U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	20-896
Supplement #:	32
Drug Name:	Xeloda (capecitabine) tablets
Indication(s):	(b) (4)
Applicant:	Hoffman – La Roche, Inc.
Date(s):	Stamp Date: June 10, 2013
	PDUFA Date: December 10, 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Jonathan Norton, PhD
Concurring Reviewers:	Kun He, PhD
	Rajeshwari Sridhara, PhD
Medical Division:	Division of Oncology Products 2
Clinical Team:	Martha Donoghue, MD
	Suzanne Demko, PA – C
	Patrician Keegan, MD
Project Manager:	Gina Davis

Keywords: Log-rank test, Cox regression, pediatric exclusivity

Xeloda (capecitabine) is approved for multiple cancer indications. The present submission (NDA 20-896/S-32) is in response to a pediatric written request (PWR), originally issued on March 16, 2005 and then finalized on July 1, 2011. This review concerns study N021125, a phase II trial of rapidly disintegrating capecitabine tablets and concomitant radiation therapy for pediatric brainstem gliomas. The applicant deems the study to have failed on the primary endpoint and is not requesting a pediatric indication.

The statistical reviewer agrees that the study failed to reject the null hypothesis on the primary endpoint of one-year progression-free survival (PFS). The one-year PFS rate of 0.08 (95% CI = (0.01, 0.14)) for patients on capecitabine was not statistically superior to the historical control rate of 0.159. This result could be taken as evidence that capecitabine is statistically *inferior*. However, the Pediatric Brain Tumor Consortium, which holds the data for the historical control group, conducted a log-rank test on the two PFS distributions and reports that it numerically favored the control arm but the difference was not statistically significant (p = .058). The log-rank test cannot be replicated by FDA because the control data were not submitted. In regard to overall survival (OS), the statistical reviewer finds that the one-year OS rate was 0.42 (95% CI = (0.29, 0.55)), which is similar to the historical control rate of 0.456.

The applicant proposes to describe the efficacy results of the study as follows, “No efficacy benefit in progression free survival or overall survival was observed when compared to a historical control cohort of patients with newly diagnosed intrinsic brainstem glioma.” This reviewer defers to the clinical review team on the proposed label changes, but urges them to consider whether the label should state that there was a negative trend on PFS.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JONATHAN D NORTON
09/19/2013

KUN HE
09/19/2013

RAJESHWARI SRIDHARA
09/26/2013