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(54) **Title:** ANTI-CTLA4 ANTIBODY AND INDOLINONE COMBINATION THERAPY FOR TREATMENT OF CANCER

A 4.1.1 Heavy Chain cDNA (SEQ ID NO:1)

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atggagtttg ggctgagctg ggttttcctc gttgctcttt taaggaggtgt ccagtgtcag   60
gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc  120
tgtgtagcgt ctggattcac cttcagtagc catggcatgc actgggtccg ccaggctcca  180
ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagaaataa atactatgca  240
gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtttctg  300
caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag aggaggtcac  360
ttcggtcctt ttgactactg gggccaggga accctggtca ccgtctcctc agcctccacc  420
aagggcccat cggtcttccc cctggcgccc tgctccagga gcacctccga gagcacagcg  480
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca  540
ggcgctctga ccagcggcgt gcacaccttc ccagctgtcc tacagtcctc aggactctac  600
tccctcagca gcgtggtgac cgtgccctcc agcaacttcg gcacccagac ctacacctgc  660
aacgtagatc acaagcccag caacaccaag gtggacaaga cagttgagcg caaatgttgt  720
gtcgagtgcc caccgtgccc agcaccacct gtggcaggac cgtcagtctt cctcttcccc  780
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacgtg cgtggtggtg  840
gacgtgagcc acgaagaccc cgaggtccag ttcaactggt acgtggacgg cgtggaggtg  900
cataatgcca agacaaagcc acgggaggag cagttcaaca gcacgttccg tgtggtcagc  960
gtcctcaccg ttgtgcacca ggactggctg aacggcaagg agtacaagtg caaggtctcc 1020
aacaaaggcc tcccagcccc catcgagaaa accatctcca aaaccaaagg gcagccccga 1080
gaaccacagg tgtacaccct gccccatcc cgggaggaga tgaccaagaa ccaggtcagc 1140
ctgacctgcc tggtcaaagg cttctacccc agcgacatcg ccgtggagtg ggagagcaat 1200
gggcagccgg agaacaacta caagaccaca cctcccatgc tggactccga cggctccttc 1260
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1320
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1380
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B 4.1.1 Heavy Chain Protein (SEQ ID NO:2)

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[QVQLVESGGG VVQPGRSLRL SCVASGFTFS SHGMHWVRQA PGKGLEWVAV IWYDGRNKYY   60
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCARGG HFGPFDYWGQ GTLVTVSS]AS  120
TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL  180
YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVECPPCPAP PVAGPSVFLF  240

PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTFRVV  300
SVLTVVHQDW LNGKEYKCKV SNKGLPAPIE KTISKTKGQP REPQVYTLPP SREEMTKNQV  360
SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPMLDSDGS FFLYSKLTVD KSRWQQGNVF  420
SCSVMHEALH NHYTQKSLSL SPGK                                          444
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(57) **Abstract:** The invention relates to administration of an anti-CTLA4 antibody, particularly human antibodies to human CTLA4, such as those having amino acid sequences of antibodies 3.1.1 , 4.1.1 , 4.8.1 , 4.10.2, 4.13.1 , 4.14.3, 6.1.1 , ticilimumab (also referred to as 11.2.1 or CP- 675,206), 11.6.1 , 11.7.1 , 12.3.1.1 , 12.9.1.1 , and ipilimumab (also referred to as 10D1 or MDX-010), in combination with an indolinone receptor tyrosine kinase inhibitor (RTKI), e.g., N-[2-diethylamino]ethyl]-5-[(Z)-(5-fluoro-2-oxo-1 ,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1 H-pyrrole-3-carboxamide (compound 1), N-[2-(ethylamino)ethyl]-5-[(Z)-(5-fluoro-2-oxo-1 ,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1 H-pyrrole-3-carboxamide (compound 2), and 5-[(Z)-(5-fluoro-2-oxo-1 ,2-dihydro-3H-indol-3-ylidene)methyl]-N-[(2S)-2- hydroxy-3-morpholin-4-ylpropyl]-2,4-dimethyl-1 H-pyrrole-3-carboxamide (compound 3), for treatment of cancer. The invention relates to administering a combination of an anti-CTLA4 antibody and an indolinone RTKI such as, inter alia, compound 1. The invention relates to neoadjuvant, adjuvant, first-line, second-line, and third-line therapy of cancer, whether localized or metastasized, and at any point(s) along the disease continuum (e.g., at any stage of the cancer).

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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