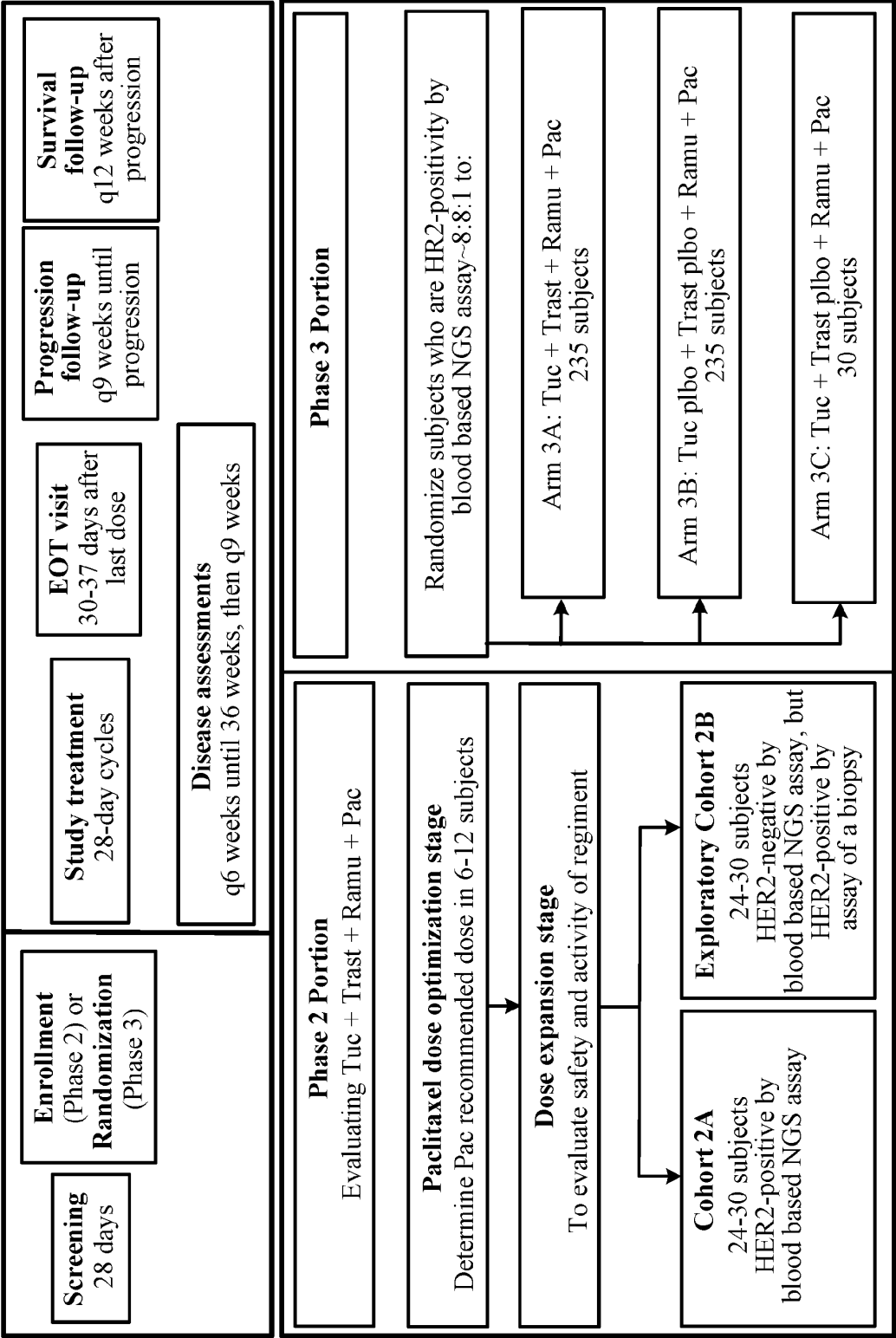
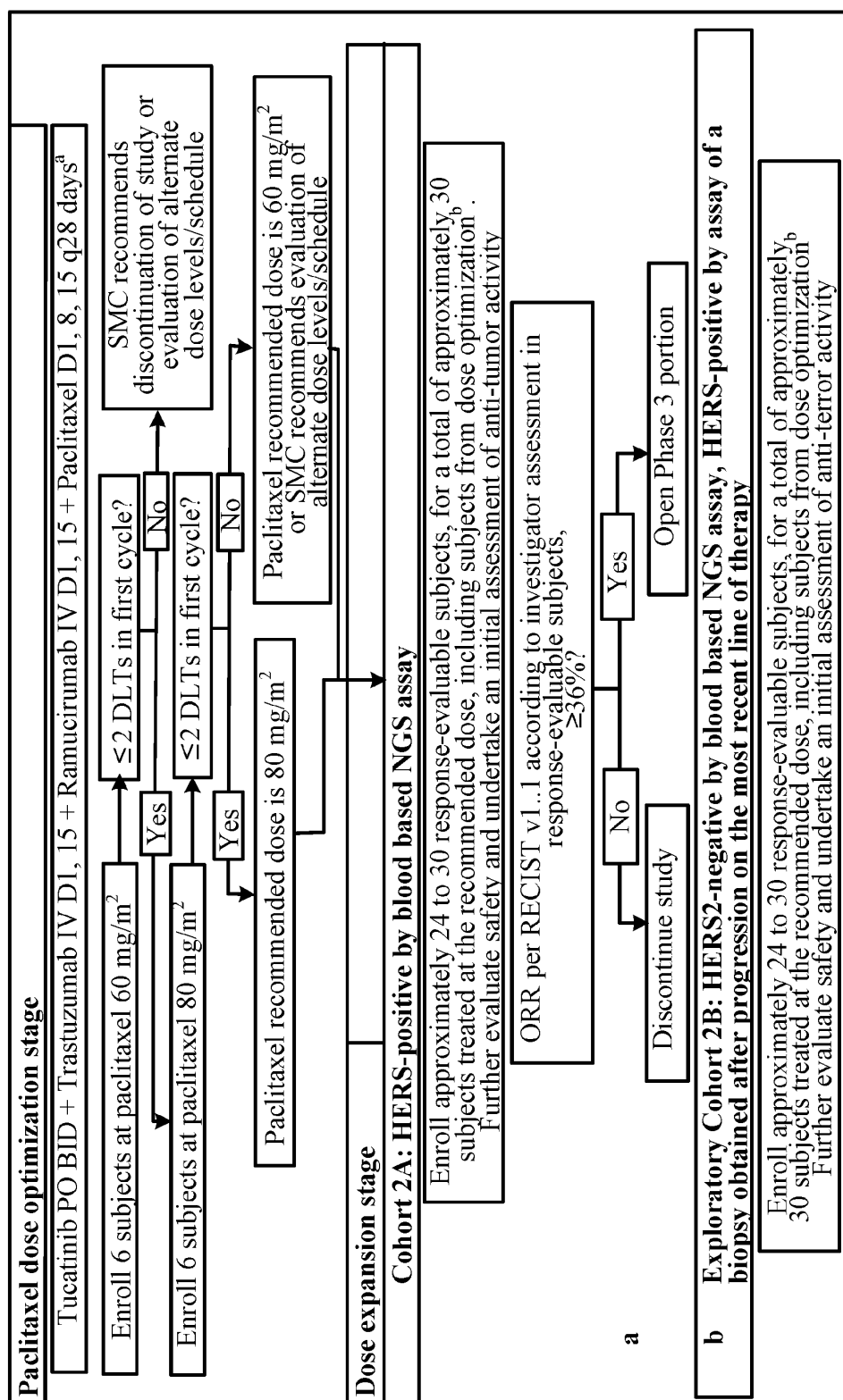


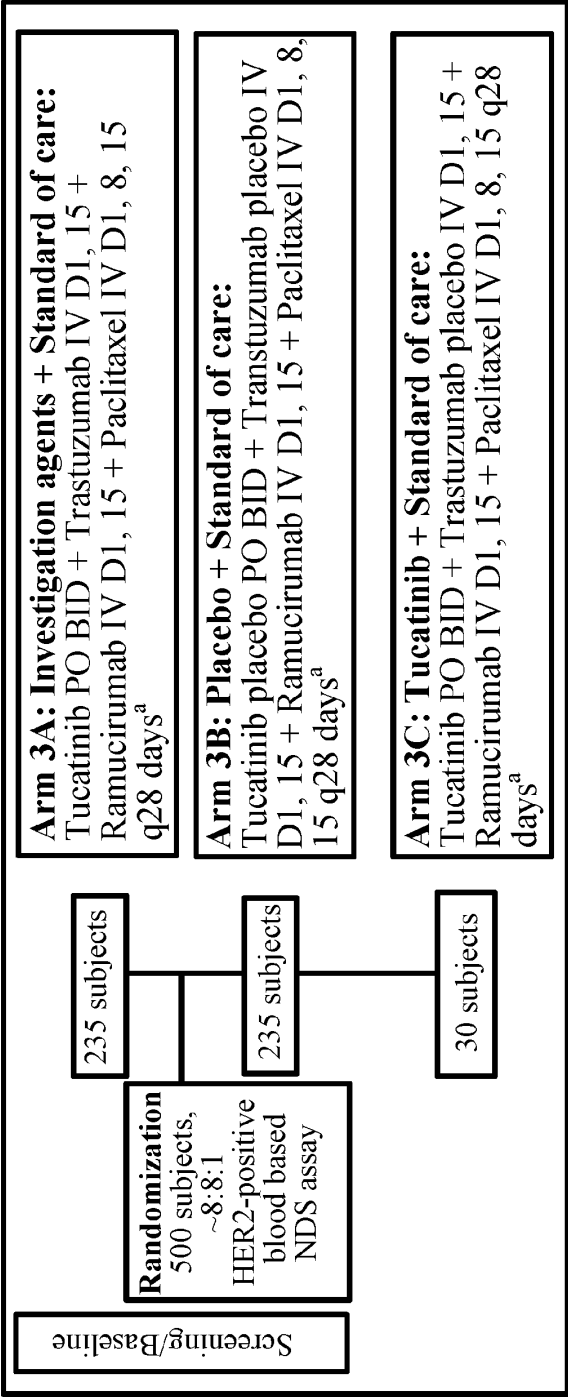


Pac=paclitaxel; plbo=placebo; Ramu=ramucirumab; Tuc=tucatinib; Trast=trastuzumab.

FIG. 1



Tucatinib will be administered at 300 mg BID PO; trastuzumab 6 mg/kg will be administered on Cycle 1 day 1, then 4 mg/kg in subsequent infusions; ramucirumab will be administered at a dose of 8 mg/kg per infusion, paclitaxel will be administered at a dose of 60 or 80 mg/m² per infusion, or an alternate dose/schedule upon recommendation of the SMC. Subjects evaluable for response will have a baseline disease assessment, receive study treatment, and have a Post-baseline assessment or discontinue treatment due to documented disease progression, clinical, progression, Treatment-related AE(s), or death.



a. Tucatinib will be administered at 300 mg BID PO; trastuzumab 6 mg/kg will be administered on Cycle 1 day 1, then 4 mg/kg in subsequent infusions; ramucirumab will be administered at a dose of 3 mg/kg per infusion; paclitaxel will be administered at the recommended dose and schedule determined in the Phase 2 in Arms 3A and 3C and at 80 mg/m² in Arm 3B.

FIG. 3

SEQ. ID NO. 1 (trastuzumab heavy chain):

EVQLVESGGGLVQPGGSLRLSCAASGFTNIKDTYIHVVRRQAPGKGLEWVARIYPTNGYT
RYADSVKGRFTISADTSKNTAYLQMNSLRADTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCTPPCPA
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSRREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYS
KLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPG

SEQ. ID NO. 2 (trastuzumab light chain):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLEYSGVP
SRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGGQTKVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYSLSSITL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ. ID NO. 3 (trastuzumab light chain variable domain):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLESGVPS
RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGGQTKVEIKRT

SEQ. ID NO. 4 (trastuzumab heavy chain variable domain):

EVQLVESGGGLVQPGGSLRLSCAASGFTNIKDTYIHVVRRQAPGKGLEWVARIYPTNGYT
RYADSVKGRFTISADTSKNTAYLQMNSLRADTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSS

FIG. 4

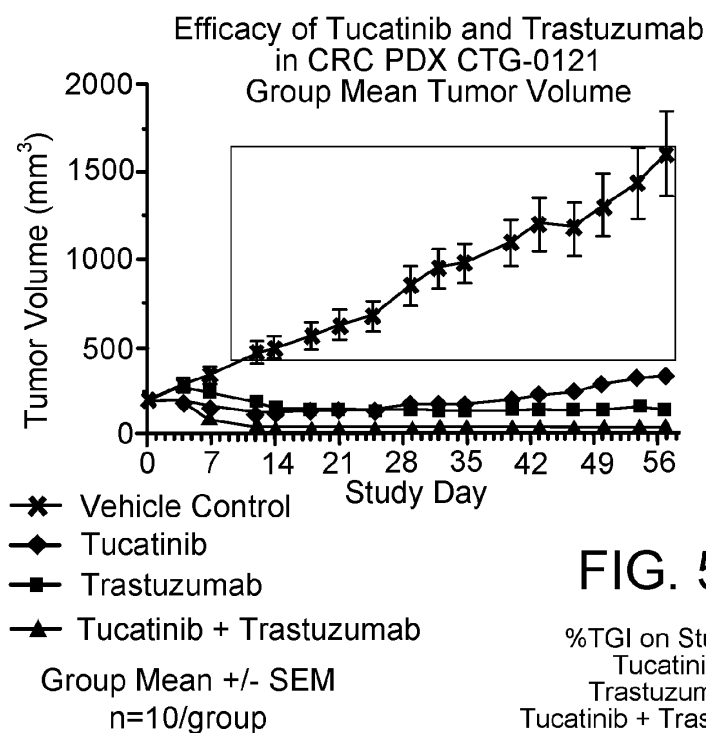


FIG. 5A

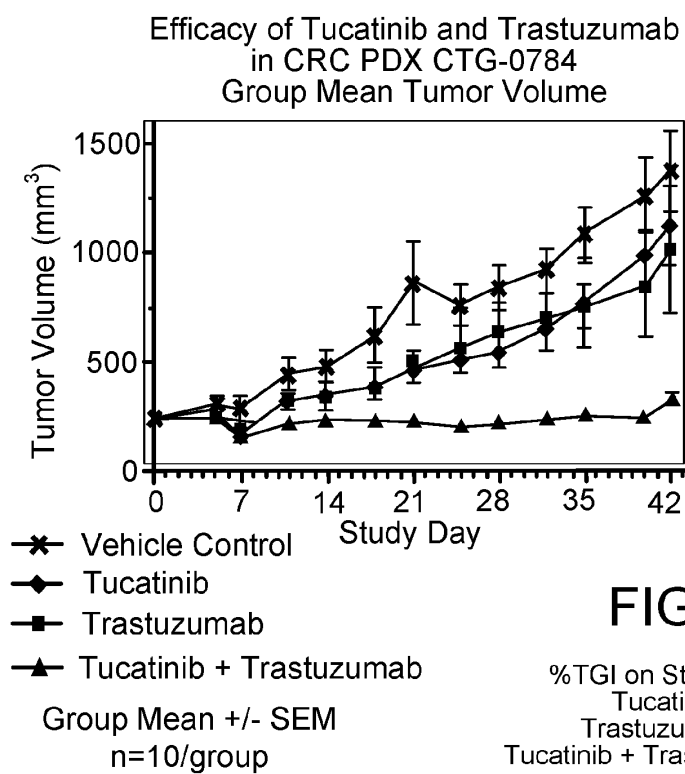


FIG. 5B

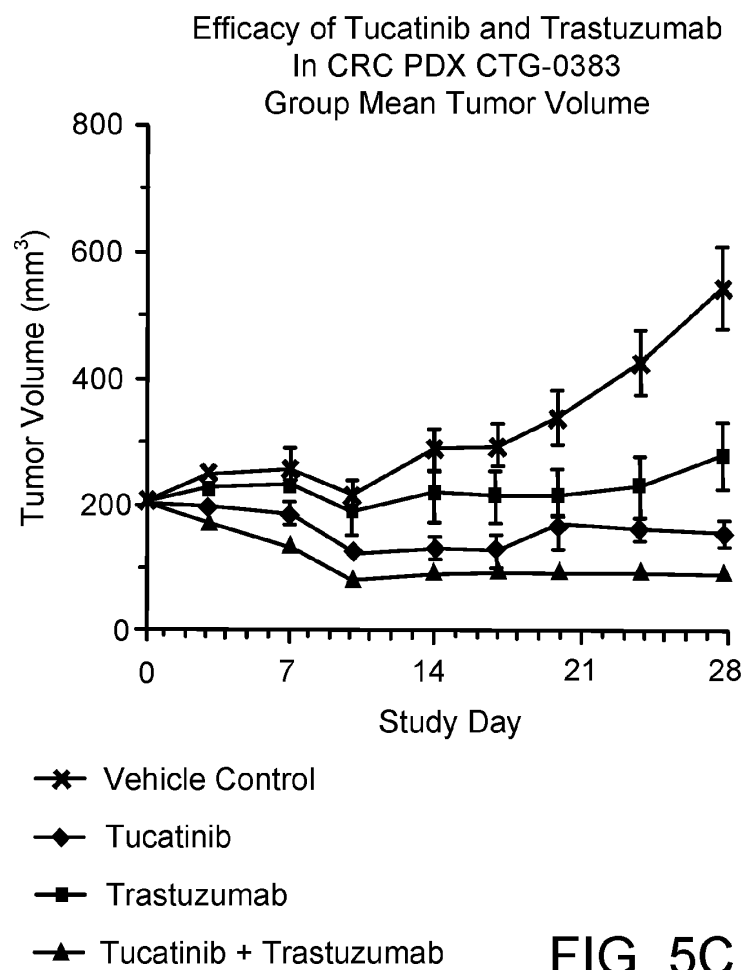
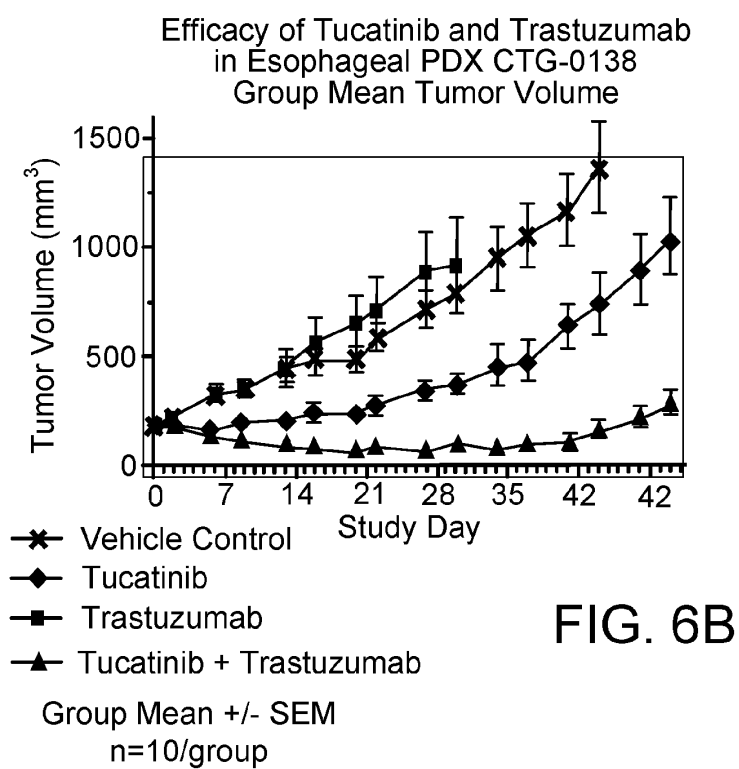
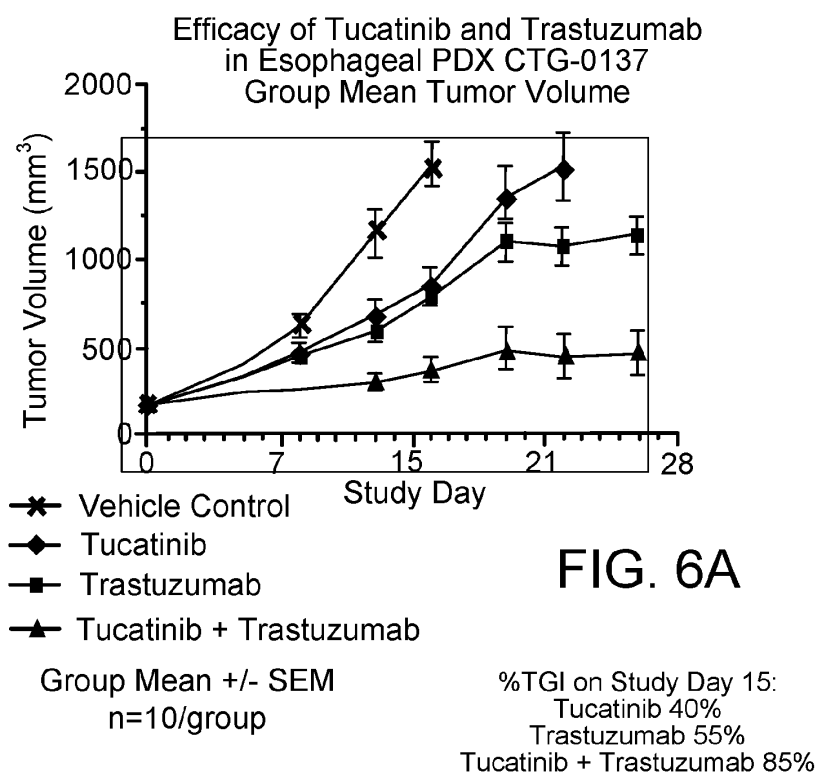
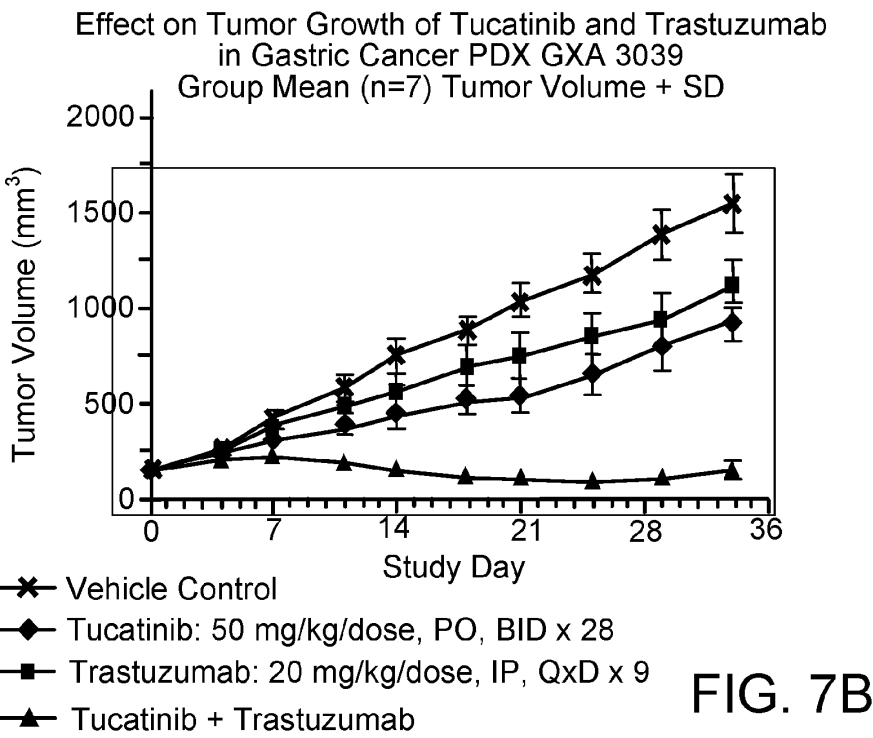
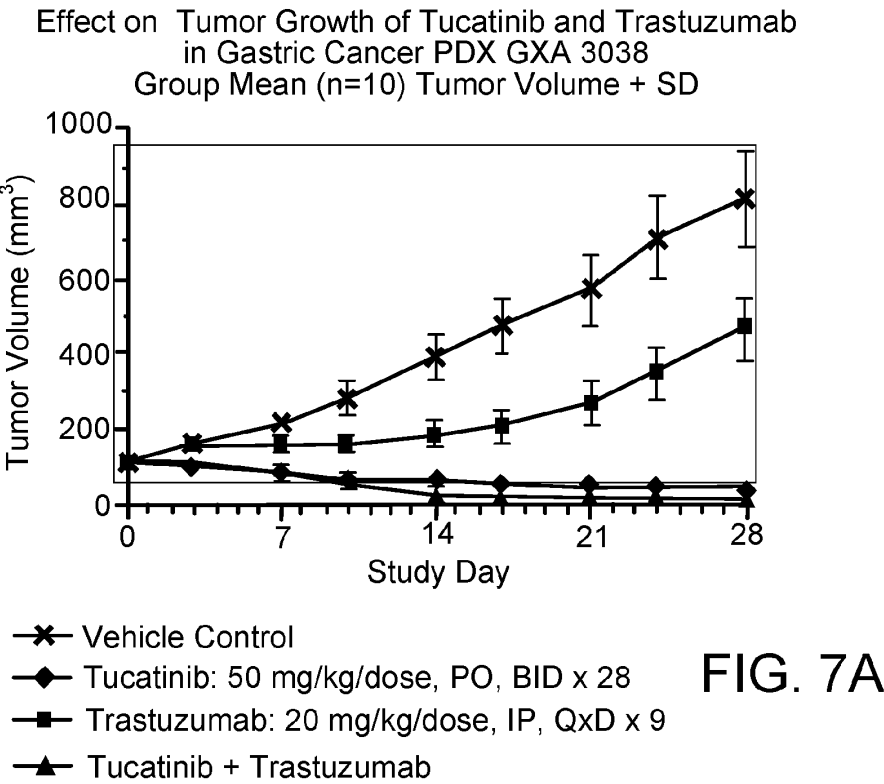


FIG. 5C

Group Mean +/- SEM
n=10/group





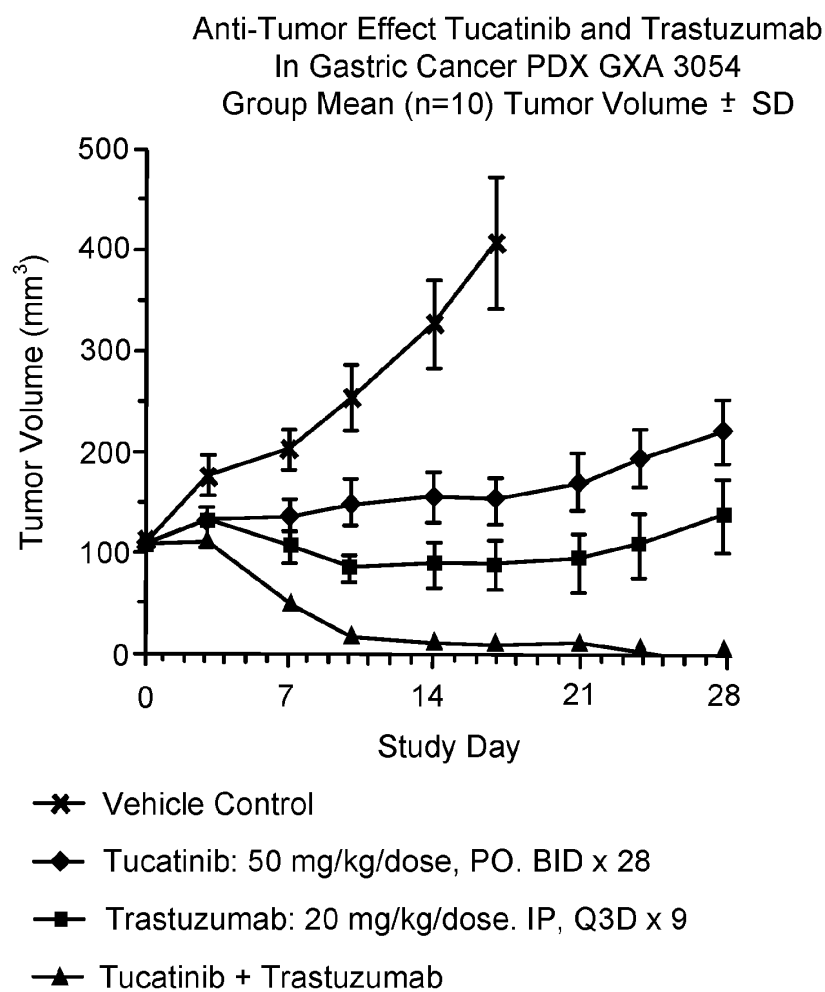


FIG. 7C

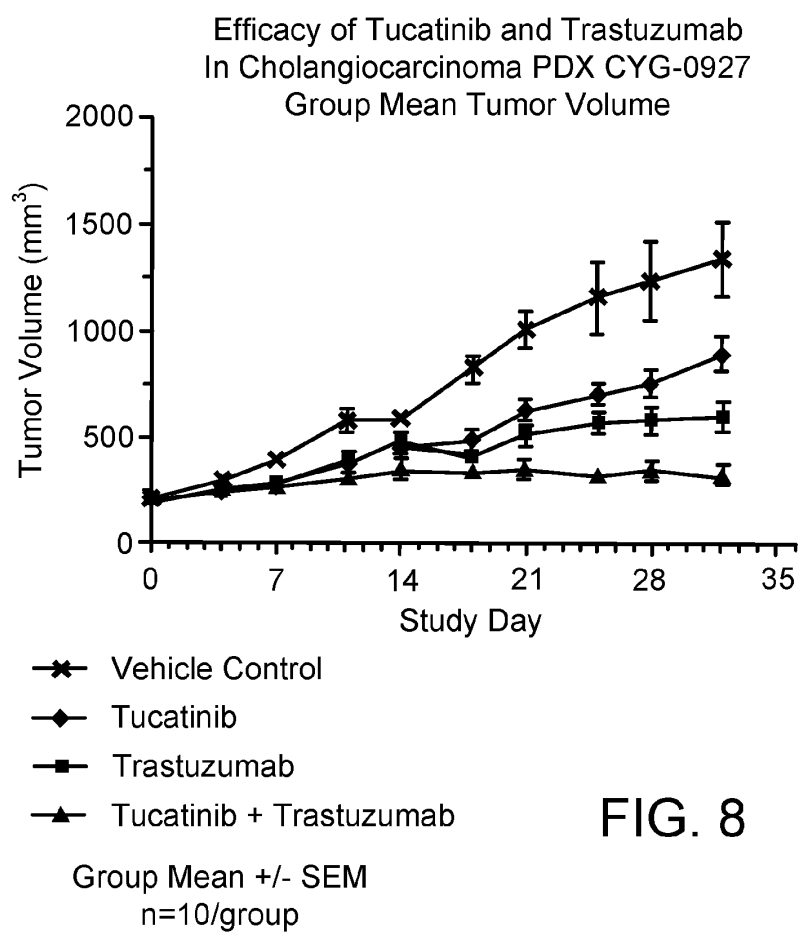


FIG. 8

