic disaggregation followed by precise density centrifugation. Drug activity is measured by delayed loss of membrane integrity and ATP content (luciferase). Lethal concentration (LC50) values are interpolated from 5-point dose response curves and compared by modified Z-Score. Concentration ranges for AUY were 6.25-100 μM and for G 1.25-20 μM.

Results: AUY and G activity compared in 22 parallel analyses by Pearson Moment revealed a correlation coefficient R = 0.59 ($p<0.005$). Activities for AUY & G by disease were generally similar favoring Heme > Sarcoma > Melanoma > Ovary > NSCLC > Breast. ERBB2 (+) breast appeared more sensitive as did several EGFr mutation (+) NSCLC specimens. Metachronous assays conducted in 3 EGFr (+) NSCLC pts revealed activity for G following Erlotinib failure. Additional studies with AUY alone and in combination are underway.

Conclusion: i) HSP90 inhibitors are active in human tumor primary cultures, ii) AUY and G activity correlate, iii) HSP90 inhibitor activities reveal disease & patient-specific profile, iv) EVA-PCD® analyses could facilitate the development of clinical strategies for the use of HSP90 inhibitors. Supported by the Vanguard Cancer Foundation & The Nagourney Institute. NVP-AUY922 was a kind gift of Novartis AG.