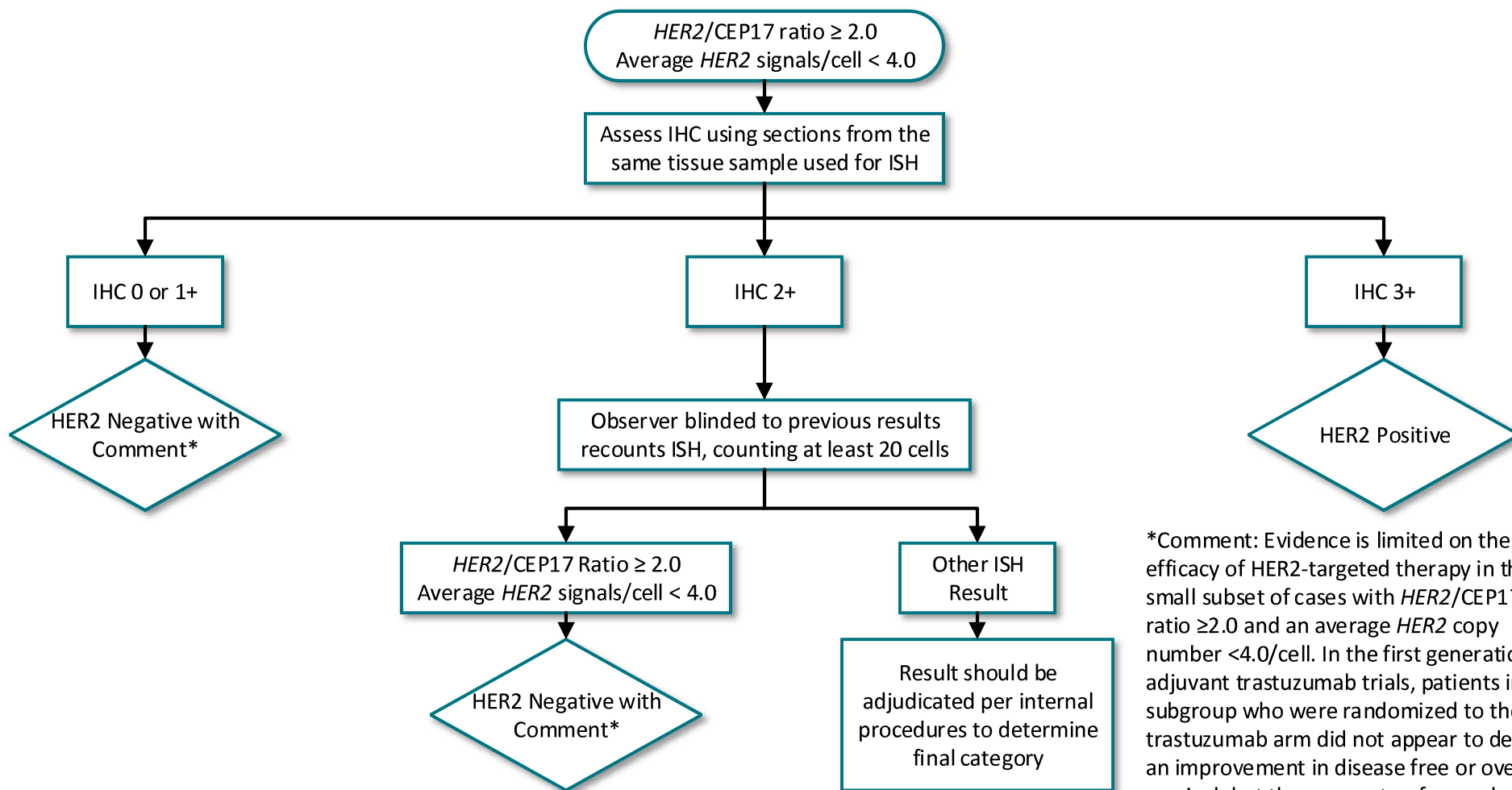


Figure 4. Clinical Question 3 “Group 2”



*Comment: Evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with *HER2/CEP17* ratio ≥ 2.0 and an average *HER2* copy number < 4.0 /cell. In the first generation of adjuvant trastuzumab trials, patients in this subgroup who were randomized to the trastuzumab arm did not appear to derive an improvement in disease free or overall survival, but there were too few such cases to draw definitive conclusions. IHC expression for HER2 should be used to complement ISH and define HER2 status. If IHC result is not 3+ positive, it is recommended that the specimen be considered HER2 negative because of the low *HER2* copy number by ISH and lack of protein overexpression.