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2079 A random effects model applied to the survival results of these ten studies yielded the
2080 historical estimate of the 5-FU versus 5-FU+LV survival comparison of log hazard ratio of
2081 1.264 with a 95% confidence interval of (1.09, 1.46) and a log hazard ratio of 0.234. The NI
2082 margin is therefore 1.09 for a fixed margin approach ruling out M_1 .
2083

2084 A summary of the survival results based on the intent-to-treat populations for each of the two
2085 Xeloda NI trials is presented in Table 9. Study 2 rules out M_1 using a fixed margin approach,
2086 but Study 1 does not.
2087

2088 **Table 9: Summary of the survival results**

Study	Hazard Ratio ¹	Log Hazard Ratio ¹	Standard Error	95% CI for the Hazard Ratio ¹
NI Study 1	1.00	-0.0036	0.0868	(0.84, 1.18)
NI Study 2	0.92	-0.0844	0.0867	(0.78, 1.09)

2089 ¹ Hazard ratios and log hazard ratios are Xeloda/5-FU+LV
2090

2091 The clinical choice of how much of the effect on survival of 5-FU+LV should be shown not
2092 to be lost by Xeloda was determined to be 50%. The synthesis approach was used to analyze
2093 whether the NI criteria of 50% loss was met. This synthesis approach to the non-inferiority
2094 test procedure for each study combines the results of each NI study with the results from the
2095 random effects meta-analysis into a normalized test statistic.
2096

2097 Based on this NI synthesis test procedure, NI Study 1 failed to demonstrate that Xeloda
2098 retained at least 50% of the historical effect of 5-FU+LV versus 5-FU on overall survival, but
2099 NI study 2 did demonstrate such an effect. It was then decided to determine what percent
2100 retention might be satisfied by the data in a statistically persuasive way. By adapting the
2101 synthesis test procedure for retention of an arbitrary percent of the 5-FU+LV historical effect,
2102 it was determined that NI Study 1 demonstrated that Xeloda lost no more than 90% of the
2103 historical effect of 5-FU+LV on overall survival and that NI Study 2 demonstrated no more
2104 than a 39% loss of the historical effect.
2105

2106 The evidence of effectiveness of Xeloda was supported by the observation that the tumor
2107 response rates were statistically significantly greater for the Xeloda arm and the fact that
2108 Xeloda and 5-FU were structurally and pharmacologically very similar.
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Example 1(A)

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2156 **Example 1(B) Refer to "General Reference" Section for synthesis methods.**

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2158 **Example 2**

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