[0028] Thus, despite prior advances, a need remains for improved compositions, and methods for treating cancers expressing HER2/neu, and particularly metastatic breast cancer and cancers expressing low levels of HER2/neu. The present invention is directed to such compositions and to methods for their use in the treatment of HER2/neu-positive breast cancer and other cancers expressing HER2/neu.

Summary:

[0029] This disclosure relates to a pharmaceutical composition that comprises a first molecule that specifically binds to HER2/neu and a second molecule that specifically binds to a cell-surface receptor that is involved in regulating an immune checkpoint (or the ligand thereof). The disclosure particularly relates to the embodiment wherein the second molecule binds to PD-1. The disclosure also relates to the use of such pharmaceutical compositions to treat cancer and other diseases.

[0030] In detail, the disclosure provides a method of treating a cancer comprising administering to a subject in need thereof, an antibody that specifically binds HER2/neu and a molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint.

[0031] The disclosure particularly concerns embodiments of such methods wherein the antibody that specifically binds HER2/neu is a "Variant Chimeric 4D5 Antibody" comprising a light chain variable domain having the amino acid sequence of **SEQ ID NO:4** and a heavy chain having an amino acid sequence selected from the group consisting of **SEQ ID NO:9**, **SEQ ID NO:11**, and **SEQ ID NO:13**.

[0031a] In one aspect, there is provided a Variant Chimeric 4D5 Antibody in combination with a molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint, for use in combination therapy for the treatment of cancer in a subject in need thereof, wherein: (a) said Variant Chimeric 4D5 Antibody comprises a light chain variable domain comprising the amino acid sequence of **SEQ ID NO:4,** and a heavy chain that comprises a variant Fc Region having at least one modification in the Fc Region that enhances ADCC activity relative to a wild-type IgG1 Fc Region, wherein said heavy chain comprises an amino acid sequence selected from the group consisting of **SEQ ID NO:9**, **SEQ ID NO:11**, and **SEQ ID NO:13**; and (b) said molecule that specifically binds a cell-surface receptor, or said ligand thereof, that regulates an immune checkpoint is an anti-PD-1 antibody or antigen-binding fragment thereof that comprises an Fc Region that exhibits reduced ADCC activity relative to a wild-type IgG1 Fc Region.

[0031b] In another aspect, there is provided use of a Variant Chimeric 4D5 Antibody in combination with a molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein: (a) said Variant Chimeric 4D5 Antibody comprises a light chain variable domain comprising the amino acid sequence of **SEQ**

ID NO:4, and a heavy chain that comprises a variant Fc Region having at least one modification in the Fc Region that enhances ADCC activity relative to a wild-type IgG1 Fc Region, wherein said heavy chain comprises an amino acid sequence selected from the group consisting of **SEQ ID NO:9**, **SEQ ID NO:11**, and **SEQ ID NO:13**; and (b) said molecule that specifically binds a cell-surface receptor, or said ligand thereof, that regulates an immune checkpoint is an anti-PD-1 antibody or antigen-binding fragment thereof comprises an Fc Region that exhibits reduced ADCC activity relative to a wild-type IgG1 Fc Region**.**

[0032] The disclosure particularly concerns the embodiment of such methods wherein the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint is an anti-PD-1 antibody, or an antigen-binding fragment thereof.

[0033] The disclosure further concerns embodiments of such methods wherein the anti-PD-1 antibody, or antigen-binding fragment thereof:

(a) competes for PD-1 binding with nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or with another anti-PD-1 antibody selected from **Table 1**; or

(b) has the three heavy chain CDRs and the three light chain CDRs of nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or of another anti-PD-1 antibody selected from **Table 1**; or

(c) has the heavy chain variable domain and the light chain variable domain of nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or of another anti-PD-1 antibody selected from **Table 1**.

[0034] The disclosure further concerns embodiments of such methods wherein the anti-PD-1 antibody, or antigen-binding fragment thereof comprises an Fc Region. The disclosure further concerns the embodiments of such methods wherein the Fc Region comprises one or more amino acid modifications that reduce the affinity of the variant Fc Region for FcγRIIIa (CD16A) and/or reduces ADCC activity. The disclosure further concerns the embodiments of such methods, wherein the modifications comprise the substitution of L234A; L235A; or L234A and L235A.

[0035] The disclosure further concerns embodiments of such methods wherein the anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or another anti-PD-1 antibody selected from **Table 1**. The disclosure further concerns embodiments of such methods wherein the antigen-binding fragment of the anti-PD-1 antibody is an antigen-binding fragment of nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or of another anti-PD-1 antibody selected from **Table 1**.

Table 1: Additional Anti-PD-1 Antibodies	
PD-1 Antibodies	**Reference**
H1M7789N; H1M7799N; H1M7800N; H2M7780N; H2M7788N; H2M7790N; H2M7791N; H2M7794N; H2M7795N; H2M7796N; H2M7798N; H4H9019P; H4xH9034P2; H4xH9035P2; H4xH9037P2; H4xH9045P2; H4xH9048P2; H4H9057P2; H4H9068P2; H4xH9119P2; H4xH9120P2; H4Xh9128p2; H4Xh9135p2; H4Xh9145p2; H4Xh8992p; H4Xh8999p; and H4Xh9008p;	US Patent Publication 2015/0203579; and PCT Patent Publication WO 2015/112800
hPD-1 mAb 2; hPD-1 mAb 7; hPD-1 mAb 9; and hPD-1 mAb 15	PCT Patent Publication WO 2017/019846

[00193] In certain embodiments PD-1 antibodies useful in the methods and compositions of the instant inventions comprise the VL and VH Domains of any of the antibodies provided above (*e.g.*, PD-1 mAb 1, PD-1 mAb 2, PD-1 mAb 3, PD-1 mAb 4, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb 7, PD-1 mAb 8, or any of the anti-PD-1 antibodies in **Table 1**), a kappa CL Domain, and an IgG4 Fc Domain, optionally lacking the C-terminal lysine residue. Such antibodies will preferably comprise an IgG4 CH1 Domain and Hinge, and more preferably comprise a stabilized IgG4 Hinge comprising an S228P substitution (wherein the numbering is according to the EU index as in Kabat).

[00194] The amino acid sequence of a kappa CL Domain (**SEQ ID NO:85**) is:

RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG
NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK
SFNRGEC

[00195] The amino acid sequence of an IgG4 CH1 Domain and Stabilized Hinge (**SEQ ID NO:86**) is:

ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV
HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES
KYGPPCPPCP

[00196] The amino acid sequence of IgG4 CH2-CH3 Domains (**SEQ ID NO:52**) is presented below.

[00197] An exemplary anti-PD-1 antibody designated "**PD-1 mAb 6-ISQ**" comprises: a light chain having the VL Domain of PD-1 mAb 6 (**SEQ ID NO:65**) wherein X_1 is S and X_2 is Q and a kappa CL (**SEQ ID NO:85**); and a heavy chain having the VH Domain of PD-1 mAb 6 (**SEQ ID NO:61**) wherein X_1 is I, an IgG4 CH1 Domain, a stabilized IgG 4 Hinge (**SEQ ID NO:86**), and IgG4 CH2-CH3 Domains (**SEQ ID NO:52**).

[00198] The amino acid sequence of the complete light chain of PD-1 mAb 6-ISQ (**SEQ ID NO:87**) is shown below (CDR_L residues are underlined):

EIVLTQSPAT LSLSPGERAT LSC**RASESVD** **NYGMSFMN**WF QQKPGQPPKL
LIH**AASNQGS** GVPSRFSGSG SGTDFTLTIS SLEPEDFAVY FC**QQSKEVPY**
TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV
THQGLSSPVT KSFNRGEC

[00199] The amino acid sequence of the complete heavy chain of PD-1 mAb 6-ISQ (**SEQ ID NO:88**) is shown below (CDR_H residues are underlined):

QVQLVQSGAE VKKPGASVKV SCKASGYSFT **SYWMN**WVRQA PGQGLEWIG**V**
IHPSDSETWL **DQKFKD**RVTI TVDKSTSTAY MELSSLRSED TAVYYCAR**EH**
YGTSPFAYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLG

[00200] Another exemplary anti-PD-1 antibody is PD-1 mAb 1 (nivolumab), which is a human antibody comprising a light chain having a VL Domain (**SEQ ID NO:19**) and a kappa CL Domain (see for example, **SEQ ID NO:85**); and a heavy chain having a VH Domain (**SEQ ID NO:15**), an IgG4 CH1 Domain and stabilized hinge (see for example, **SEQ ID NO:86**), and IgG4 CH2-CH3 Domains (see for example, **SEQ ID NO:54**).

[00201] Another exemplary anti-PD-1 antibody is PD-1 mAb 2 (pembrolizumab), which is a humanized antibody comprising a light chain having a VL Domain (**SEQ ID NO:27**) and a kappa CL Domain (see for example, **SEQ ID NO:85**); and a heavy chain having a VH Domain (**SEQ ID NO:23**); an IgG4 CH1 and stabilized IgG4 Hinge (see for example, **SEQ ID NO:86**); and IgG4 CH2-CH3 Domains (see for example, **SEQ ID NO:52**).

What is claimed is:

Claim 1. A Variant Chimeric 4D5 Antibody in combination with a molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint, for use in combination therapy for the treatment of cancer in a subject in need thereof, wherein:

(a) said Variant Chimeric 4D5 Antibody comprises a light chain variable domain comprising the amino acid sequence of **SEQ ID NO:4,** and a heavy chain that comprises a variant Fc Region having at least one modification in the Fc Region that enhances ADCC activity relative to a wild-type IgG1 Fc Region, wherein said heavy chain comprises an amino acid sequence selected from the group consisting of **SEQ ID NO:9**, **SEQ ID NO:11**, and **SEQ ID NO:13**; and

(b) said molecule that specifically binds a cell-surface receptor, or said ligand thereof, that regulates an immune checkpoint is an anti-PD-1 antibody or antigen-binding fragment thereof that comprises an Fc Region that exhibits reduced ADCC activity relative to a wild-type IgG1 Fc Region.

Claim 2. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 1, wherein said anti-PD-1 antibody, or antigen-binding fragment thereof:

(a) comprises the three heavy chain CDRs and the three light chain CDRs of nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or an anti-PD-1 antibody selected from Table 1, wherein said CDRs are according to Kabat; or

(b) comprises the heavy chain variable domain and the light chain variable domain of nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or an anti-PD-1 antibody selected from Table 1.

Claim 3. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 1 or 2, wherein said anti-PD-1 antibody or antigen-binding fragment thereof comprises an Fc Region.

Claim 4. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 3, wherein said anti-PD-1 antibody or antigen-binding fragment thereof, comprises a variant Fc Region having at least one modification in the Fc Region that reduces ADCC activity, or an IgG4 Fc Region.

Claim 5. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 4, wherein said anti-PD-1 antibody or antigen-binding fragment thereof, comprises a variant IgG4 Hinge comprising a stabilizing substitution.

Claim 6. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 5, wherein said anti-PD-1 antibody or antigen-binding fragment thereof, comprises a variant IgG4 Hinge comprising an S228P substitution, numbered according to Kabat.

Claim 7. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-6, wherein said anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, antibody EH12.2H7, antibody hPD-1 mAb 2, antibody hPD-1 mAb 7, antibody hPD-1 mAb 9, antibody hPD-1 mAb 15, or an anti-PD-1 antibody selected from Table 1.

Claim 8. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-7, wherein:

(a) said Variant Chimeric 4D5 Antibody is for administration at a dosage of 6-18 mg/kg and said anti-PD-1 antibody is for administration at a fixed dosage of 100-500 mg; or

(b) said Variant Chimeric 4D5 Antibody is for administration at a dosage of 6-18 mg/kg and said anti-PD-1 antibody is for administration at a dosage of 1-10 mg/kg.

Claim 9. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-8, wherein said Variant Chimeric 4D5 Antibody is for administration at a dosage of 6-18 mg/kg every three weeks and

said anti-PD-1 antibody is for administration at a fixed dosage of 200 mg every three weeks.

Claim 10. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-8, wherein said Variant Chimeric 4D5 Antibody is for administration at a dosage of 6-18 mg/kg every three weeks and said anti-PD-1 antibody is for administration at a dosage of 1-10 mg/kg every three weeks.

Claim 11. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 8-10, wherein said Variant Chimeric 4D5 Antibody is for administration at a dosage selected from 6 mg/kg, 10 mg/kg, 15 mg/kg and 18 mg/kg every three weeks.

Claim 12. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 8, 10 or 11, wherein said anti-PD-1 is for administration at a dosage selected from 1 mg/kg, 2 mg/kg, 3 mg/kg and 10 mg/kg every three weeks.

Claim 13. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-12, wherein said Variant Chimeric 4D5 Antibody and said molecule that specifically binds a cell-surface receptor, or ligand thereof, that regulates an immune checkpoint are for concurrent administration in a single pharmaceutical composition.

Claim 14. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-12, wherein said Variant Chimeric 4D5 Antibody and said molecule that specifically binds a cell-surface receptor, or ligand thereof, that

regulates an immune checkpoint are for administration in separate pharmaceutical compositions within a 24-hour period of each other.

Claim 15. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-12, wherein one of said Variant Chimeric 4D5 Antibody and said molecule that specifically binds a cell-surface receptor, or ligand thereof, that regulates an immune checkpoint is for administration at least 24 hours, or more, after the administration of the other of said Variant Chimeric 4D5 Antibody and said molecule that specifically binds a cell-surface receptor, or ligand thereof, that regulates an immune checkpoint.

Claim 16. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-15, wherein said cancer is a cancer in which HER2/neu is expressed.

Claim 17. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 16, wherein said cancer is a breast cancer, gastric cancer, prostate cancer, uterine cancer, ovarian cancer, colon cancer, endometrial cancer, adrenal carcinoma, non-small cell lung cancer, head and neck cancer, laryngeal cancer, liver cancer, renal cancer, glioblastoma, or pancreatic cancer.

Claim 18. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-17, in further combination with a third therapeutic agent selected from the group consisting of an anti-angiogenic agent, an anti-neoplastic agent, a chemotherapeutic agent, and a cytotoxic agent.

Claim 19. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 18, wherein the third therapeutic agent is for concurrent administration with

said Variant Chimeric 4D5 Antibody and/or said molecule that specifically binds a cell-surface receptor, or ligand thereof, that regulates an immune checkpoint.

Claim 20. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to claim 18, wherein the third therapeutic agent is for administration separately from said Variant Chimeric 4D5 Antibody and/or said molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint.

Claim 21. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-20, wherein said Variant Chimeric 4D5 Antibody is margetuximab.

Claim 22. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody is pembrolizumab.

Claim 23. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody is nivolumab.

Claim 24. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody is pidilizumab.

Claim 25. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody comprises the heavy chain variable domain and the light chain variable domain of antibody hPD-1 mAb 2 (SEQ ID NO:53 and SEQ ID NO:57).

Claim 26. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody comprises the heavy chain variable domain and the light chain variable domain of antibody hPD-1 mAb 7 (SEQ ID NO:61 and SEQ ID NO:65).

Claim 27. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody comprises the heavy chain variable domain and the light chain variable domain of antibody hPD-1 mAb 9 (SEQ ID NO:69 and SEQ ID NO:73).

Claim 28. The Variant Chimeric 4D5 Antibody and the molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint for the use according to any one of claims 1-21, wherein said anti-PD-1 antibody comprises the heavy chain variable domain and the light chain variable domain of antibody hPD-1 mAb 15 (SEQ ID NO:77 and SEQ ID NO:81).

Claim 29. Use of a Variant Chimeric 4D5 Antibody in combination with a molecule that specifically binds a cell-surface receptor, or a ligand thereof, that regulates an immune checkpoint, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein:

(a) said Variant Chimeric 4D5 Antibody comprises a light chain variable domain comprising the amino acid sequence of **SEQ ID NO:4,** and a heavy chain that comprises a variant Fc Region having at least one modification in the Fc Region that enhances ADCC activity relative to a wild-type IgG1 Fc Region, wherein said heavy chain comprises an amino acid sequence selected from the group consisting of **SEQ ID NO:9**, **SEQ ID NO:11**, and **SEQ ID NO:13**; and

(b) said molecule that specifically binds a cell-surface receptor, or said ligand thereof, that regulates an immune checkpoint is an anti-PD-1 antibody or antigen-binding fragment thereof comprises an Fc Region that exhibits reduced ADCC activity relative to a wild-type IgG1 Fc Region.