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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

(54) **Title:** TRIPLE COMBINATION ANTIBODY THERAPIES

Figure 1A

Human IgG1 constant region
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 1)

Human IgG1 D265A constant region
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 2)

Human IgG1 N267A constant region
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 3)

Human IgG2 constant region
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 4)

Human IgG3 constant region
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 5)

Human IgG4 constant region (Wild Type)
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 6)

Human IgG4 constant region (S241I hinge mutant)
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 7)

Human kappa light chain
RTVAALNFIHPSDEQKSGTASVVCILNNFYPRFAKQVQWVDNAIQGNSQSFVTPQSDKSTYSLSSTIILSKADYEKKHYACLVTHQGL
SSPVTKSFNRGEC (SEQ ID NO: 8)

Human lambda light chain
GQVKAATSVTIFPSSFLQANKATVCTISDFYPAVTVAWKADRSFVAGVETTPSKAGNKNYAAASYLSLTPQWKSRSYSCQVTHGCS
TVEKTVAPTECS (SEQ ID NO: 9)

Figure 1B

Human IgG4 constant region (Wild Type)
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 6)

Human IgG4 constant region (S241I hinge mutant)
ASTKGPSVFPLAPSSKPGTAAAGCLVLDYPPEVTVSWNSGALISGVHFFPAVLQSSGLYSIVYVPSSELTGTQYICNVNHRKPSNTKVD
KKEVEKSCDKHTCTCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVSVLT
LTLHQDWLNGKEYKCKVSNKALPAPIEKTSKARGQPREPQVYTLPPSDEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYKTPPPVLDSDCSF
FLYSRLTVDKSRWQGCNVFSCSVMHFAHLHNYTQKSLSPGK (SEQ ID NO: 7)

Human kappa light chain
RTVAALNFIHPSDEQKSGTASVVCILNNFYPRFAKQVQWVDNAIQGNSQSFVTPQSDKSTYSLSSTIILSKADYEKKHYACLVTHQGL
SSPVTKSFNRGEC (SEQ ID NO: 8)

Human lambda light chain
GQVKAATSVTIFPSSFLQANKATVCTISDFYPAVTVAWKADRSFVAGVETTPSKAGNKNYAAASYLSLTPQWKSRSYSCQVTHGCS
TVEKTVAPTECS (SEQ ID NO: 9)

- (57) **Abstract:** The present invention is directed to triple combination therapies with anti-TIGIT antibodies, anti-PVRIG antibodies, and checkpoint inhibitors, including anti-PD-1 or anti-PD-L1 antibodies.

[Continued on next page]

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