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(71) **Applicant:** MEDIMMUNE, LLC [US/US]; One Medimmune Way, Gaithersburg, Maryland 20878 (US).

**Inventors: RANADE, Koustubh;** c/o Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US). **HIGGS, Brandon W.;** c/o Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US).

**RAJA, Rajiv G.;** c/o Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US). **BRO-HAWN, Philip Z.;** c/o Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US). **SI, Han;** c/o Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US). **KUZIORA, Mike;** c/o Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US).

(74) **Agent: MENSAH, Kwame N.**; Medimmune, LLC, One Medimmune Way, Gaithersburg, Maryland 20878 (US).

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**(54) Title:** BLOOD-BASED TUMOR MUTATION BURDEN PREDICTS OVERALL SURVIVAL IN NON-SMALL CELL LUNG CANCER

|        |        |         |         |        |         |        |        |         |        |        |         |
|--------|--------|---------|---------|--------|---------|--------|--------|---------|--------|--------|---------|
| ABL1   | ABL2   | ACVR1B  | ACVR2A  | ADARB2 | ADORA1  | ADORA2 | AFEN   | AKT1    | AKT1S1 | AKT2   | AKT3    |
| ALB    | ALK    | ALOX12B | ALOX15B | ALOX5  | AMER1   | APC    | APEX1  | AR      | ARAF   | ARFIP1 | ARHGAP3 |
| ARID1A | ARID1B | ARID2   | ASXL1   | ATM    | ATR     | ATRX   | AURKA  | AURKB   | AXIN1  | AXIN2  | AXL     |
| B2M    | BAP1   | BARD1   | BCL2    | BCL2L1 | BCL2L2  | BCL8   | BCOR   | BCORL1  | BCR    | BRCC3  | BIM     |
| BRAF   | BRCA1  | BRCA2   | BRE1    | BRE2   | BRIP1   | BTG1   | BTG2   | BTX     | BUB1B  | CARD11 |         |
| CASP8  | CASP9  | CBL     | CBLB    | CND1   | CND2    | CND3   | CNCE1  | CD274   | CD79A  | CD79B  | CD7     |
| GDC73  | CDH1   | CDK12   | CDK4    | CDK6   | CDK9    | CDKN1A | CDKN1B | CDKN2A  | CDKN2G | CEBPA  | CEP350  |
| CHEK1  | CHEK2  | CIC     | CNOT3   | CREBBP | CRLF    | CRLF1  | CSF1R  | CTCF    | CTLA4  | CIN3A3 | CTNNA1  |
| CUL3   | CUX1   | C4D     | DAXX    | DDIT3  | DDR1    | DDR2   | DEPDC5 | DEPTOR  | DOSR1  | DL14   | DNMT3A  |
| DOT1L  | DYRK2  | EBF3    | EBF3L   | EGFR   | EPHA1   | E1F4A1 | E1F4A2 | E1F4A3  | E1F4B  | E1F4E  | E1F4F2  |
| ELF3   | EML4   | ERBB1   | EP300   | EPCAM  | EPHA3   | EPHA5  | EPHA7  | EPH6    | ERBB2  | ERBB3  | ERBB4   |
| ERCC1  | ERCC2  | ERCC3   | ERCC4   | ERCC6  | ERCC6   | ERCC8  | ERG    | ERRP1   | ESR1   | ETV1   | ETV4    |
| ETB    | ETV6   | ESR1    | FOX1    | EZH2   | FAAP100 | FAAP20 | FAF24  | FAM178A | FAM18C | FANGA  | FANCB   |
| FANCD1 | FANCD2 | FANCD3  | FANCF   | FANCI  | FANCL   | FANCL  | FANCL  | FAS     | FAT1   | FBXW7  | FBN1    |
| FGF10  | FGF14  | FGF19   | FGF23   | FGF3   | FGF4    | FGF6   | FGFR1  | FGFR2   | FGFR3  | FGFR4  | FGFR5   |
| FLCN   | FLT1   | FLT3    | FLT4    | FOXA1  | FOXO1   | FOXO2  | FOXO3  | FRS2    | FUSP1  | FZD1   | FZD10   |
| FZD2   | FZD3   | FZD4    | FZD6    | FZD6   | FZD7    | FZD8   | FZD9   | GAS6    | GATA1  | GATA2  | GATA3   |
| GATA6  | GEN1   | GNA1    | GNA11   | GNA13  | GRN4    | GNAS   | GRIN2A | GSK3B   | HDAC2  | HELQ   | HES1    |
| HEY1   | HEYL   | HGF     | HGF3H3  | HNF1A  | HNR4    | HNR4A1 | IDH1   | IDH2    | IDO1   | IFNG   | IFNGR1  |
| IFNGR2 | IGF1   | IGF1R   | IGF2    | IGF2R  | IKK1    | IKZF1  | IL2RG  | IL7R    | INHBA  | INPP4B | IRF1    |
| IRF4   | IRS2   | JAK1    | JAK2    | JAK3   | JUN     | KAT5A  | KDMAA  | KDMAA   | KDM5B  | KDM5C  | KDM6A   |
| KDR    | KEAP1  | KIT     | KLHL8   | KMT2A  | KMT2D   | KMT2D  | KMT2D  | KMT2D   | LGR4   | LGR6   | LGR6    |
| LGR4   | LGR6   | LRP1B   | LRP2    | LRP5   | LRP6    | MAD2L2 | MAD2K1 | MAD2K2  | MAD2K4 | MAD3K1 | MAD4K3  |

**Complete**

Parties

## Fusion

CNV

Figure 1

**(57) Abstract:** The disclosure generally relates to methods for treating non-small cell lung cancer patients based on use of blood-based tumor mutation burden to predict overall survival in patients treated with durvalumab, tremelimumab, and/or a chemotherapy agent. The disclosure also relates to methods for treating non-small cell lung cancer patients based on identification of mutations in circulating tumor DNA associated with sensitivity or resistance to immunotherapy.

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## **BLOOD-BASED TUMOR MUTATION BURDEN PREDICTS OVERALL SURVIVAL IN NON-SMALL CELL LUNG CANCER**

### **FIELD OF THE DISCLOSURE**

The present disclosure generally relates to methods for treating non-small cell lung cancer patients based on use of blood-based tumor mutation burden to predict overall survival in patients treated with durvalumab and/or tremelimumab, and/or a chemotherapy agent. The disclosure also relates to methods for treating non-small cell lung cancer patients based on identification of mutations in circulating tumor DNA associated with sensitivity or resistance to immunotherapy.

### **BACKGROUND OF THE DISCLOSURE**

Non-small cell lung cancer ("NSCLC") patients with high pretreatment tumor mutational burden ("TMB") have demonstrated improved outcomes after treatment with immune checkpoint inhibitors (Yarchoan *et al.*, *N. Engl. J. Med.* 377(25): 2500-01 (2017); Snyder *et al.*, *N. Engl. J. Med.* 371(23): 2189-99 (2014); Le *et al.*, *Science* 357(6349): 409-13 (2017); Rizvi *et al.*, *Science* 348(6230): 124-28 (2015); Rizvi *et al.*, *J. Clin. Oncol.* 36(7): 633-41 (2018); Hellmann *et al.*, *Cancer Cell* 33(5): 843-52 (2018); Carbone *et al.*, *N. Engl. J. Med.* 376(25): 2415-26 (2017); Hellmann *et al.*, *N. Engl. J. Med.* 378(22): 2093-104 (2018)). TMB measured in the blood has also emerged as a promising new approach to enrich for NSCLC patients responding to PD-1/L1 therapy (Gandara *et al.*, *Ann. Oncol.* 28 (Suppl 5): v460-v496 (2017); Planchard *et al.*, *Ann. Oncol.* 29 (Suppl 4): iv192-iv237 (2018)). Reports have shown that NSCLC patients in both first- and second-line settings with high blood TMB ("bTMB") had improved progression-free survival and response rates. However, a correlation between either tissue TMB ("tTMB") or bTMB with overall survival in NSCLC patients treated with an anti-PD-1/L1 antibody has not been shown.

## SUMMARY OF THE DISCLOSURE

The disclosure provides a method of predicting success of cancer treatment in a patient in need thereof, comprising determining the patient's tumor mutational burden (TMB), wherein a high TMB predicts success of treatment.

5       The disclosure also provides a method of treating cancer in a patient in need thereof, comprising: (a) determining the patient's TMB; (b) determining whether the TMB is high or low; and (c) treating or continuing treatment if TMB is high or not treating or discontinuing treatment if TMB is low.

10       The disclosure further provides a method of predicting success of cancer treatment in a patient in need thereof, comprising determining if the patient has a somatic mutation in AT-rich interactive domain-containing protein 1A gene (*ARID1A*), wherein a somatic mutation predicts success of treatment.

15       The disclosure further provides a method of treating cancer in a patient in need thereof, comprising: (a) determining whether the patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene; and (b) treating or continuing treatment if patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene.

20       Other features and advantages of the disclosure will be apparent from the detailed description, and the claims.

## BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

**Figure 1** shows the list of genes included in the TMB analysis.

25       **Figure 2** shows overall survival in patients with PD-L1 expression on tumor cells (TC)  $\geq 25\%$  treated with durvalumab (D) versus chemotherapy (CT) or durvalumab and tremelimumab (D+T) versus chemotherapy (CT).

30       **Figure 3** shows progression free survival (PFS) in patients with PD-L1 expression on tumor cells (TC)  $\geq 25\%$  treated with durvalumab versus chemotherapy or durvalumab and tremelimumab versus chemotherapy.

**Figure 4** shows a primary analysis population. The analysis was performed using a Cox proportional hazards model with a term for treatment and the subgroup covariate of interest. Subgroups were according to sex, age, immune cell PD-L1 expression, histology, smoking history, and race. The analysis of subgroups according to performance status was post hoc.

\*97.54% CI is shown.

**Figure 5** shows correlation of two TMB measurement tools in the MYSTIC study. The correlation plot is based on 352 patients with matched blood and tissue TMB data. The reference line is estimated using linear regression.

**Figures 6A-6C** show overall survival in the ITT and blood and tissue TMB evaluable populations.

**Figure 7** shows analysis of overall survival across blood TMB cut-offs.

**Figure 8** shows overall survival rates in patient with blood TMB  $\geq 16$  and  $< 16$  mut/Mb.

**Figure 9** shows a Venn diagram indicating overlap of patient subgroups based on blood TMB and PD-L1. \*Percentages are calculated from the intention-to-treat population (all randomized patients; N=1118).

**Figure 10** shows overall survival rates in patient with blood TMB  $\geq 20$  and  $< 20$  mut/Mb.

**Figure 11** shows progression free survival (PFS) in patient with blood TMB  $\geq 20$  and  $< 20$  mut/Mb.

**Figures 12A-12B** shows overall survival rates in patient with blood TMB  $\geq 10$  and  $< 10$  mut/Mb.

**Figure 13** shows the TMB Algorithm.

**Figure 14** shows overall survival (OS) in patients with PD-L1 expression on tumor cells (TC)  $\geq 50\%$  treated with durvalumab and tremelimumab (D+T) versus chemotherapy (CT).

**Figure 15** shows overall survival (OS) in patients with PD-L1 expression on tumor cells (TC)  $\geq 1\%$  treated with durvalumab and tremelimumab (D+T) versus chemotherapy (CT).

**Figure 16** shows that combining bTMB high or tumor cells (TC)  $< 1\%$  improves prevalence but reduces efficacy.

**Figure 17** shows that combining bTMB high or tumor cells (TC)  $\geq 25\%$  improves prevalence but reduces efficacy.

**Figure 18** shows the prevalence of mutations in the genes *KEAP1*, *STK11*, and *ARID1A* in patients in MYSTIC study. 324 (of 943 evaluable) patients had mutations in one of the 3 genes *KEAP1*, *STK11*, or *ARID1A*.

**Figure 19** shows prevalence of mutations according to histology and treatment. *STK11* and *KEAP1* mutations were more prevalent in patients with nonsquamous histology compared with squamous histology. *STK11*, *KEAP1*, and *ARID1A* mutation prevalence was balanced between treatment arms.

**Figure 20** shows prevalence of mutations according to bTMB status.

**Figure 21** shows prevalence of mutations according to PD-L1 expression.

**Figure 22** shows objective response rates for treatment with durvalumab and tremelimumab (durvalumab + tremelimumab), durvalumab monotherapy (durvalumab), or chemotherapy according to mutation status in patients.

**Figure 23** shows overall survival for *KEAP1*m vs *KEAP1*wt in all mutation-evaluable patients treated with durvalumab and tremelimumab, durvalumab monotherapy, or chemotherapy. Patients treated with durvalumab and tremelimumab, durvalumab monotherapy, or chemotherapy were included in each group; m=mutation-positive; mOS=median overall survival; wt=wild type.

**Figure 24** shows overall survival for *KEAP1*m vs *KEAP1*wt in patients treated with durvalumab monotherapy versus chemotherapy or durvalumab + tremelimumab versus chemotherapy.

**Figure 25** shows overall survival for *STK11*m vs *STK11*wt in all mutation-evaluable patients. Patients treated with durvalumab and tremelimumab, durvalumab monotherapy, or chemotherapy were included in each group.

**Figure 26** shows overall survival for *STK11*m vs *STK11*wt in patients treated with durvalumab monotherapy versus chemotherapy or durvalumab + tremelimumab versus chemotherapy.

**Figure 27** shows overall survival for *STK11*m/*KEAP1*m and *STK11*m/*KRAS*m versus wild type in all mutation-evaluable patients. Patients treated with durvalumab and tremelimumab, durvalumab monotherapy, or chemotherapy were included in each group.

**Figure 28** shows overall survival for *ARID1Am* and *ARID1Awt* in all mutation-evaluable patients. Patients treated with durvalumab and tremelimumab, durvalumab monotherapy, or chemotherapy were included in each group.

**Figure 29** shows overall survival for *ARID1Am* vs *ARID1wt* in patients treated with  
5 durvalumab monotherapy versus chemotherapy or durvalumab + tremelimumab versus chemotherapy.

## DETAILED DESCRIPTION OF THE DISCLOSURE

The present disclosure generally relates to methods for treating non-small cell lung cancer patients based on use of blood-based tumor mutation burden to predict overall survival in patients treated with durvalumab and/or tremelimumab, and/or a chemotherapy agent. The disclosure also relates to methods for treating non-small cell lung cancer patients based on identification of mutations in circulating tumor DNA (ctDNA) associated with sensitivity or resistance to immunotherapy.

The disclosure is based, at least in part, on the identification of unique patient subsets through bTMB. As described herein, bTMB was more predictive of overall survival than levels of PD-L1 expression for durvalumab treatment in combination with tremelimumab. In some embodiments, bTMB is also more predictive of overall survival than levels of PD-L1 expression for durvalumab monotherapy treatment +/- a chemotherapy agent. In further embodiments, bTMB is more predictive of overall survival than levels of PD-L1 expression for durvalumab treatment in combination with tremelimumab +/- a chemotherapy agent.

As utilized in accordance with the present disclosure, unless otherwise indicated, all technical and scientific terms shall be understood to have the same meaning as commonly understood by one of ordinary skill in the art. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

In some embodiments provided herein is a method of predicting success of cancer treatment in a patient in need thereof, comprising determining the patient's tumor mutational burden (TMB), wherein a high TMB predicts success of treatment.

"Tumor mutational burden" or "TMB" refers to the quantity of mutations found in a tumor. TMB varies among different tumor types. Some tumor types have a higher rate of mutation than others. TMB can be measured by a variety of tools known in the field. In certain embodiments, these tools are the Foundation Medicine and Guardant Health measurement tools. As described herein, evaluation of potential neoantigen encoding mutations in a particular set of genes was found to be correlative for treatment with durvalumab in combination with tremelimumab. Determining whether a tumor has high or low levels of tumor mutational burden can be determined by comparison to a reference population having similar tumors and determining median or mean level of expression. In some embodiments, a high TMB is defined as  $\geq 12$  to  $\geq 20$  mutations/megabase (mut/Mb). In other embodiments, a high TMB is defined as

≥ 16 mutations/megabase (mut/Mb). In other embodiments, a high TMB is defined as ≥ 20 mutations/megabase (mut/Mb).

As used herein the term "MYSTIC" refers to Study NCT02453282, which is a phase III open label first line therapy study of durvalumab, with or without tremelimumab, versus standard of care in NSCLC.

In some embodiments, the method comprises treatment with durvalumab. The term "durvalumab" as used herein refers to an antibody that selectively binds PD-L1 and blocks the binding of PD-L1 to the PD-1 and CD80 receptors, as disclosed in U.S. Patent No. 9,493,565 (referred to as "2.14H9OPT"), which is incorporated by reference herein in its entirety. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity ("ADCC"). Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation *in vitro* and inhibits tumor growth in a xenograft model via a T-cell dependent mechanism.

In some embodiments, the methods disclosed herein comprise treatment with tremelimumab. The term "tremelimumab" as used herein refers to an antibody that selectively binds a CTLA-4 polypeptide, as disclosed in U.S. Patent No. 8,491,895 (referred to as "clone 11.2.1"), which is incorporated by reference herein in its entirety. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T-cell activation. Tremelimumab shows minimal specific binding to Fc receptors, does not induce natural killer (NK) ADCC activity, and does not deliver inhibitory signals following plate-bound aggregation.

In some embodiments, the methods disclosed herein comprise treatment with a chemotherapy agent comprising at least one of abraxane, carboplatin, gemcitabine, cisplatin, pemetrexed, or paclitaxel. In some embodiments, the chemotherapy agent comprises abraxane + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, pemetrexed + carboplatin, pemetrexed + cisplatin, or paclitaxel + carboplatin.

In some embodiments, the methods disclosed herein comprise treatment with durvalumab, tremelimumab, and a chemotherapy agent. In other embodiments, the methods disclosed herein comprise treatment with durvalumab and a chemotherapy agent. In other embodiments, the methods disclosed herein comprise treatment with durvalumab.

In some embodiments, the patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene. *STK11* and *KEAP1* mutation status was prognostic for OS in patients with metastatic non-small cell lung cancer (mNSCLC). In some embodiments, mutations in *STK11* or *KEAP1* mNSCLC are prognostic for shorter OS as compared to patients with wildtype *STK11* or *KEAP1* mNSCLC. In some embodiments, mutations in *ARID1A* are used as a biomarker predictive of improved OS in patients receiving durvalumab + tremelimumab treatment.

The term "ARID1A" encompasses "full-length" unprocessed ARID1A as well as any form of ARID1A that results from processing in the cell. The term also encompasses naturally occurring variants of ARID1A, *e.g.*, splice variants or allelic variants.

The term "*KEAP1*" encompasses "full-length" unprocessed *KEAP1* as well as any form of *KEAP1* that results from processing in the cell. The term also encompasses naturally occurring variants of *KEAP1*, *e.g.*, splice variants or allelic variants.

The term "STK11" encompasses "full-length" unprocessed STK11 as well as any form of STK11 that results from processing in the cell. The term also encompasses naturally occurring variants of STK11, *e.g.*, splice variants or allelic variants.

The term "K-Ras" encompasses "full-length" unprocessed K-Ras as well as any form of K-Ras that results from processing in the cell. The term also encompasses naturally occurring variants of K-Ras, *e.g.*, splice variants or allelic variants.

In some embodiments provided herein is a method of treating cancer in a patient in need thereof, comprising:

- (a) determining the patient's TMB;
- (b) determining whether the TMB is high or low; and
- (c) treating or continuing treatment if TMB is high or not treating or discontinuing treatment if TMB is low.

Determining whether a TMB is high may vary from tumor type to tumor type. Determining whether a tumor has high or low levels of tumor mutational burden can be determined by comparison to a reference population having similar tumors and determining median or mean level of expression. In some embodiments, the levels of TMB are divided as low (1–5 mutations/mb), intermediate (6–15 mutations/mb), and high ( $\geq 16$  mutations/mb).

In some embodiments, the success of treatment is determined by an increase in OS as compared to standard of care. "Standard of care" (SOC) and "platinum-based chemotherapy" refer to chemotherapy treatment comprising at least one of abraxane, carboplatin, gemcitabine, cisplatin, pemetrexed, or paclitaxel. In some embodiments, the SOC comprises abraxane + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, pemetrexed + carboplatin, pemetrexed + cisplatin, or paclitaxel + carboplatin.

As used herein, Overall Survival ("OS") relates to the time-period beginning on the date of treatment until death due to any cause. OS may refer to overall survival within a period of time such as, for example, 12 months, 18 months, 24 months, and the like.

In some embodiments, provided herein is a method of predicting success of cancer treatment in a patient in need thereof, comprising determining if the patient has a somatic mutation in AT-rich interactive domain-containing protein 1A gene (*ARID1A*), wherein a somatic mutation predicts success of treatment.

In some embodiments, provided herein is a method of treating cancer in a patient in need thereof, comprising: (a) determining whether the patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene; and (b) treating or continuing treatment if patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene.

The term "patient" is intended to include human and non-human animals, particularly mammals.

In some embodiments, the methods disclosed herein relate to treating a subject for a tumor disorder and/or a cancer disorder. In some embodiments, the cancer is selected from melanoma, breast cancer, pancreatic cancer, lung cancer (*e.g.*, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), hepatocellular carcinoma, cholangiocarcinoma or biliary tract cancer, gastric cancer, oesophagus cancer, head and neck cancer, renal cancer, cervical cancer, colorectal cancer, or urothelial bladder cancer.

The terms "treatment" or "treat" as used herein refer to therapeutic treatment. Those in need of treatment include subjects having cancer. In some embodiments, the methods disclosed herein can be used to treat tumors. In other embodiments, treatment of a tumor includes

inhibiting tumor growth, promoting tumor reduction, or both inhibiting tumor growth and promoting tumor reduction.

The terms "administration" or "administering" as used herein refer to providing, contacting, and/or delivering a compound or compounds by any appropriate route to achieve the desired effect. Administration may include, but is not limited to, oral, sublingual, parenteral (e.g., intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection), transdermal, topical, buccal, rectal, vaginal, nasal, ophthalmic, via inhalation, and implants.

The terms "pharmaceutical composition" or "therapeutic composition" as used herein refer to a compound or composition capable of inducing a desired therapeutic effect when properly administered to a subject. In some embodiments, the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one antibody of the disclosure.

Without limiting the disclosure, a number of embodiments of the disclosure are described below for purpose of illustration.

## EXAMPLES

The Examples that follow are illustrative of specific embodiments of the disclosure, and various uses thereof. They are set forth for explanatory purposes only and should not be construed as limiting the scope of the invention in any way.

### **Example 1: Durvalumab with or without Tremelimumab in Metastatic Non-Small-Cell Lung Cancer**

The MYSTIC study described herein was a phase 3 study which compared durvalumab, with or without tremelimumab, with platinum-based chemotherapy as first-line treatment for metastatic NSCLC.

#### ***Patients***

Adult patients with Stage IV NSCLC were eligible provided they had not previously received systemic therapy for advanced/metastatic NSCLC, had Eastern Cooperative Oncology Group performance status 0-1, measurable disease according to Response Evaluation Criteria in

Solid Tumors version 1.1 (RECIST v1.1) (Chaft *et al.*, *Cancer Res.* 78(13 Suppl) (abstr. CT113) (2018)), and known tumor PD-L1 expression status prior to randomization. Patients with sensitizing *EGFR* mutations or *ALK* rearrangements, and those with symptomatic, unstable brain metastases were excluded.

5

### ***Study Design and Treatment***

Patients were randomized in a 1:1:1 ratio, with stratification according to PD-L1 TC  $\geq 25\%$  versus  $< 25\%$  and histology, to receive durvalumab 20 mg/kg every 4 weeks, durvalumab 20 mg/kg plus tremelimumab 1 mg/kg every 4 weeks (up to four doses), or 4-6 cycles of platinum-based doublet chemotherapy. Patients continued treatment until objective disease progression (according to RECIST v1.1), development of an adverse event (AE) that necessitated treatment discontinuation, or withdrawal of consent.

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### ***Endpoints and Assessments***

The primary endpoints were Overall Survival (OS; time from randomization to death from any cause) for both immunotherapy arms compared with chemotherapy, and Progression Free Survival (PFS; time from randomization to objective disease progression by blinded independent central review [BICR] or death) for durvalumab plus tremelimumab compared with chemotherapy, all in patients with PD-L1 TC  $\geq 25\%$ . Primary endpoints were to be evaluated in patients with PD-L1 TC  $\geq 25\%$ . Secondary endpoints included PFS for durvalumab versus chemotherapy, objective response rate (ORR) and duration of response (DOR) for both immunotherapy arms compared with chemotherapy (all in patients with PD-L1 TC  $\geq 25\%$ ), and safety and tolerability. Investigation of the relationship between biomarkers, including TMB, and clinical outcomes were also determined.

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PD-L1 expression was evaluated using multiple cut-offs at a central laboratory using the VENTANA PD-L1 (SP263) immunohistochemistry (IHC) assay (Ventana Medical Systems, Tucson, AZ, USA) (Rebelatto *et al.*, *Diagn. Pathol.* 11(1): 95 (2016)). Tumor samples obtained within 3 months prior to screening were permitted. Strong analytical agreement has been demonstrated across the dynamic range between the Dako PD-L1 IHC 22C3 pharmDx and VENTANA PD-L1 (SP263) IHC assays (Hirsch *et al.*, *J. Thorac. Oncol.* 12(2): 208-22 (2017); Ratcliffe *et al.*, *Clin. Cancer Res.* 23(14): 3585-91 (2017)).

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Tumor response was assessed by BICR using RECIST v1.1, with imaging performed every 6 weeks for the first 48 weeks, then every 8 weeks, until confirmed disease progression. Patients were followed for survival. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

5 Blood TMB was evaluated using the GuardantOMNI next-generation sequencing platform (Guardant Health, Redwood City, CA, USA) comprised of 500 genes (Figure 1). All genes shown in Figure 1 are potential identifiers of TMB, and the relevance of each gene or combination of genes will vary by patient.

10 The OMNI TMB algorithm incorporates somatic single nucleotide variants (SNVs), short insertions/deletions (indels), copy number amplifications and fusions, and is optimized to calculate TMB on blood samples with low cell-free circulating tumor DNA content (Merck Sharp & Dohme. Keytruda® (pembrolizumab) Summary of Product Characteristics. Updated March 2019. Available at: <https://www.medicines.org.uk/emc/product/6947/smpc> (last accessed May 1, 2019); Reck *et al.*, *N. Engl. J. Med.* 375(19): 1823-33 (2016)). Both synonymous and  
15 nonsynonymous SNVs and indels were included, with removal of those with low shedding values, low diversity, and associations with clonal hematopoiesis, germline and oncogenic driver or drug resistance mechanisms. Tissue TMB was evaluated using the FoundationOne tissue next-generation sequencing platform (Foundation Medicine, Cambridge, MA, USA). The algorithm has been described previously (Merck Sharp & Dohme. Keytruda® (pembrolizumab)  
20 prescribing information. Updated April 2019. Available at: [https://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf) (last accessed May 1, 2019)).

### ***Statistical Analysis***

25 Approximately 1092 patients, including 480 with PD-L1 TC  $\geq 25\%$ , were needed to obtain 231 PFS events for the primary PFS analysis across the durvalumab plus tremelimumab and chemotherapy groups and 225 OS events for the primary OS analysis across each treatment group comparison.

30 Efficacy was analyzed on an intention-to-treat (ITT) basis, including all randomized patients or subsets of this population based on PD-L1 expression or TMB levels. Safety analyses included all patients who received at least one dose of study treatment (as-treated population).

To control the type I error at 5% (two-sided), a hierarchical multiple testing procedure with gatekeeping strategy was used across endpoints, analysis populations, and treatment regimens. The primary PFS analysis was performed using a stratified log-rank test adjusting for histology, with hazard ratio (HR) and 99.5% confidence interval (CI) estimated using a Cox proportional hazards model. The primary OS analysis was performed using similar methodology, with HRs estimated with two-sided 97.54% and 98.77% CIs for comparisons of durvalumab and durvalumab plus tremelimumab, respectively, with chemotherapy. Survival curves were generated using the Kaplan-Meier method.

For secondary analyses performed on the PD-L1 TC  $\geq 1\%$  and ITT populations, the stratification was additionally adjusted for PD-L1 expression status (TC  $\geq 25\%$  vs. TC  $< 25\%$ ). Odds ratios and 95% CI for comparing ORR between treatment groups were calculated using a logistic regression model, adjusted for the same factors as PFS and OS. Prespecified TMB analysis was performed using an unstratified log-rank test, with HRs and 95% CIs estimated using a Cox proportional hazards model.

## Results

Of 1118 randomized patients, 1092 (97.7%) received at least one dose of study treatment (369 received durvalumab, 371 durvalumab plus tremelimumab, and 352 chemotherapy). In the chemotherapy group, the most common regimen was gemcitabine plus carboplatin (49.5%) and pemetrexed plus carboplatin (54.5%) in patients with squamous and nonsquamous histology, respectively. A total of 488 patients had PD-L1 TC  $\geq 25\%$  (primary analysis population; 43.6% of randomized patients). The baseline demographics and disease characteristics of patients with PD-L1 TC  $\geq 25\%$  were generally consistent with the ITT population and balanced between treatment groups.

Among patients with PD-L1 TC  $\geq 25\%$ , 25 in the durvalumab group, 18 in the durvalumab plus tremelimumab group, and 1 in the chemotherapy group remained on study treatment. Of these patients, 5 in the durvalumab group and 1 in the durvalumab plus tremelimumab group were treated through progression, and 5 in the durvalumab plus tremelimumab group received retreatment with tremelimumab. After discontinuation of study treatment, 73 (44.8%) patients in the durvalumab group, 61 (37.4%) in the durvalumab plus tremelimumab group, and 95 (58.6%) in the chemotherapy group received subsequent systemic

cancer therapy. Among these patients, immunotherapy was received by 10 (13.7%) of 73 in the durvalumab group, 5 (8.2%) of 61 in the durvalumab plus tremelimumab group, and 64 (67.4%) of 95 in the chemotherapy group.

## 1. Efficacy

Median follow-up for OS was 30.2 months (range, 0.3-37.2). Durvalumab and durvalumab plus tremelimumab did not statistically significantly improve OS compared with chemotherapy in patients with PD-L1 TC  $\geq 25\%$ . The median OS was 16.3 months with durvalumab versus 12.9 with chemotherapy (HR for death, 0.76; 97.54% CI, 0.56-1.02;  $P=0.036$ ) (Figure 2). The 24-month OS rate was 38.3% (95% CI, 30.7-45.7) in the durvalumab group and 22.7% (16.5-29.5) with chemotherapy. Most planned patient subgroups treated with durvalumab had numerical improvement in OS versus chemotherapy (Figure 4). The median OS was 11.9 months and the 24-month OS rate was 35.4% (95% CI, 28.1-42.8) with durvalumab plus tremelimumab (HR for death vs. chemotherapy, 0.85; 98.77% CI, 0.61-1.17;  $P=0.202$ ) (Figure 2). OS in the ITT population and in subgroups defined by different PD-L1 expression levels (TC  $<1\%$ ,  $\geq 1\%$ ,  $\geq 25-49\%$ , and  $\geq 50\%$ ) is shown in Table 1.

Table 1: Overall Survival in the ITT Population and by PD-L1 Expression Subgroup.

|                                       |                                                         | <b>Durvalumab<br/>Monotherapy</b> | <b>Durvalumab +<br/>Tremelimumab</b> | <b>Chemotherapy</b> |
|---------------------------------------|---------------------------------------------------------|-----------------------------------|--------------------------------------|---------------------|
| <b>ITT population*</b>                | <b>Number of<br/>events/patients</b>                    | 278/374                           | 278/372                              | 297/372             |
|                                       | <b>Median overall<br/>survival, months<br/>(95% CI)</b> | 12.3 (10.1–14.9)                  | 11.2 (9.5–12.9)                      | 11.8 (10.5–13.3)    |
|                                       | <b>Hazard ratio (95%<br/>CI)<sup>†</sup></b>            | 0.96 (0.81–1.13)                  | 0.94 (0.79–<br>1.10) <sup>‡</sup>    | –                   |
| <b>PD-L1 TC <math>\geq 1\%</math></b> | <b>Number of patients</b>                               | 194/279                           | 221/296                              | 226/289             |
|                                       | <b>Median overall<br/>survival, months<br/>(95% CI)</b> | 14.6 (10.5–17.7)                  | 10.9 (9.1–13.5)                      | 12.3 (10.6–14.6)    |
|                                       | <b>Hazard ratio (95%</b>                                | 0.88 (0.73–                       | 1.01 (0.83–                          | –                   |

|                         |                                                 |                               |                               |                  |
|-------------------------|-------------------------------------------------|-------------------------------|-------------------------------|------------------|
|                         | CI) <sup>†</sup>                                | 1.07) <sup>§</sup>            | 1.21) <sup>‡</sup>            |                  |
| <b>PD-L1 TC ≥25–49%</b> | <b>Number of patients</b>                       | 33/45                         | 45/55                         | 46/55            |
|                         | <b>Median overall survival, months (95% CI)</b> | 11.1 (6.2–22.5)               | 10.5 (5.3–16.7)               | 13.3 (8.4–16.3)  |
|                         | <b>Hazard ratio (95% CI)<sup>†</sup></b>        | 0.78 (0.49–1.23)              | 0.95 (0.62–1.45)              | –                |
| <b>PD-L1 TC ≥50%</b>    | <b>Number of patients</b>                       | 75/118                        | 68/108                        | 82/107           |
|                         | <b>Median overall survival, months (95% CI)</b> | 18.3 (13.6–22.8)              | 15.2 (8.0–26.5)               | 12.7 (10.3–15.1) |
|                         | <b>Hazard ratio (95% CI)<sup>†</sup></b>        | 0.76 (0.55–1.04) <sup>§</sup> | 0.77 (0.56–1.07) <sup>§</sup> | –                |
| <b>PD-L1 TC &lt;1%</b>  | <b>Number of patients</b>                       | 84/95                         | 57/76                         | 71/83            |
|                         | <b>Median overall survival, months (95% CI)</b> | 10.1 (6.7–12.2)               | 11.9 (9.3–18.6)               | 10.3 (7.9–12.9)  |
|                         | <b>Hazard ratio (95% CI)<sup>†</sup></b>        | 1.18 (0.86–1.62) <sup>§</sup> | 0.73 (0.51–1.04) <sup>§</sup> | –                |

\*The ITT population includes all randomized patients. <sup>†</sup>Hazard ratio for death compared with chemotherapy. <sup>‡</sup>Secondary endpoint. <sup>§</sup>Prespecified subgroup analysis. CI, confidence interval; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; TC, tumor cell.

5 Median follow-up for PFS was 10.6 months (range, 0–18). There was no statistically significant difference in PFS between the durvalumab and chemotherapy groups (secondary endpoint; Figure 3) or between durvalumab plus tremelimumab and chemotherapy groups (primary endpoint; Figure 3). Median PFS was 3.9 months (95% CI, 2.8–5.0) with durvalumab plus tremelimumab versus 5.4 (4.6–5.8) with chemotherapy (HR for disease progression or death, 10 1.05; 99.5% CI, 0.72–1.53; P=0.705); the 12-month PFS rate was 25.8% (95% CI, 18.9–33.1) with durvalumab plus tremelimumab versus 14.3% (8.4–21.7) with chemotherapy.

ORR among patients with PD-L1 TC ≥25% was 35.6% in the durvalumab group, 34.4% in the durvalumab plus tremelimumab group, and 37.7% in the chemotherapy group (Table 2). The median DOR was not reached in the immunotherapy arms versus 4.4 months with 15 chemotherapy. More patients remained in response at 12 months in the immunotherapy

treatment groups (61.3%, 54.9%, and 18.0% in the durvalumab, durvalumab plus tremelimumab, and chemotherapy arms, respectively) (Table 2).

Table 2: Summary of Tumor Response among Patients with PD-L1 TC  $\geq 25\%$ .

|                                                                           | <b>Durvalumab<br/>Monotherapy<br/>(n=163)</b> | <b>Durvalumab plus<br/>Tremelimumab<br/>(n=163)</b> | <b>Chemotherapy<br/>(n=162)</b> |
|---------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------|---------------------------------|
| <b>ORR<sup>*,†</sup>, n (%)</b>                                           | 58 (35.6)                                     | 56 (34.4)                                           | 61 (37.7)                       |
| <b>Estimated odds ratio vs.<br/>chemotherapy (95%<br/>CI)<sup>‡</sup></b> | 0.91<br>(0.58–1.44)                           | 0.87<br>(0.55–1.36)                                 | –                               |
| <b>Best objective response, n<br/>(%)</b>                                 |                                               |                                                     |                                 |
| <b>Complete response<sup>†</sup></b>                                      | 1 (0.6)                                       | 0                                                   | 0                               |
| <b>Partial response<sup>†</sup></b>                                       | 57 (35.0)                                     | 56 (34.4)                                           | 61 (37.7)                       |
| <b>Stable disease <math>\geq 6</math> weeks</b>                           | 50 (30.7)                                     | 45 (27.6)                                           | 66 (40.7)                       |
| <b>Progressive disease</b>                                                | 53 (32.5)                                     | 59 (36.2)                                           | 25 (15.4)                       |
| <b>Not evaluable</b>                                                      | 2 (1.2)                                       | 3 (1.8)                                             | 10 (6.2)                        |
| <b>Median DOR<sup>§</sup>, months<br/>(95% CI)</b>                        | NR (9.7–NR)                                   | NR (6.7–NR)                                         | 4.4 (3.5–5.5)                   |
| <b>Remaining in response<br/>(%) at:</b>                                  |                                               |                                                     |                                 |
| <b>6 months</b>                                                           | 66.9                                          | 67.6                                                | 32.4                            |
| <b>12 months</b>                                                          | 61.3                                          | 54.9                                                | 18.0                            |

Primary analysis population. \*ORR by blinded independent central review per RECIST v1.1 is defined as the number (%) of patients with at least 1 visit response of complete response or partial response. <sup>†</sup>Responses included unconfirmed responses. <sup>‡</sup>Analysis was performed using logistic regression adjusting for histology (squamous vs. all other), with 95% CI calculated by profile likelihood. An odds ratio  $>1$  favors immunotherapy. <sup>§</sup>DOR was calculated using the Kaplan–Meier technique and was defined as the time from the first documentation of complete response/partial response until the date of progression, death or the last evaluable RECIST assessment for patients that do not progress or for patients who progress or die after two or more missed visits. CI, confidence interval; DOR, duration of response; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TC, tumor cell.

Blood and tissue pretreatment samples from 809 (72%) and 460 (41%) of 1118 randomized patients, respectively, were evaluable for TMB. TMB values did not correlate with PD-L1 expression levels (blood: Spearman's  $\rho = 0.05$ , Pearson's  $r = 0.01$ ; tissue: Spearman's  $\rho = 0.09$ , Pearson's  $r = 0.06$ ). Among patients with matched samples (n=352; 31% of randomized patients), bTMB and tTMB were correlated (Spearman's  $\rho = 0.6$ , Pearson's  $r = 0.7$ ; Figure 5). Baseline characteristics in the bTMB and tTMB evaluable populations were consistent with the ITT population and balanced between treatment groups. OS in the TMB evaluable populations was consistent with the ITT population in the three treatment arms (Figures 6A-6C). HR for death improved gradually as the bTMB threshold was increased for durvalumab plus tremelimumab versus chemotherapy (Figures 7-8). Blood TMB  $\geq 20$  mut/Mb

was selected for further analysis based on a clinically relevant effect size for durvalumab plus tremelimumab and the patient population deriving benefit. For context, tTMB  $\geq 10$  mut/Mb was studied based on a threshold shown to be predictive for PFS and response in previous trials of nivolumab plus ipilimumab in NSCLC (Hellmann *et al.*, *N. Engl. J. Med.* 378(22): 2093-104 (2018); Ready *et al.*, *J. Clin. Oncol.* 37(12): 992-1000 (2019)). Further analyses at tTMB thresholds above 10 mut/Mb were limited by small sample sizes. In patients with bTMB  $\geq 20$  mut/Mb or tTMB  $\geq 10$ , there were greater proportions of patients with a smoking history and squamous histology compared with the corresponding lower TMB subgroups. Overlap between the bTMB  $\geq 20$  mut/Mb population and the PD-L1 TC  $\geq 25\%$  population was minimal (9% of randomized patients; Figure 9).

Blood TMB  $\geq 20$  mut/Mb was associated with improved OS for durvalumab plus tremelimumab versus chemotherapy (median, 21.9 vs. 10.0 months; unadjusted HR for death, 0.49 [95% CI, 0.32-0.74]; Figure 10); 24-month OS rates were 48.1% (95% CI, 35.5-59.7) with durvalumab plus tremelimumab versus 19.4% (11.0-29.5) with chemotherapy. In contrast, there was no improvement in OS for durvalumab plus tremelimumab versus chemotherapy in patients with bTMB  $< 20$  mut/Mb (median, 8.5 vs. 11.6 months; unadjusted HR for death, 1.16 [95% CI, 0.93-1.45]; Figure 10). Blood TMB  $\geq 20$  mut/Mb, but not bTMB  $< 20$  mut/Mb, was also associated with improved PFS (Figure 11) and ORR (Table 3) for durvalumab plus tremelimumab versus chemotherapy.

Table 3: Analysis of Tumor Response among Patients with Blood TMB  $\geq 20$  mut/Mb and  $< 20$  mut/Mb.

|                                                                                 | Blood TMB $\geq 20$ mut/Mb    |                                  |                     | Blood TMB $< 20$ mut/Mb        |                                   |                      |
|---------------------------------------------------------------------------------|-------------------------------|----------------------------------|---------------------|--------------------------------|-----------------------------------|----------------------|
|                                                                                 | Durvalumab Monotherapy (n=77) | Durvalumab + Tremelimumab (n=64) | Chemotherapy (n=70) | Durvalumab Monotherapy (n=209) | Durvalumab + Tremelimumab (n=204) | Chemotherapy (n=185) |
| <b>ORR*, n (%)</b>                                                              | 23 (29.9)                     | 31 (48.4)                        | 15 (21.4)           | 43 (20.6)                      | 34 (16.7)                         | 58 (31.4)            |
| <b>Estimated odds ratio immunotherapy vs. chemotherapy (95% CI)<sup>†</sup></b> | 1.56 (0.74–3.36)              | 3.44 (1.65–7.46)                 |                     | 0.57 (0.36–0.89)               | 0.44 (0.27–0.71)                  |                      |
| <b>Estimated odds ratio combination therapy vs.</b>                             |                               | 2.21 (1.11–4.45)                 |                     |                                | 0.77 (0.47–1.27)                  |                      |

|                                                    |            |            |               |             |               |               |
|----------------------------------------------------|------------|------------|---------------|-------------|---------------|---------------|
| <b>durvalumab<br/>(95% CI)<sup>†</sup></b>         |            |            |               |             |               |               |
| <b>Median DOR<sup>‡</sup>,<br/>months (95% CI)</b> | NR (NR–NR) | NR (NR–NR) | 4.1 (3.0–4.3) | NR (5.9–NR) | 11.1 (5.6–NR) | 4.1 (2.8–5.6) |
| <b>Remaining in<br/>response (%) at:</b>           |            |            |               |             |               |               |
| <b>6 months</b>                                    | 86.5       | 85.6       | 14.4          | 64.0        | 66.6          | 33.3          |
| <b>12 months</b>                                   | 80.3       | 81.7       | 7.2           | 59.1        | 48.2          | 14.3          |

Primary analysis population. \*ORR by blinded independent central review per RECIST v1.1 is defined as the number (%) of patients with at least 1 visit response of complete response or partial response. Responses included unconfirmed responses.

<sup>†</sup>Analysis was performed using logistic regression, with 95% CI calculated by profile likelihood. An odds ratio >1 favors the first comparator listed. <sup>‡</sup>DOR was calculated using the Kaplan–Meier technique and was defined as the time from the first documentation of complete response/partial response until the date of progression, death or the last evaluable RECIST assessment for patients that do not progress or for patients who progress or die after two or more missed visits. CI, confidence interval; DOR, duration of response; Mb, megabase; mut, mutations; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand-1; TC, tumor cell; TMB, tumor mutational burden.

For patients with bTMB  $\geq 20$  mut/Mb receiving durvalumab alone, the median OS was 12.6 months (unadjusted HR for death vs. chemotherapy, 0.72; 95% CI, 0.50–1.05). The HR for death for durvalumab plus tremelimumab versus durvalumab was 0.74 (95% CI, 0.48–1.11; Figure 10) supporting an additional contribution of tremelimumab.

Tissue TMB  $\geq 10$  mut/Mb, but not tTMB  $< 10$  mut/Mb, was associated with numerically longer OS in both immunotherapy groups versus chemotherapy. The median OS was 16.6 months with durvalumab plus tremelimumab, 18.6 with durvalumab, and 11.9 with chemotherapy. The HR for death was 0.72 (95% CI, 0.48–1.09) for durvalumab plus tremelimumab versus chemotherapy and 0.70 (0.47–1.06) for durvalumab versus chemotherapy (Figures 12A–12B).

Two blood-based algorithms showed improvement of outcomes for D+T as compared to chemotherapy (V2 and V3; *see* Figure 13). The V2 algorithm was selected for its simplicity over V3, though both showed similar predictive potential.

TMB was more predictive of OS than level of PD-L1 expression for D+T in MYSTIC regardless of the cut point used. This did not correlate with high PD-L1 expression, and thus, unique patient subsets were identified with bTMB (Figure 9). Additionally, the combination of bTMB and PD-L1 expression increases the patient prevalence but reduces the effect size (Figures 16 and 17).

## 2. Safety

The median actual duration of treatment was 16.0 weeks (range, 0.4-148.6) for durvalumab; 16.0 (0.6-161.3) and 12.0 weeks (0.6-32.0) for durvalumab and tremelimumab, respectively, in the combination arm; and 17.9 weeks (1.1-137.4) for chemotherapy.

All-grade AEs that were considered by the investigator to be treatment-related (TRAEs) occurred in 54.2%, 60.1%, and 83.0% of patients treated with durvalumab, durvalumab plus tremelimumab, and chemotherapy, respectively. Rates of grade  $\geq 3$  TRAEs were lower with durvalumab (14.9%) and durvalumab plus tremelimumab (22.9%) than with chemotherapy (33.8%), and fewer patients had TRAEs leading to discontinuation in the durvalumab group (5.4% vs. 13.2% and 9.4%, respectively). Treatment-related deaths occurred in 2 patients (0.5%) in the durvalumab group, 6 (1.6%) in the durvalumab plus tremelimumab group, and 3 (0.9%) in the chemotherapy group. Safety in the PD-L1 TC  $\geq 25\%$  primary analysis population and the bTMB  $\geq 20$  mut/Mb population was consistent with the overall safety population.

Immune-mediated AEs were reported in 13.6% of patients in the durvalumab group, 28.3% in the durvalumab plus tremelimumab group, and 3.4% in the chemotherapy group. These events were of grade 3 or 4 in 4.1%, 10.8%, and 0.6% of patients, respectively.

Analyses identified a bTMB threshold of  $\geq 20$  mut/Mb for optimal OS benefit and clinically meaningful improvement in both PFS and response with durvalumab plus tremelimumab in this study.

### **Example 2: Mutations in ctDNA associated with sensitivity or resistance to immunotherapy in mNSCLC: analysis from the MYSTIC trial**

This example investigated associations between selected mutations and survival outcomes. Circulating tumour DNA from baseline plasma specimens was profiled using the GuardantOMNI platform. Samples were available from 1003 patients (89.7% of ITT population). 943 samples were mutation-evaluable. Survival outcomes were analysed in patients with or without non-synonymous somatic mutations in *STK11*, *KEAP1*, or *ARID1A*, or *KRAS*.

The study demonstrated that poorer outcomes were observed across treatment arms in patients with metastatic NSCLC ("mNSCLC") and mutations in serine/threonine kinase 11 gene

(*STK11*) or Kelch-like ECH-associated protein 1 gene (*KEAP1*) as compared to those without the corresponding mutations. In patients receiving D+T, AT-rich interactive domain-containing protein 1A gene mutation (*ARID1A*m) was associated with survival benefits as compared with AT-rich interactive domain-containing protein 1A wild type gene (*ARID1A*wt).

- 5 In the mutation-evaluable population, *STK11*m, *KEAP1*m, and *ARID1A*m frequencies were 16%, 18%, and 12%, respectively (19%, 20%, and 11% [nonsquamous]; 7%, 13%, and 15% [squamous]) (Figures 18-21). Across treatment arms, patients with *STK11*m or *KEAP1*m had a shorter median OS ("mOS") than patients with *STK11*wt (D, 10.3 vs 13.3 months; D+T, 4.4 vs 11.3 months; CT, 6.7 vs 13.1 months) or *KEAP1*wt (D, 7.6 vs 14.6 months; D+T, 9.2 vs 11.3  
10 months; CT, 6.3 vs 13.3 months) mNSCLC (Figures 22-27). In the D+T arm, patients with *ARID1A*m had a longer mOS than patients with *ARID1A*wt mNSCLC (D, 8.6 vs 13.7 months; D+T, 23.2 vs 9.8 months; CT, 10.6 vs 12.4 months) (Figures 28-29).

- All patents and publications mentioned in this specification are herein incorporated by  
15 reference to the same extent as if each independent patent and publication was specifically and individually indicated to be incorporated by reference. Citation or identification of any reference in any section of this application shall not be construed as an admission that such reference is available as prior art to the present invention.

**What is claimed is:**

Claim 1: A method of predicting success of cancer treatment in a patient in need thereof,  
5 comprising determining the patient's tumor mutational burden (TMB), wherein a high TMB predicts success of treatment.

Claim 2: The method of claim 1, wherein a high TMB is defined as  $\geq 12$  to  $\geq 20$  mutations/megabase (mut/Mb).

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Claim 3: The method of claim 2, wherein a high TMB is defined as  $\geq 16$  mutations/megabase (mut/Mb).

Claim 4: The method of claim 2, wherein a high TMB is defined as  $\geq 20$  mutations/megabase (mut/Mb).

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Claim 5: The method of claim 1, wherein the cancer treatment comprises treatment with durvalumab.

Claim 6: The method of claim 5, wherein the cancer treatment further comprises treatment with tremelimumab.

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Claim 7: The method of claim 5 or claim 6, wherein the cancer treatment further comprises treatment with a chemotherapy agent.

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Claim 8: The method of claim 7, wherein the chemotherapy agent comprises at least one of abraxane, carboplatin, gemcitabine, cisplatin, pemetrexed, or paclitaxel.

Claim 9: The method of claim 1, wherein the patient has a somatic mutation in at least one  
30 of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene.

Claim 10: A method of treating cancer in a patient in need thereof, comprising:

- (a) determining the patient's TMB;
- (b) determining whether the TMB is high or low; and
- (c) treating or continuing treatment if TMB is high or not treating or discontinuing treatment if TMB is low.

Claim 11: The method of claim 10, wherein a high TMB is defined as  $\geq 12$  to  $\geq 20$  mutations/megabase (mut/Mb).

Claim 12: The method of claim 11, wherein a high TMB is defined as  $\geq 16$  mutations/megabase (mut/Mb).

Claim 13: The method of claim 11, wherein a high TMB is defined as  $\geq 20$  mutations/megabase (mut/Mb).

Claim 14: The method of claim 10, wherein the treatment comprises treatment with durvalumab.

Claim 15: The method of claim 14, wherein the treatment further comprises treatment with tremelimumab.

Claim 16: The method of claim 14 or claim 15, wherein the treatment further comprises treatment with a chemotherapy agent.

Claim 17: The method of claim 16, wherein the chemotherapy agent comprises at least one of abraxane, carboplatin, gemcitabine, cisplatin, pemetrexed, or paclitaxel.

Claim 18: The method of claim 1 or claim 10, wherein success of treatment is determined by an increase in OS as compared to standard of care.

Claim 19: The method of claim 10, wherein the patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene.

5 Claim 20: A method of predicting success of cancer treatment in a patient in need thereof, comprising determining if the patient has a somatic mutation in AT-rich interactive domain-containing protein 1A gene (*ARID1A*), wherein a somatic mutation predicts success of treatment.

10 Claim 21: The method of claim 20, wherein the cancer treatment comprises treatment with durvalumab.

Claim 22: The method of claim 20, wherein the cancer treatment further comprises treatment with tremelimumab.

15 Claim 23: The method of claim 21 or claim 22, wherein the cancer treatment further comprises treatment with a chemotherapy agent.

20 Claim 24: The method of claim 23, wherein the chemotherapy agent comprises at least one of abraxane, carboplatin, gemcitabine, cisplatin, pemetrexed, or paclitaxel.

Claim 25: A method of treating cancer in a patient in need thereof, comprising:  
(a) determining whether the patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene; and  
25 (b) treating or continuing treatment if patient has a somatic mutation in at least one of serine/threonine kinase 11 gene (*STK11*), Kelch-like ECH-associated protein 1 gene (*KEAP1*), AT-rich interactive domain-containing protein 1A gene (*ARID1A*), or *K-Ras* gene.

30 Claim 26: The method of claim 25, wherein the treatment comprises treatment with durvalumab.

Claim 27: The method of claim 26, wherein the treatment further comprises treatment with tremelimumab.

Claim 28: The method of claim 26 or claim 27, wherein the treatment further comprises  
5 treatment with a chemotherapy agent.

Claim 29: The method of claim 28, wherein the chemotherapy agent comprises at least one of abraxane, carboplatin, gemcitabine, cisplatin, pemetrexed, or paclitaxel.

|        |        |         |         |        |         |        |        |         |         |         |          |                                      |
|--------|--------|---------|---------|--------|---------|--------|--------|---------|---------|---------|----------|--------------------------------------|
| ABL1   | ABL2   | ACVR1B  | ACVR2A  | ADARB2 | ADRBAG  | ADRBG4 | AEDN   | AKT1    | AKT1S1  | AKT2    | AKT3     | Complete<br>Partial<br>Fusion<br>CNV |
| ALB    | ALK    | ALOX12B | ALOX15B | ALOX5  | AMER1   | APC    | APEX1  | AR      | ARAF    | ARHGAP1 | ARHGAP35 |                                      |
| ARID1A | ARID1B | ARID2   | ASK1    | ATM    | ATR     | ATRX   | AURKA  | AURKB   | AXIN1   | AXIN2   | AXL      |                                      |
| B3M    | BAP1   | BARD1   | BCL2    | BCL2L1 | BCL2L2  | BCL6   | BCOR   | BCORL1  | BCR     | BRD3    | B3M      |                                      |
| BRAF   | BRCA1  | BRCA2   | BRI2    | BRI3   | BRI4    | BRI1   | SIG1   | BRD2    | BTB     | RUSB    | CARD11   | Complete<br>Partial<br>Fusion<br>CNV |
| CASP8  | CASP9  | CBL     | CBLB    | CCND1  | CCND2   | CCND3  | CCNE1  | CD274   | CD79A   | CD79B   | CDC7     |                                      |
| CDC73  | CDH1   | CDK12   | CDK4    | CDK6   | CDK9    | CDKN1A | CDKN1B | CDKN2A  | CDKN2C  | CEBPA   | CEP350   |                                      |
| CHEK1  | CHEK2  | CIC     | CICB    | CHREBP | CHL     | CHL1   | CSF1R  | CTCF    | CTLA4   | CTNNA3  | CTNNA1   |                                      |
| CUL3   | CUX1   | CUX2    | DAXX    | DDR1   | DDR2    | DDR2   | DEPDC5 | DEPTOR  | DCEB1   | DLI4    | DNMT3A   | Complete<br>Partial<br>Fusion<br>CNV |
| DOT1L  | DYRK2  | E2F3    | ECOTL   | EGFR   | EF1A1   | EIF4A1 | EIF4A2 | EIF4A3  | EIF4B   | EIF4E   | EIF4E2   |                                      |
| ELF3   | EMIL4  | EMSY    | EP300   | EPCAM  | EPHA3   | EPHA5  | EPHA7  | EPH8    | ERBB2   | ERBB3   | ERBB4    |                                      |
| ERCC1  | ERCC2  | ERCC3   | ERCC4   | ERCC6  | ERCC8   | ERCC8  | ERG    | ESRR1   | ESR1    | ETV1    | ETV4     |                                      |
| ETV5   | ETV6   | ETV6    | ETV6    | EZH2   | FAAP100 | FAAP20 | FAAP24 | FAM175A | FAM175C | FANCA   | FANCB    | Complete<br>Partial<br>Fusion<br>CNV |
| FANCD1 | FANCD2 | FANCD3  | FANCF   | FANCG  | FANCI   | FANCL  | FANCM  | FAS     | FAT1    | FBXW7   | FEN1     |                                      |
| FGF10  | FGF14  | FGF19   | FGF23   | FGF3   | FGF4    | FGF6   | EGFR1  | EGFR2   | EGFR3   | FGFR4   | FGFR4    |                                      |
| FLCN   | FLT1   | FLT3    | FLT4    | FOXO1  | FOXO2   | FOXO3  | FOXO1  | FRS2    | FRS3    | FZD1    | FZD10    |                                      |
| FZD2   | FZD3   | FZD4    | FZD5    | FZD6   | FZD7    | FZD8   | FZD8   | GAS8    | GATA1   | GATA2   | GATA3    | Complete<br>Partial<br>Fusion<br>CNV |
| GATA6  | GEN1   | GSD4    | GNA11   | GNA13  | GNAQ    | GNAS   | GRB2   | GSK3B   | HDAC2   | HELO    | HES1     |                                      |
| HEY1   | HEYL   | HGF     | HISTH3G | HNF1A  | HNRAS   | HNRAS  | IDH1   | IDH2    | IDO1    | IFNG    | IFNGR1   |                                      |
| IFNGR2 | IGF1   | IGF1R   | IGF2    | IGF2R  | IGF3    | IGF3   | IL2RG  | IL7R    | INBA    | INPP4B  | IRF1     |                                      |
| IGF4   | IGF5   | JAK1    | JAK2    | JAK3   | JUN     | KAT5A  | KDMA   | KDMA    | KDM5B   | KDM5C   | KDM6A    | Complete<br>Partial<br>Fusion<br>CNV |
| KDR    | KEAP1  | KIT     | KLHL3   | KMT2A  | KMT2D   | KMT2D  | KRAS   | LGR4    | LGR5    | LGR6    | LIG1     |                                      |
| LG4    | LMO1   | LRP1B   | LRP2    | LRP5   | LRP6    | MAD2L2 | MAP2K1 | MAP2K2  | MAP2K4  | MAP3K1  | MAP4K3   |                                      |

Figure 1

|         |          |         |         |         |         |         |        |        |         |         |         |
|---------|----------|---------|---------|---------|---------|---------|--------|--------|---------|---------|---------|
| MAPK1   | MAPK3    | MAPKAP1 | MAPK    | MCL1    | MCC1    | MDM2    | MDM4   | MED12  | MEF2B   | MEN1    | MEIK1   |
| MEI     | MITF     | MLH1    | MLH3    | MLST8   | MPL     | MDM4    | MDM4   | MSH2   | MSH3    | MSH6    | MTOR    |
| MUTYH   | MAS      | MYC     | MYCL    | MYCN    | MYD88   | MSH     | NF1    | NF2    | NFE2L2  | NFSA    | NFEB1   |
| NKX2-1  | NOTCH1   | NOTCH2  | NOTCH3  | NOTCH4  | NPM1    | NPRL2   | NPRL3  | NRAS   | NG2     | NTRK1   | NTRK2   |
| NTRK3   | NUMB     | NUP93   | NUTM1   | NKX3    | PALB2   | PARG    | PARP1  | P492   | PAX5    | PBRM1   | PCDH15  |
| PDCD1   | PDCD1LG2 | PDCD4   | PDCD4   | PDCD4   | PDCD4   | PIAS4   | PIK3CB | PIK3CA | PIK3CB  | PIK3CD  | PIK3CG  |
| PK3R1   | PK3R2    | PK3R3   | PIM1    | PIN1    | PIM1    | PLEKHS1 | PLG1   | PMS2   | POLD1   | POLE    | POLH    |
| POLO    | POU2F2   | PPARG   | PPM1D   | PPP2R1A | PPP2R2A | PPP3CA  | PPP3CA | PPP3C  | PRDM1   | PREX1   | PREX2   |
| PTEN    | PTEN     | PTEN    | PTCH1   | PTEN    | PTEN    | PTEN    | RAC1   | RAC1B  | RAC1    | RAC2    | RAD51   |
| RAD51B  | RAD51C   | RAD51D  | RAD51E  | RAD51L  | RAF1    | RARA    | RASA1  | RB1    | RBM10   | REI1    | REV3L   |
| RGS1    | RHEB     | RHOA    | RHOB    | RICTOR  | RIT1    | RNF43   | ROBO1  | ROBO2  | ROS1    | ROSA1   | RPS27A  |
| RPS6KA3 | RPS8KB1  | RPTOR   | RRAGC   | RSP01   | RSP04   | RUNX1   | RLKAT1 | SDH3   | SDH3    | SDH3    | SESN2   |
| SETD2   | SF3B1    | SF3B1   | SLC34A2 | SLC11   | SLC11   | SMAD2   | SMAD3  | SMAD4  | SMARCA2 | SMARCA4 | SMARCB1 |
| SMO     | SOC1     | SOC3    | SOC1    | SOC10   | SOC2    | SOX9    | SPEN   | SPOP   | SRC     | SRPF    | SRV     |
| STAG2   | STAT3    | STAT4   | STK11   | STN19   | SUFU    | STK     | TBC1D7 | TEK    | TEK     | TERF    | TET2    |
| TGFBR2  | TM6SF2   | TM6SF2  | TM6SF2  | TM6SF2  | TM6SF2  | TOP1    | TOP2A  | TP53   | TP53BP1 | TP53    | TP53    |
| TRAF3   | TSC1     | TSC2    | TSHR    | TSHR    | TSHR    | UCAF1   | UGT1   | UGT1   | UGT1    | VHL     | WEE1    |
| WDR3    | WRN      | WT1     | WDR3    | XPA     | XPC     | XPO1    | XPC1   | XRCC2  | XRCC3   | XRCC4   | XRCC6   |
| XPC     | XPA      | ZNF217  | ZNF703  | ZNF3    | ZNF3    |         |        |        |         |         |         |

Complete

Partial

Fusion

CNV

Figure 1 cont'd.

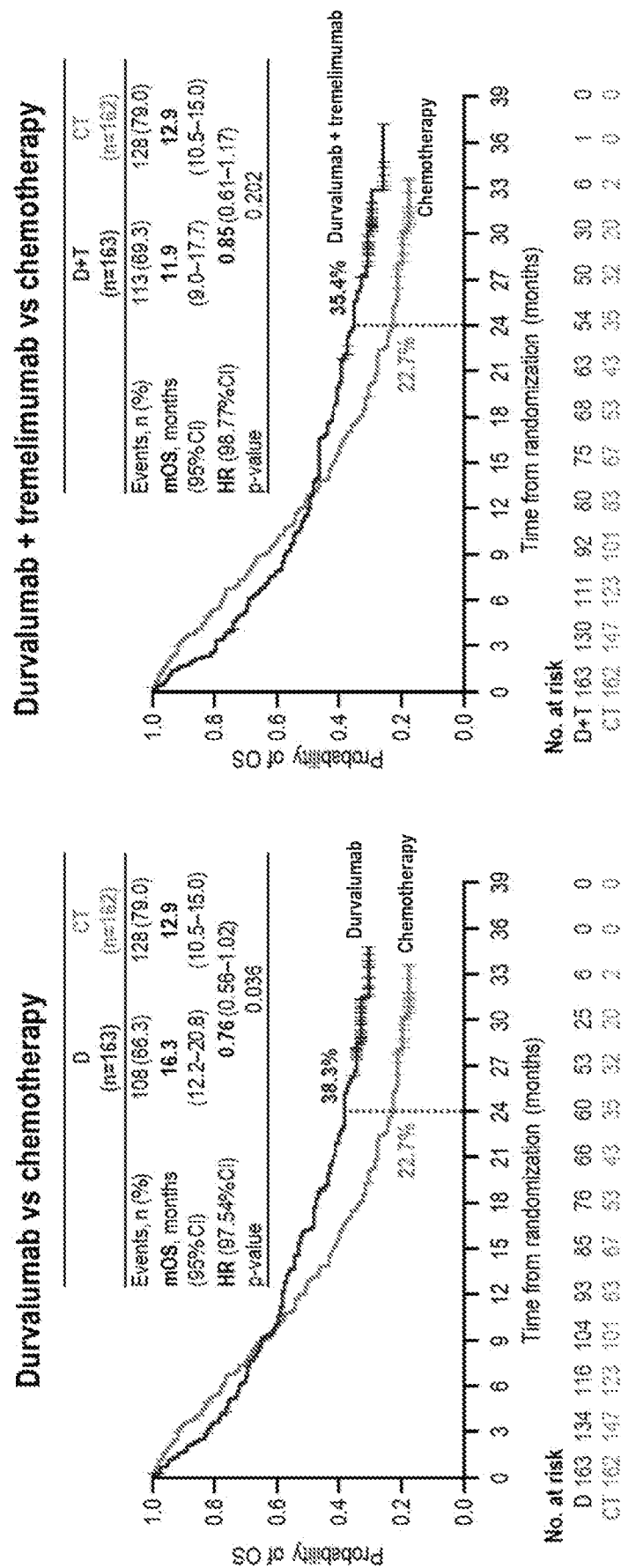
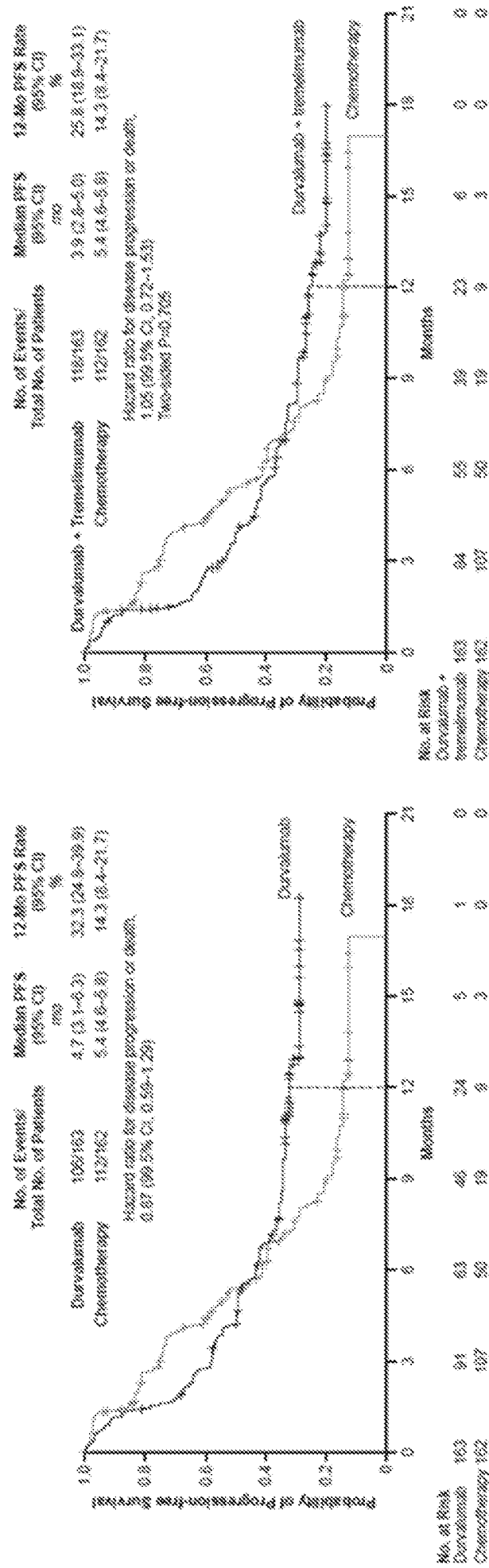


Figure 2



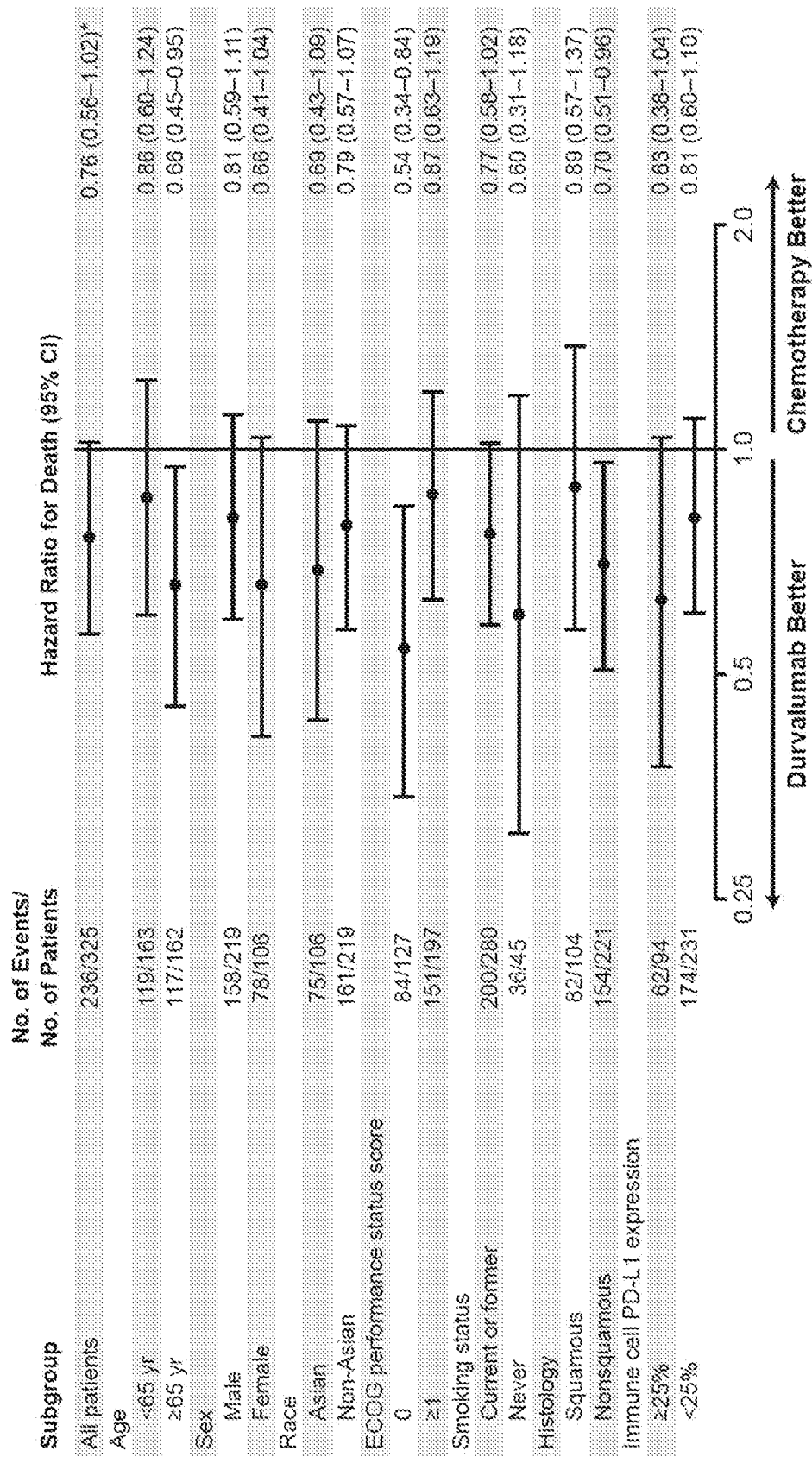


Figure 4

|                                 | Durvalumab<br>Monotherapy<br>(n=374) | Durvalumab +<br>Tremelimumab<br>(n=372) | Chemotherapy<br>(n=372) | Total<br>(n=1118) |
|---------------------------------|--------------------------------------|-----------------------------------------|-------------------------|-------------------|
| Tissue samples available, n (%) | 242 (64.7)                           | 253 (68.0)                              | 240 (64.5)              | 735 (65.7)        |
| Tissue TMB evaluable, n (%)     | 145 (38.8)                           | 164 (44.1)                              | 151 (40.6)              | 460 (41.1)        |
| Blood samples available, n (%)  | 338 (90.4)                           | 338 (90.9)                              | 327 (87.9)              | 1003 (89.7)       |
| Blood TMB evaluable, n (%)      | 286 (76.5)                           | 268 (72.0)                              | 255 (68.5)              | 809 (72.4)        |

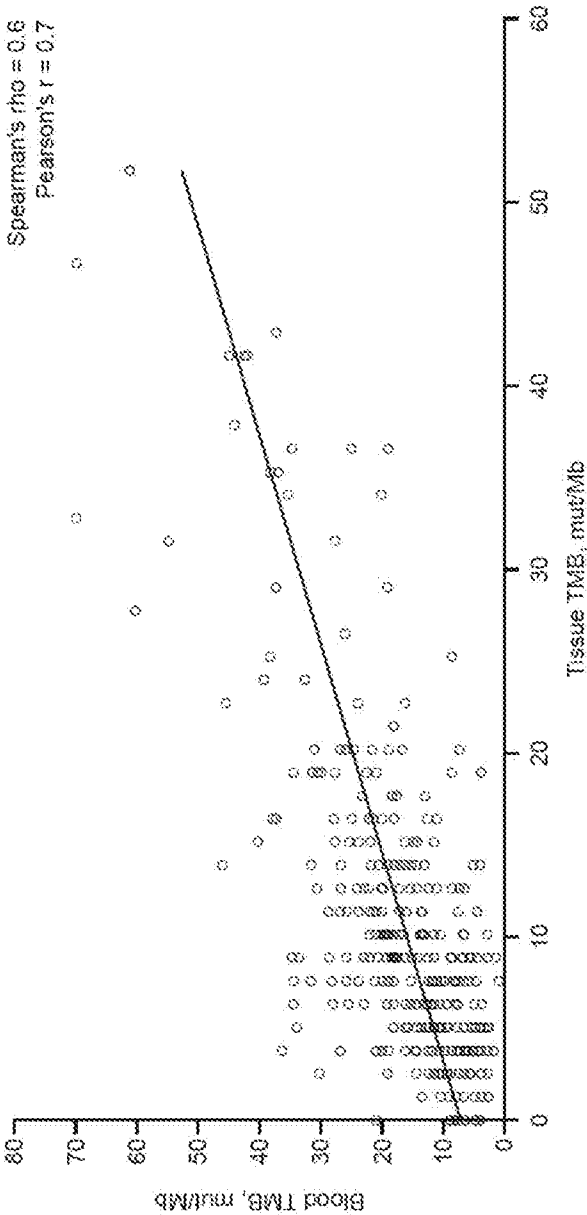


Figure 5

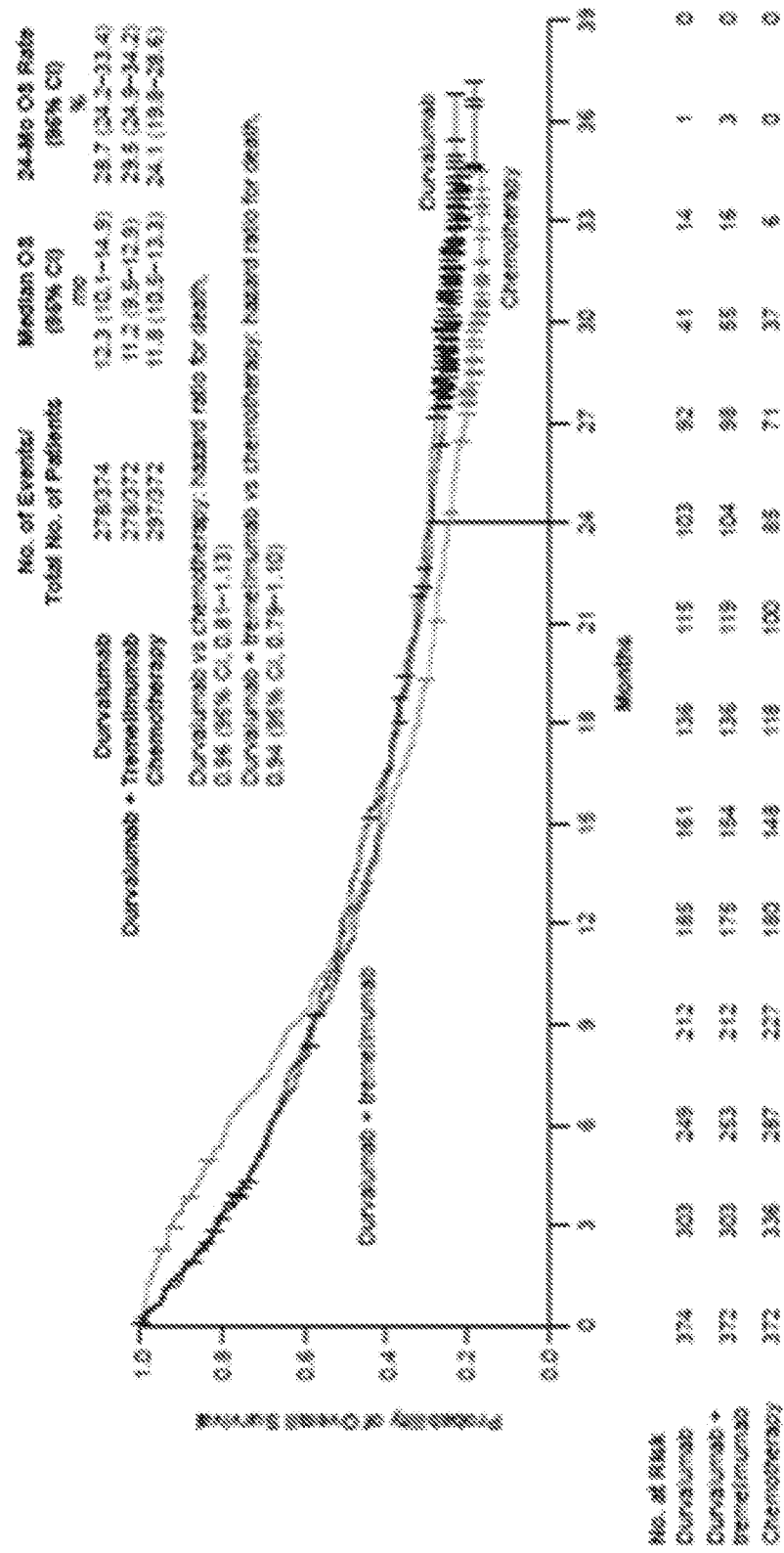


Figure 6A

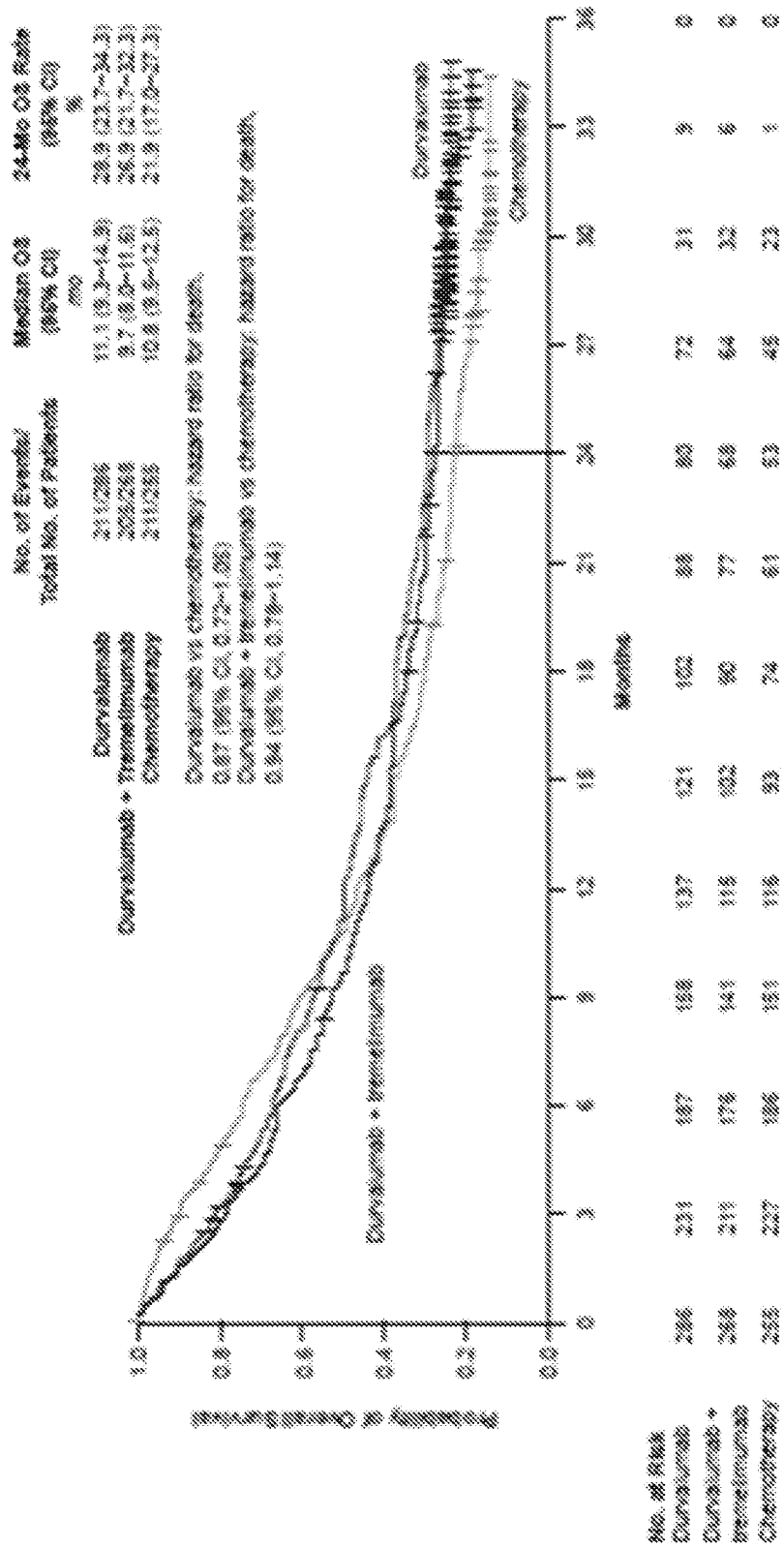


Figure 6B

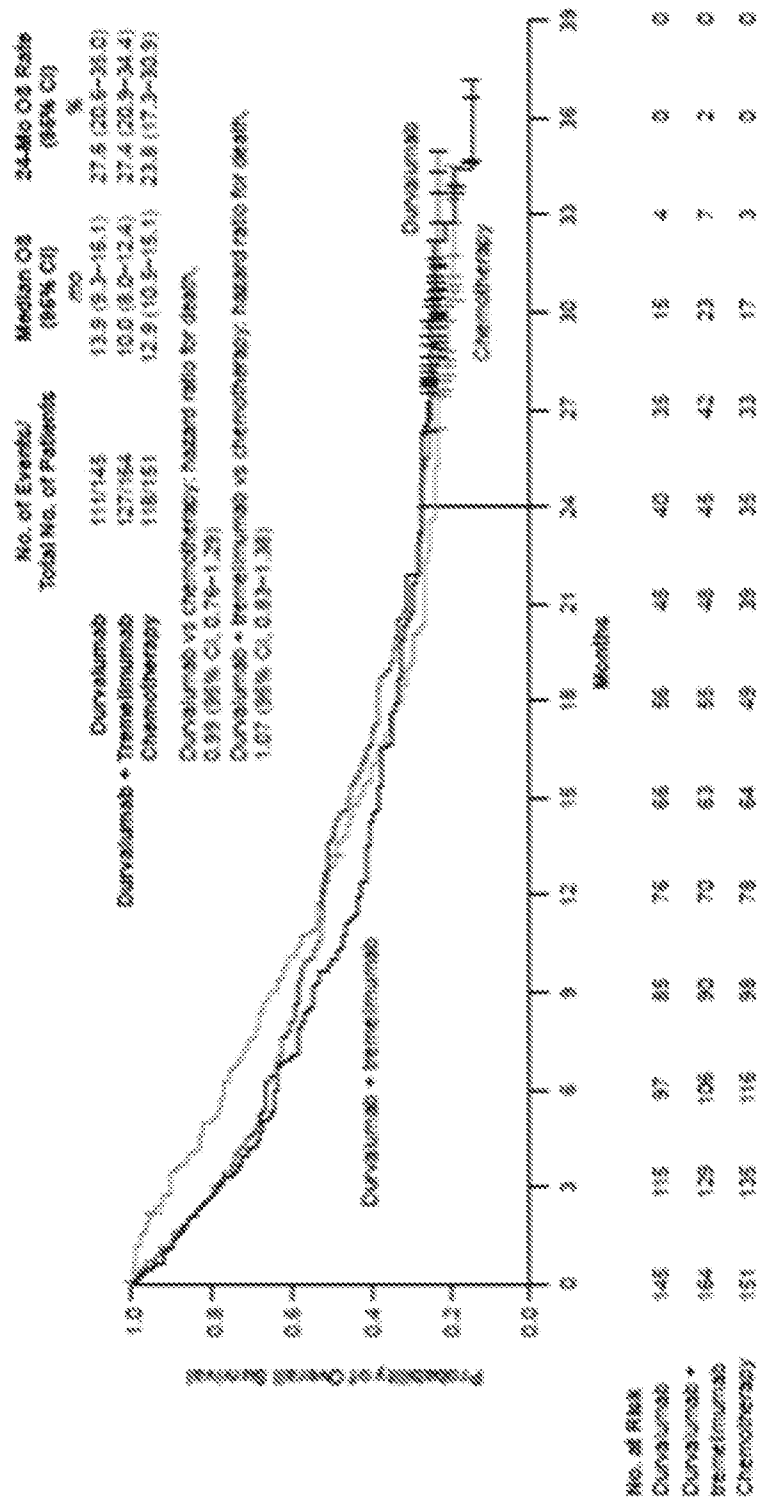


Figure 6C

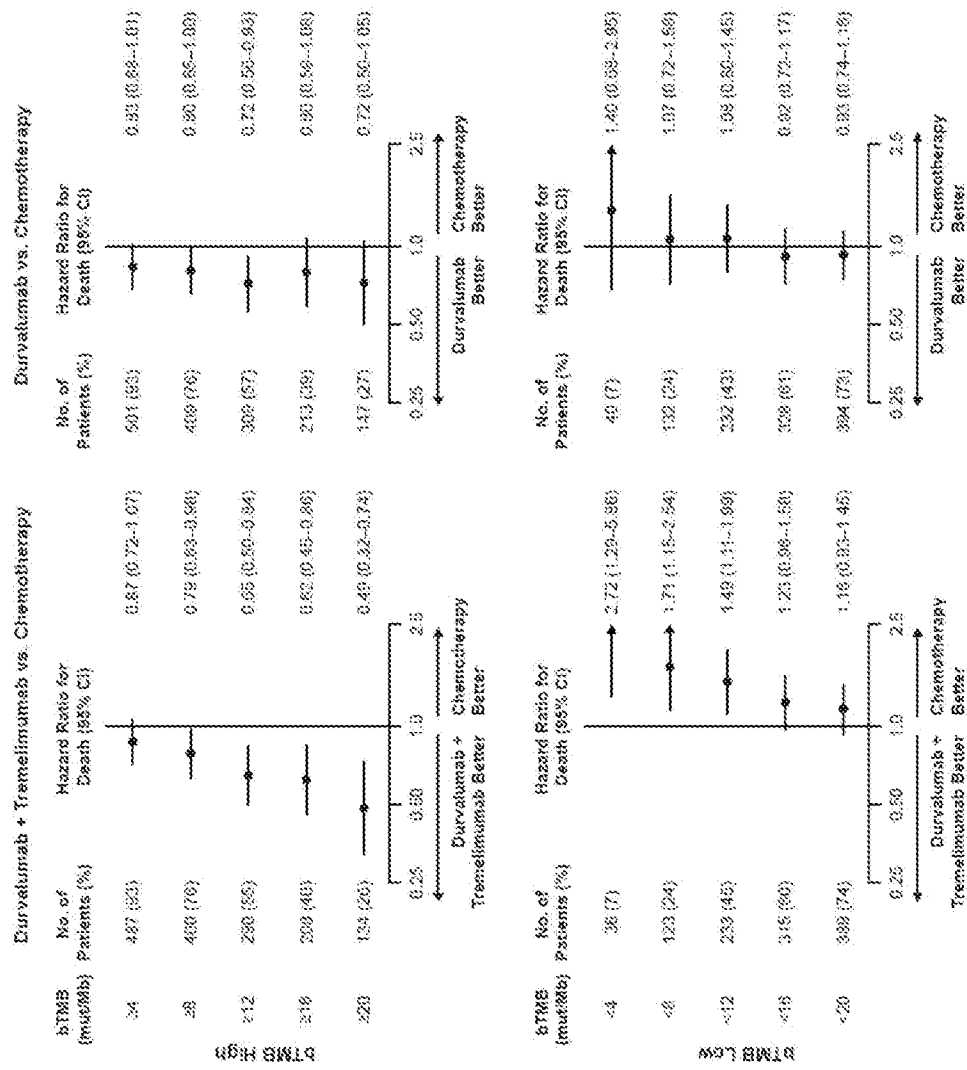
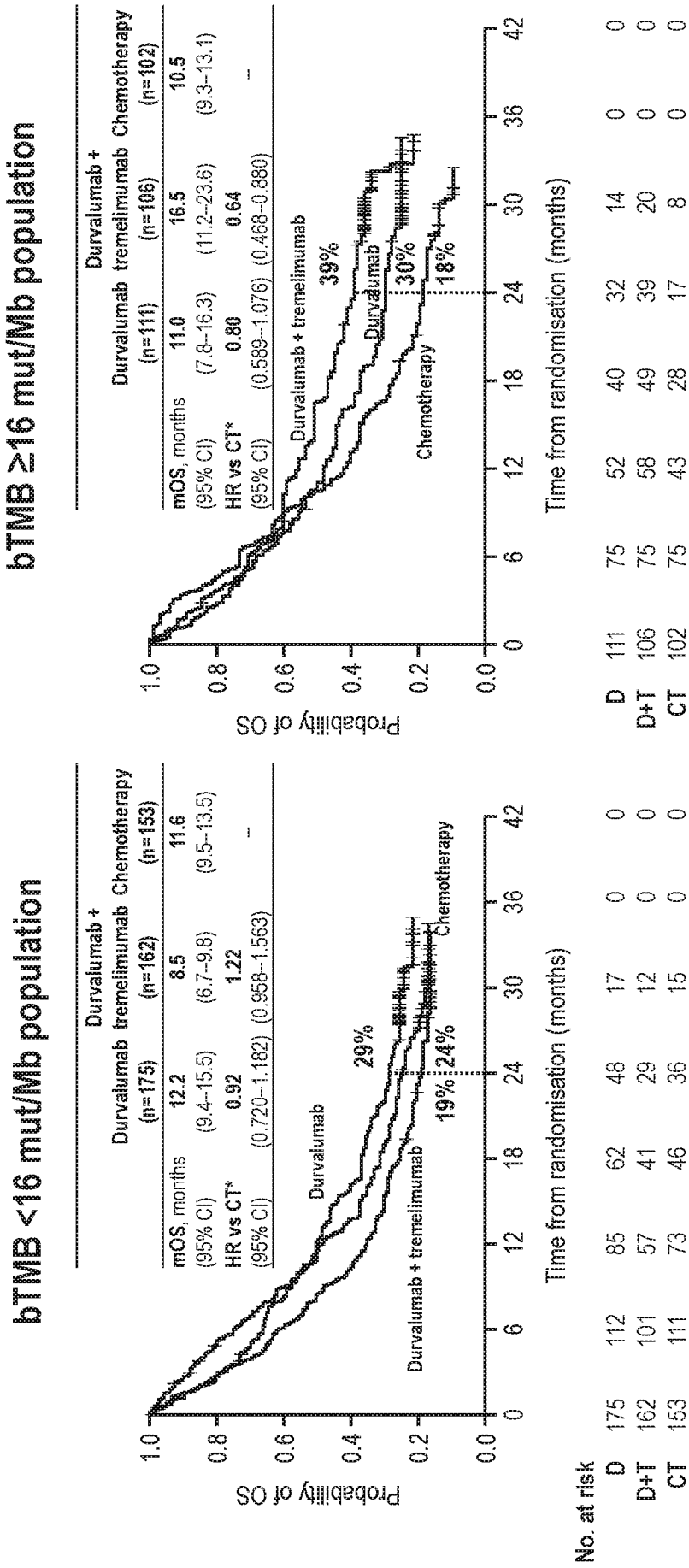


Figure 7



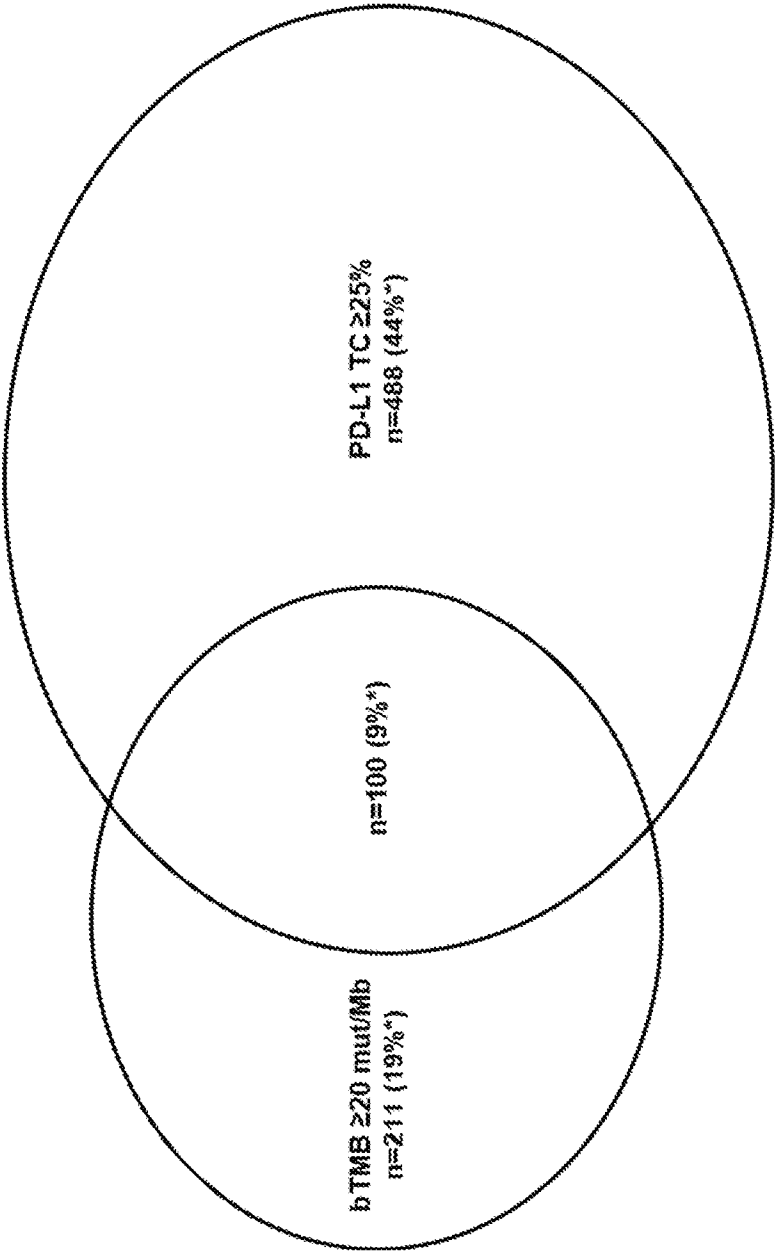


Figure 9

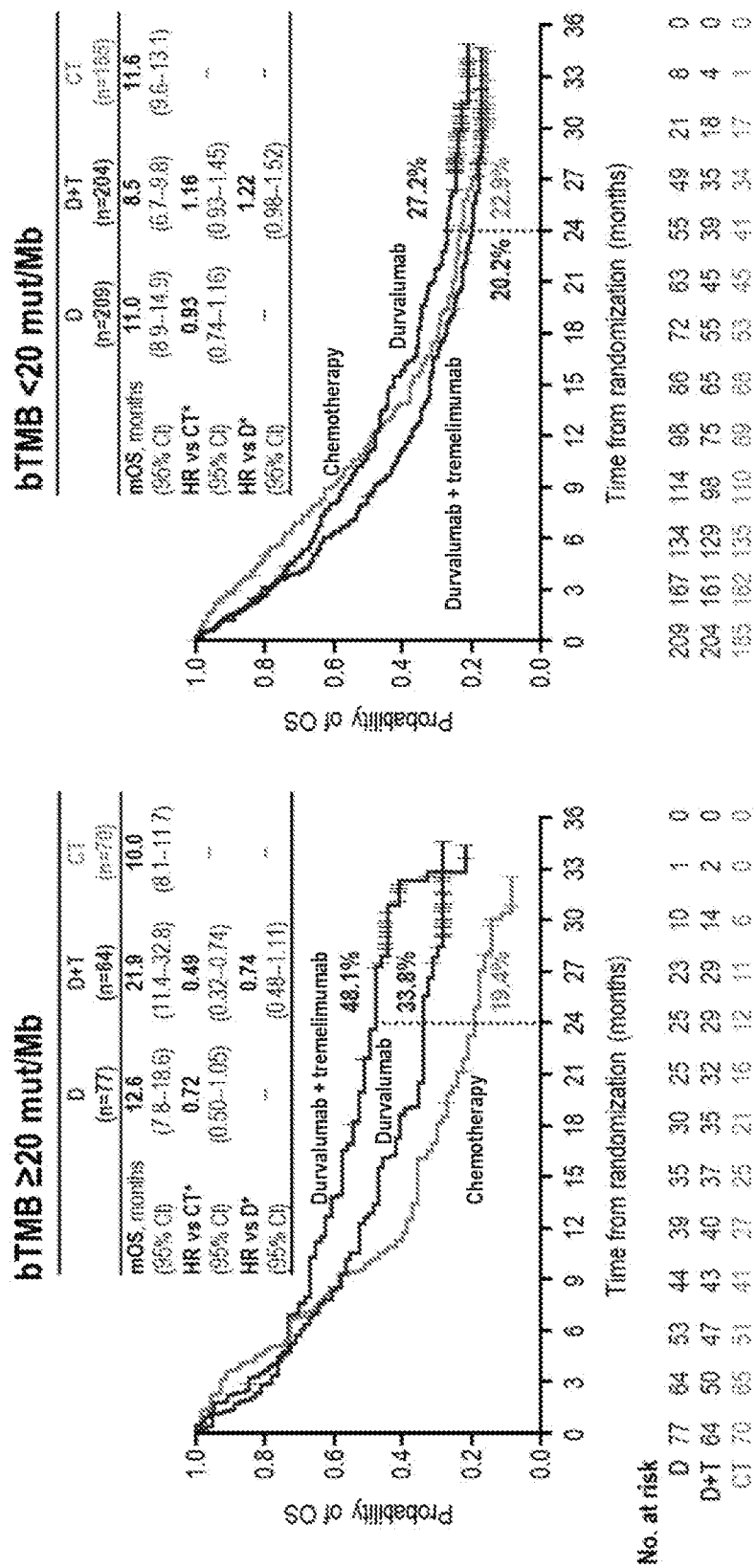


Figure 10

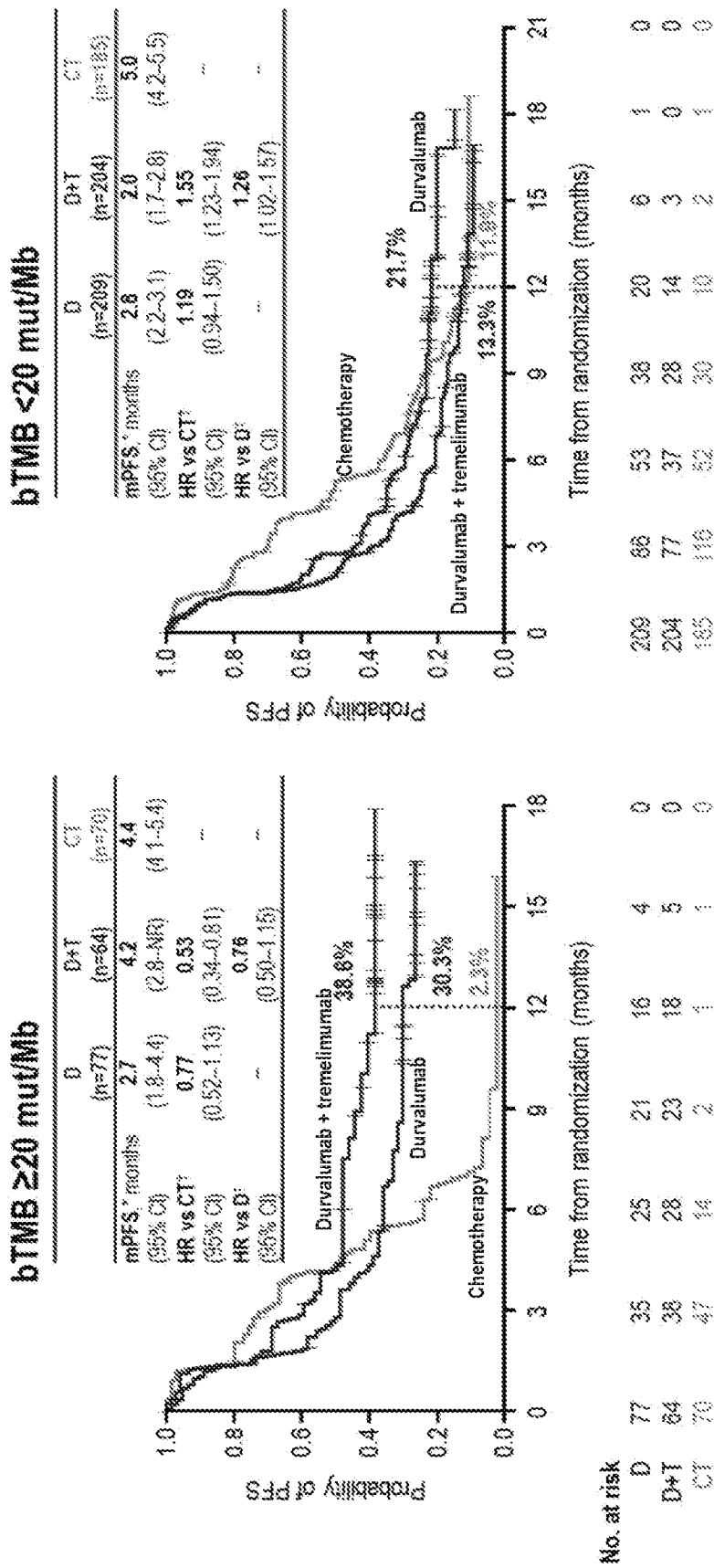


Figure 11

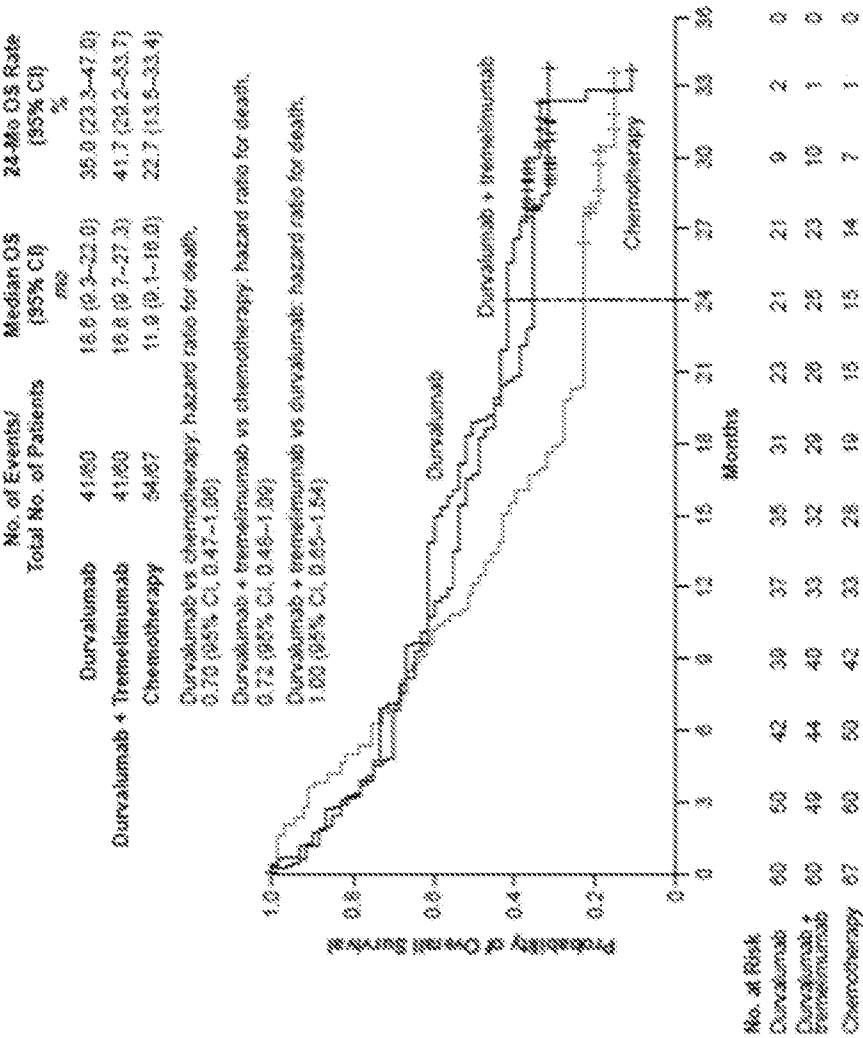


Figure 12A

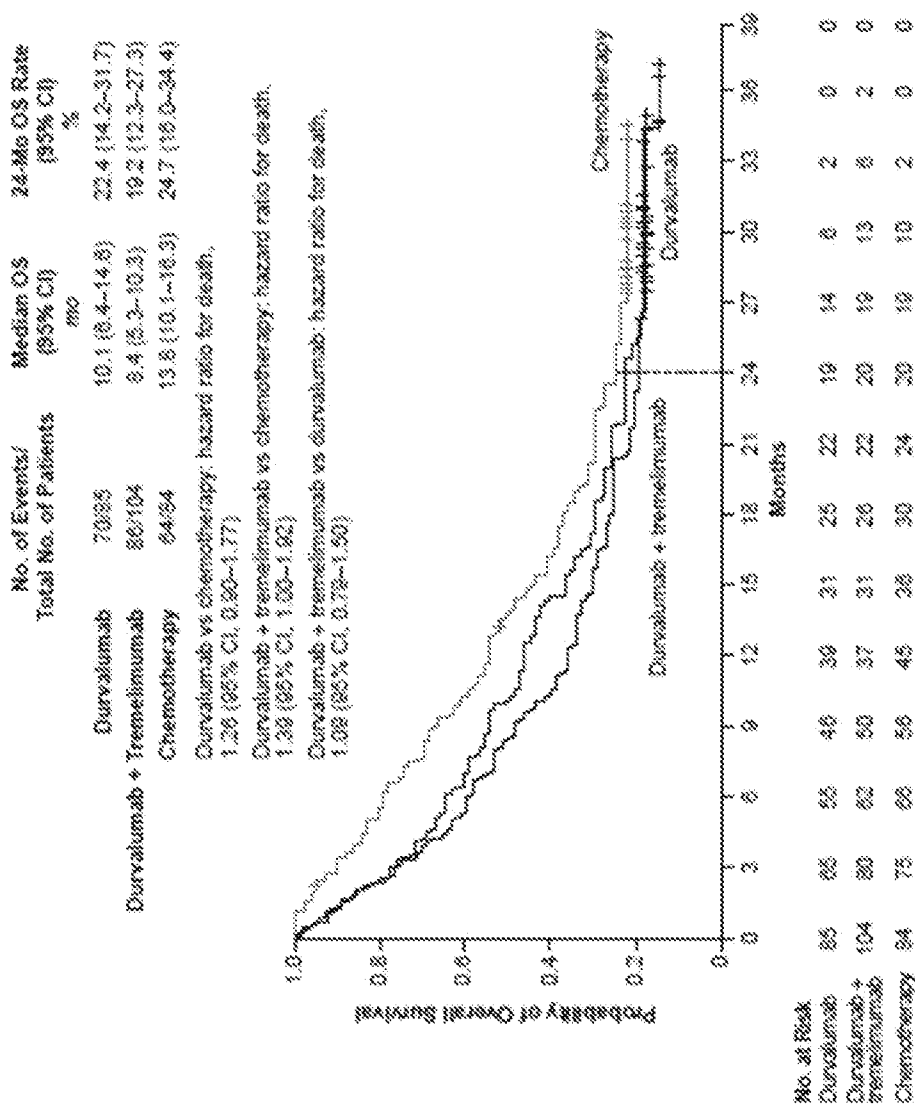


Figure 12B

| Method                                                                                                                                                                                                                 | Factors                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| <b>Count:</b> <ul style="list-style-type: none"><li>• Somatic</li><li>• Reportable regions (exonic and splice sites)</li><li>• SNVs &amp; Indels</li><li>• Including synonymous</li><li>• All MAFs</li></ul>           | <div>✓</div> <div>✓</div> <div>✓</div> <div>✓</div> <div>✓</div> |
| <b>Exclude:</b> <ul style="list-style-type: none"><li>• Curated list of CH genes and variants</li><li>• Putative driver and resistance mutations</li><li>• Low clonality mutations</li></ul>                           | <div>✓</div> <div>✓</div> <div>✗</div>                           |
| <b>Correct</b> for low tumor shedding and/or low diversity                                                                                                                                                             | <div>✓</div>                                                     |
| <b>Divide</b> by: <ul style="list-style-type: none"><li>• Panel size (Mb)</li></ul>                                                                                                                                    | <div>✓</div>                                                     |
| Assess whether sample is <b>Evaluable</b> based on: <ul style="list-style-type: none"><li>• Low shedding (based on max-MAF) and/or low diversity (due to low input cfDNA)</li><li>• Dominated by CH variants</li></ul> | <div>✓</div> <div>✓</div>                                        |

Figure 13

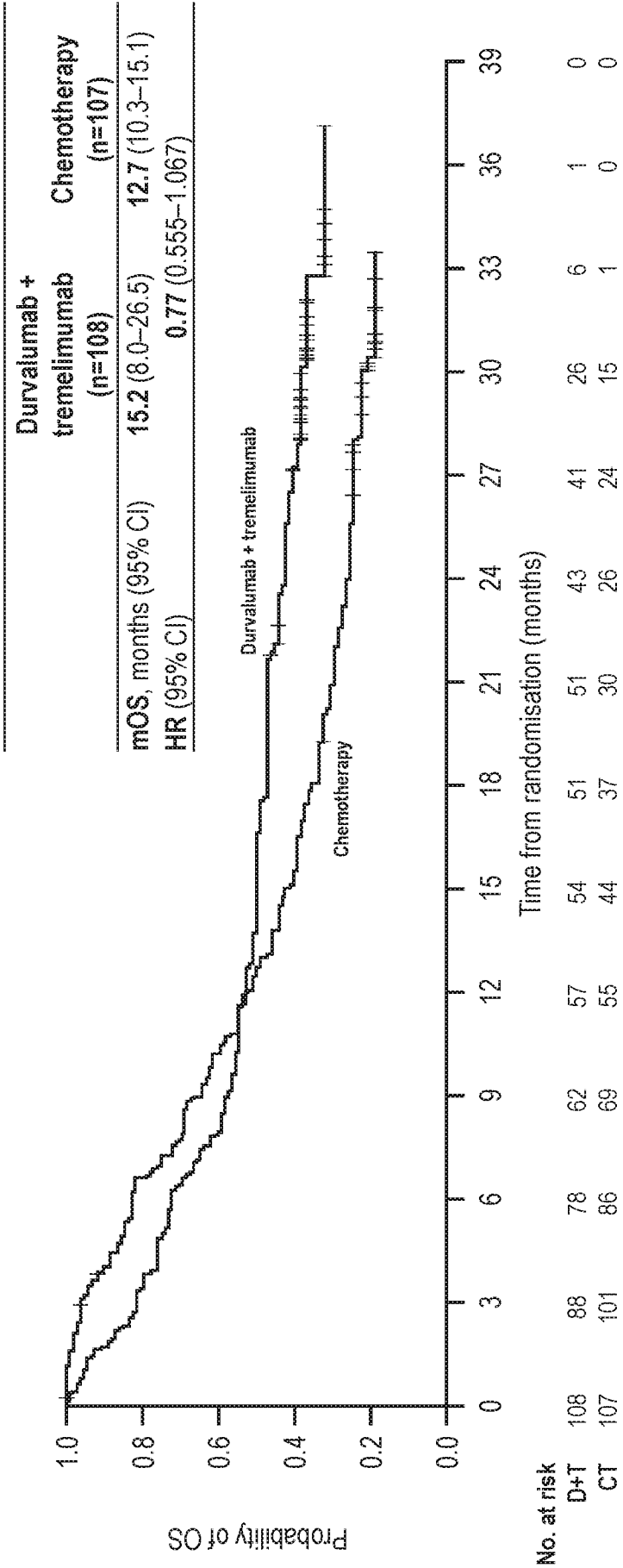
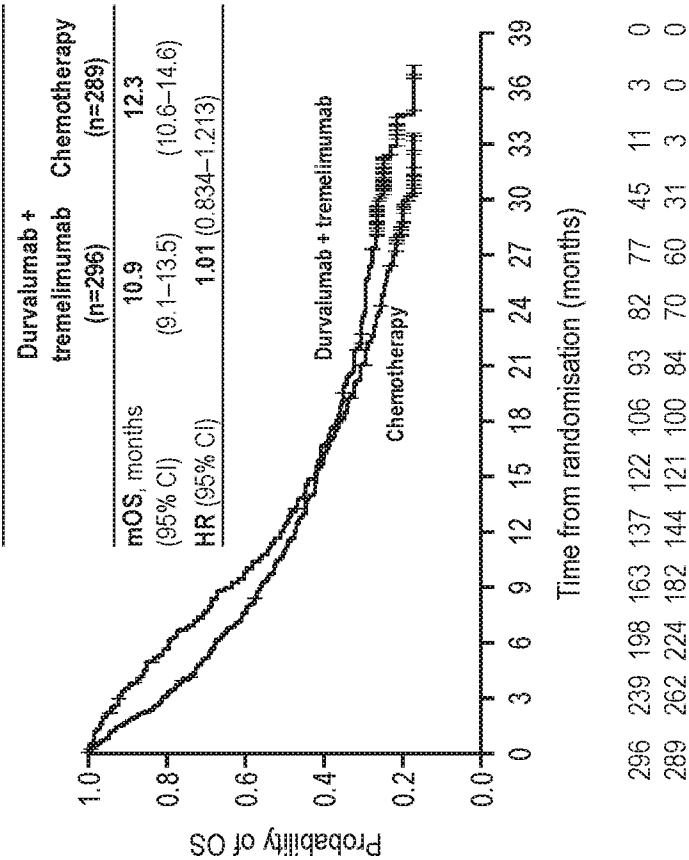


Figure 14

PD-L1 TC  $\geq 1\%$  population



PD-L1 TC  $< 1\%$  population

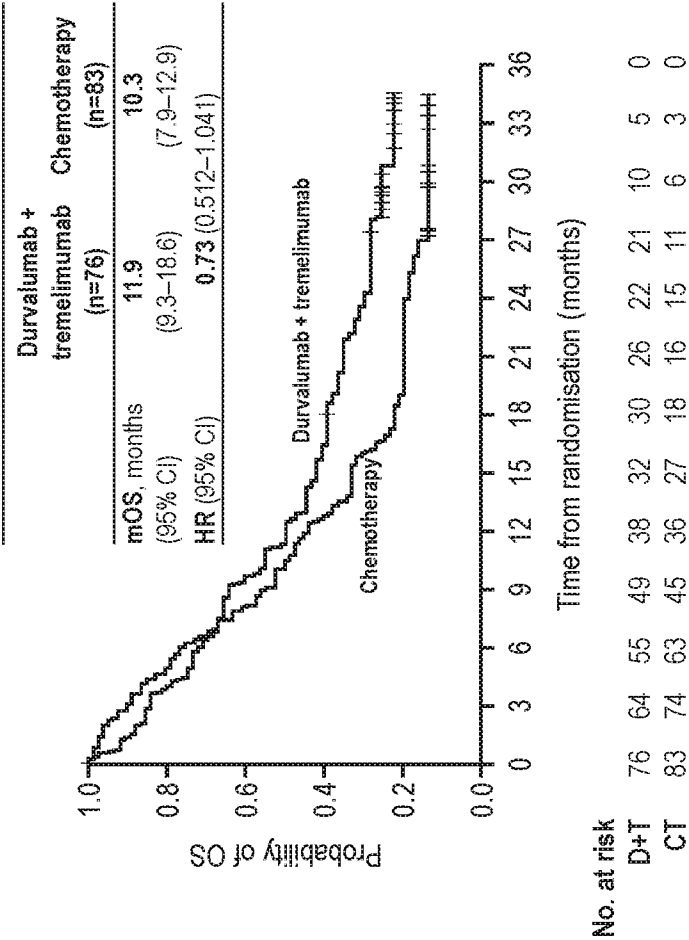


Figure 15

## TMB Combo vs Soc

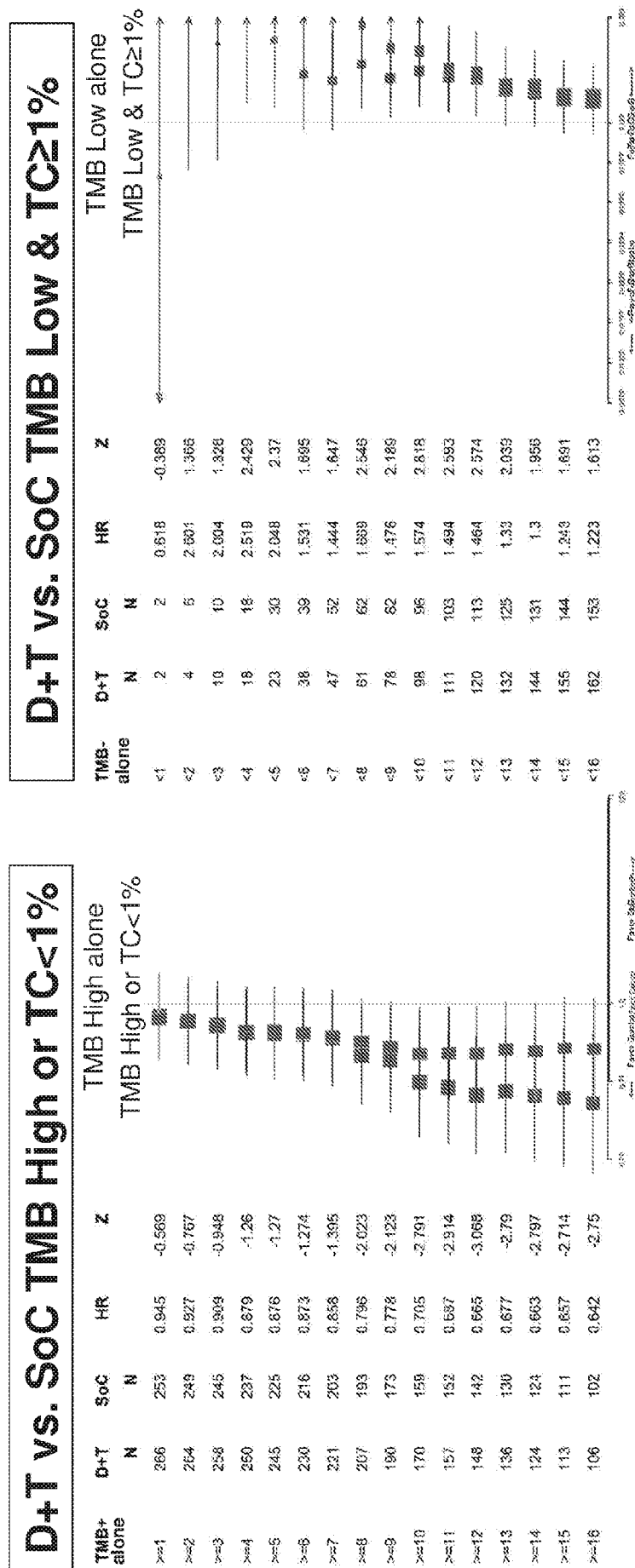
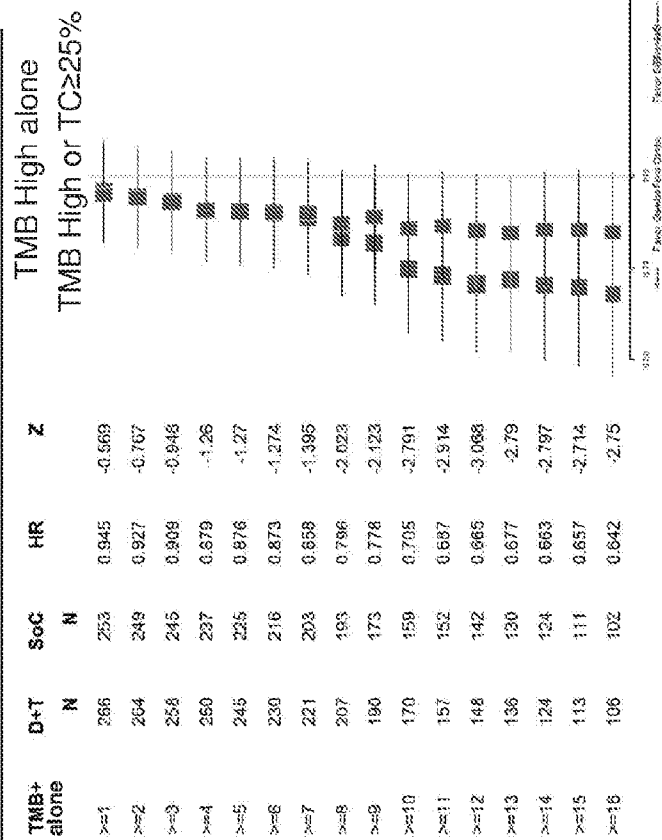


Figure 16

## TMB Combo vs Soc

D+T vs. Soc TMB+ or TC $\geq$ 25%

## D+T vs. Soc TMB- &amp; TC&lt;25%

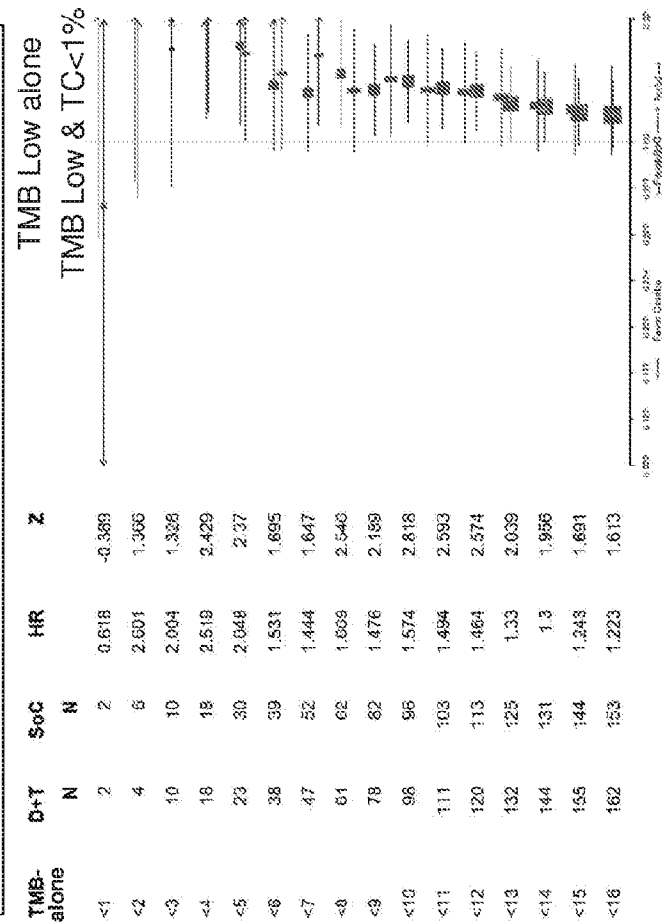
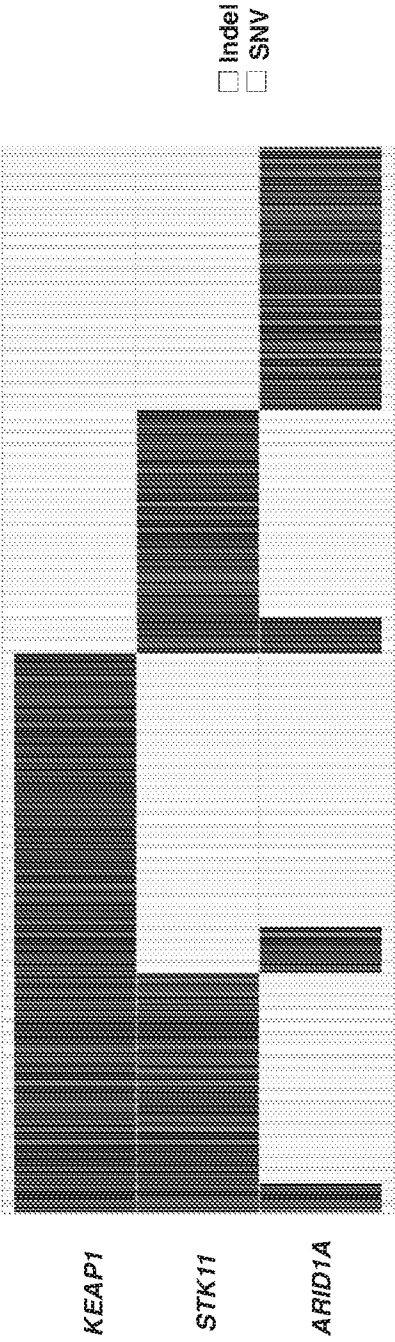


Figure 17



|        | Total mutations, * n | SNV, n (%) | Indel, n (%) |
|--------|----------------------|------------|--------------|
| KEAP1  | 190                  | 168 (88)   | 22 (12)      |
| STK11  | 155                  | 110 (71)   | 45 (29)      |
| ARID1A | 129                  | 97 (75)    | 32 (25)      |

\*The mutations are mutually exclusive; Indel, insertion or deletion; SNV, single nucleotide variant

Figure 18

|               | All<br>mutation-evaluable | Histology                       |                              | Treatment             |                         |                        |
|---------------|---------------------------|---------------------------------|------------------------------|-----------------------|-------------------------|------------------------|
|               |                           | Nonsquamous<br>(N=671)<br>n (%) | Squamous<br>(N=272)<br>n (%) | D<br>(N=312)<br>n (%) | D+T<br>(N=322)<br>n (%) | CT<br>(N=309)<br>n (%) |
| <i>KEAP1</i>  | 170 (18)                  | 134 (20)                        | 36 (13)                      | 54 (17)               | 63 (20)                 | 53 (17)                |
| <i>STK11</i>  | 147 (16)                  | 127 (19)                        | 20 (7)                       | 55 (18)               | 51 (16)                 | 41 (13)                |
| <i>ARID1A</i> | 114 (12)                  | 72 (11)                         | 42 (15)                      | 43 (14)               | 39 (12)                 | 32 (10)                |

Figure 19

Figure 20

|               | bTMB ≥20 mut/Mb<br>(N=211)* |             | bTMB <20 mut/Mb<br>(N=598)* |             | P value |
|---------------|-----------------------------|-------------|-----------------------------|-------------|---------|
|               | Mut<br>n (%)                | WT<br>n (%) | Mut<br>n (%)                | WT<br>n (%) |         |
| <i>KEAP1</i>  | 53 (25.1)                   | 158 (74.9)  | 109 (18.2)                  | 489 (81.8)  | 0.04    |
| <i>STK11</i>  | 46 (21.8)                   | 165 (78.2)  | 97 (16.2)                   | 501 (83.8)  | 0.07    |
| <i>ARID1A</i> | 48 (22.7)                   | 163 (77.3)  | 61 (10.2)                   | 537 (89.8)  | <0.0001 |

Figure 21

|        | PD-L1 TC ≥25%<br>(N=411)* |             | PD-L1 TC <25%<br>(N=532)* |             | P value |
|--------|---------------------------|-------------|---------------------------|-------------|---------|
|        | Mut<br>n (%)              | WT<br>n (%) | Mut<br>n (%)              | WT<br>n (%) |         |
| KEAP1  | 63 (15.3)                 | 348 (84.7)  | 107 (20.1)                | 425 (79.9)  | 0.06    |
| STK11  | 51 (12.4)                 | 360 (87.6)  | 96 (18)                   | 436 (82)    | 0.02    |
| ARID1A | 56 (13.6)                 | 355 (86.4)  | 58 (10.9)                 | 474 (89.1)  | 0.23    |

\* STK11 mutations were negatively associated with PD-L1 TC ≥25%

Figure 22

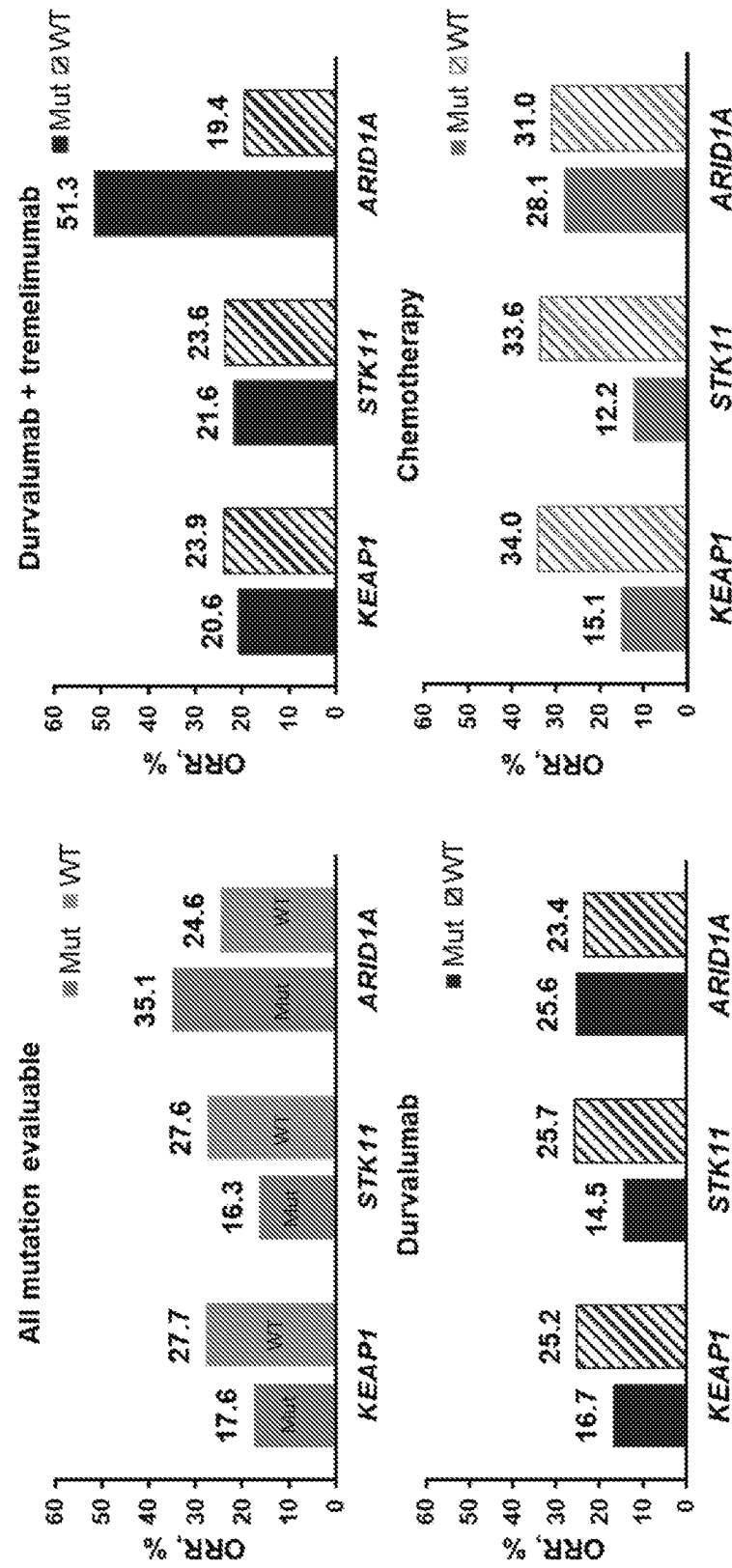


Figure 23

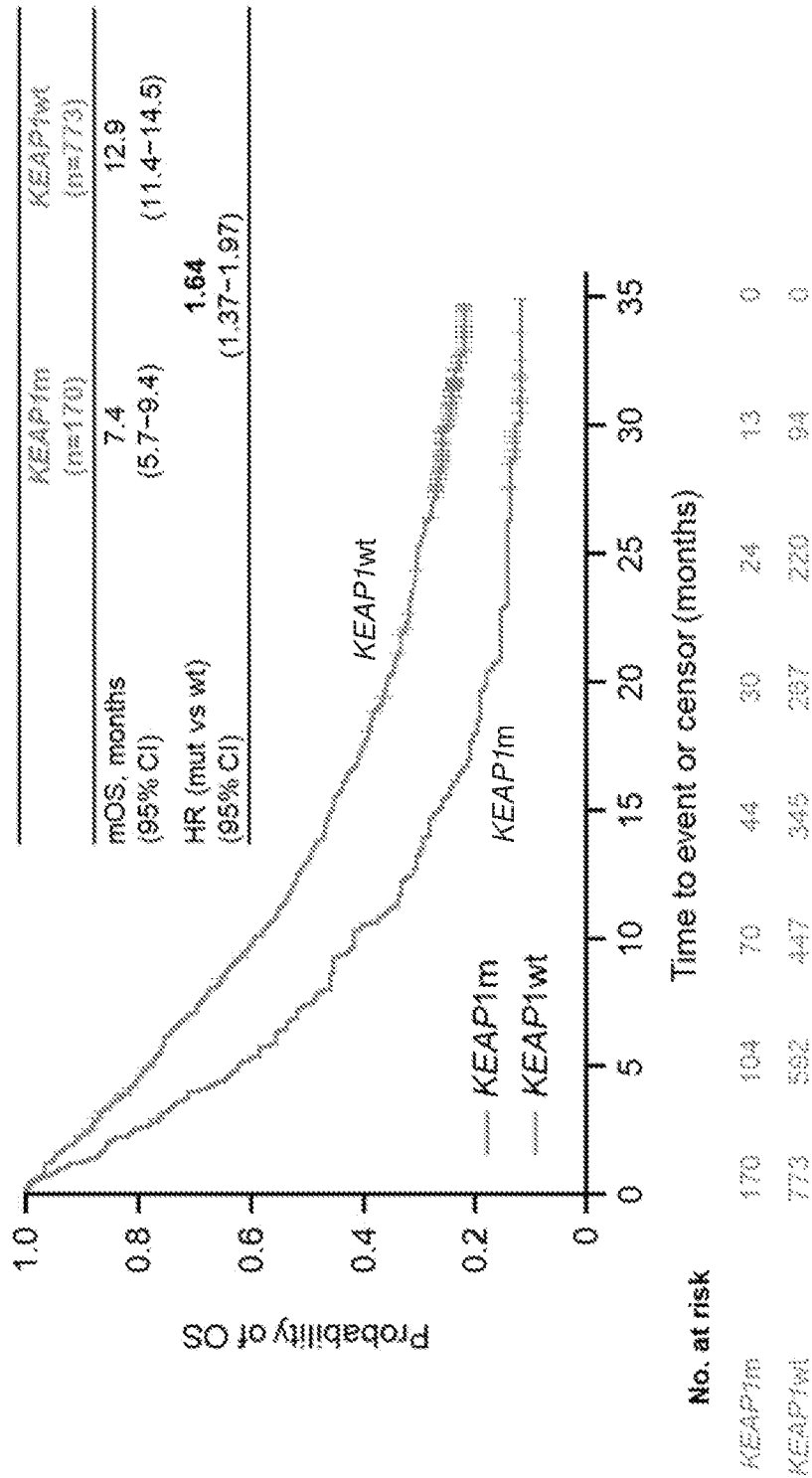


Figure 24

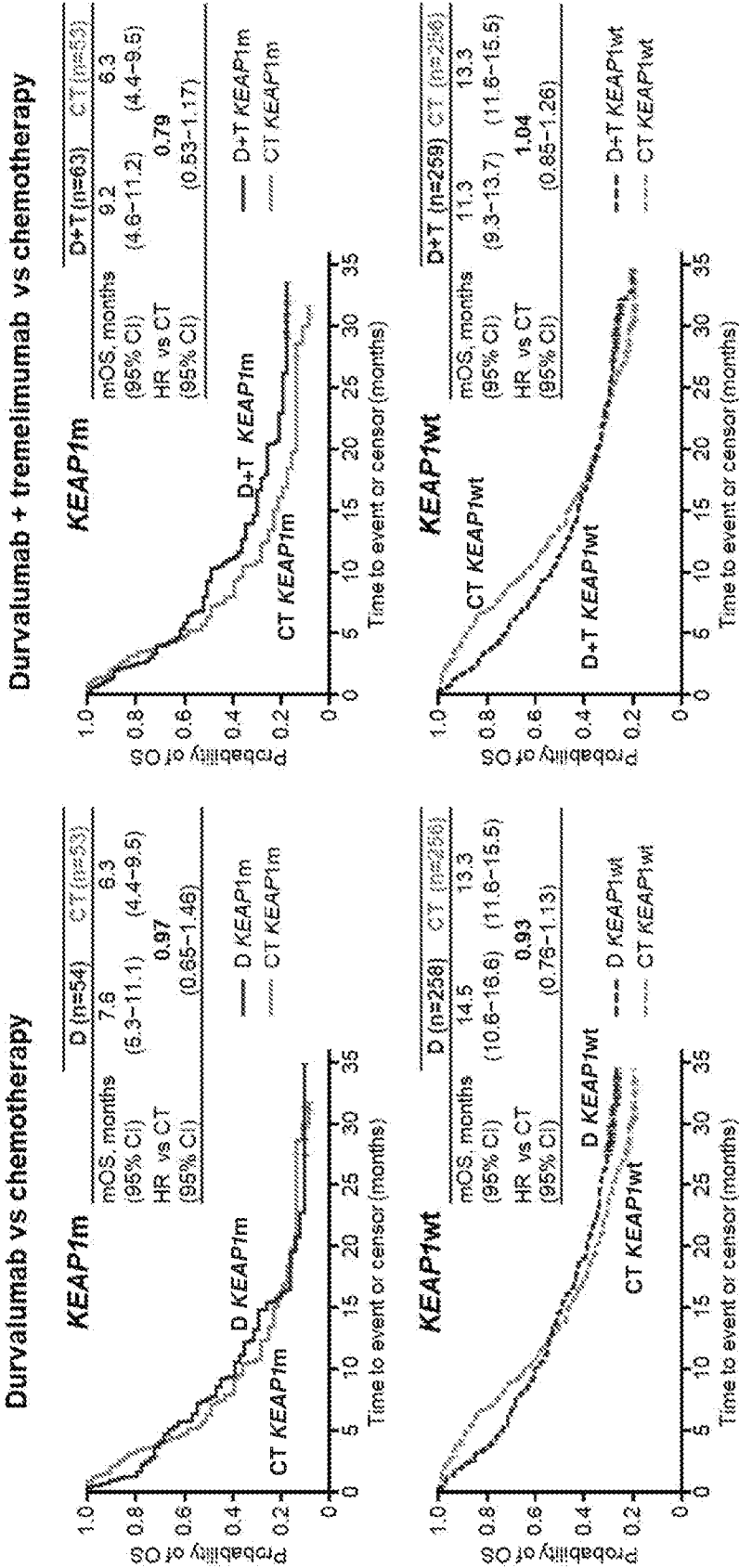


Figure 25

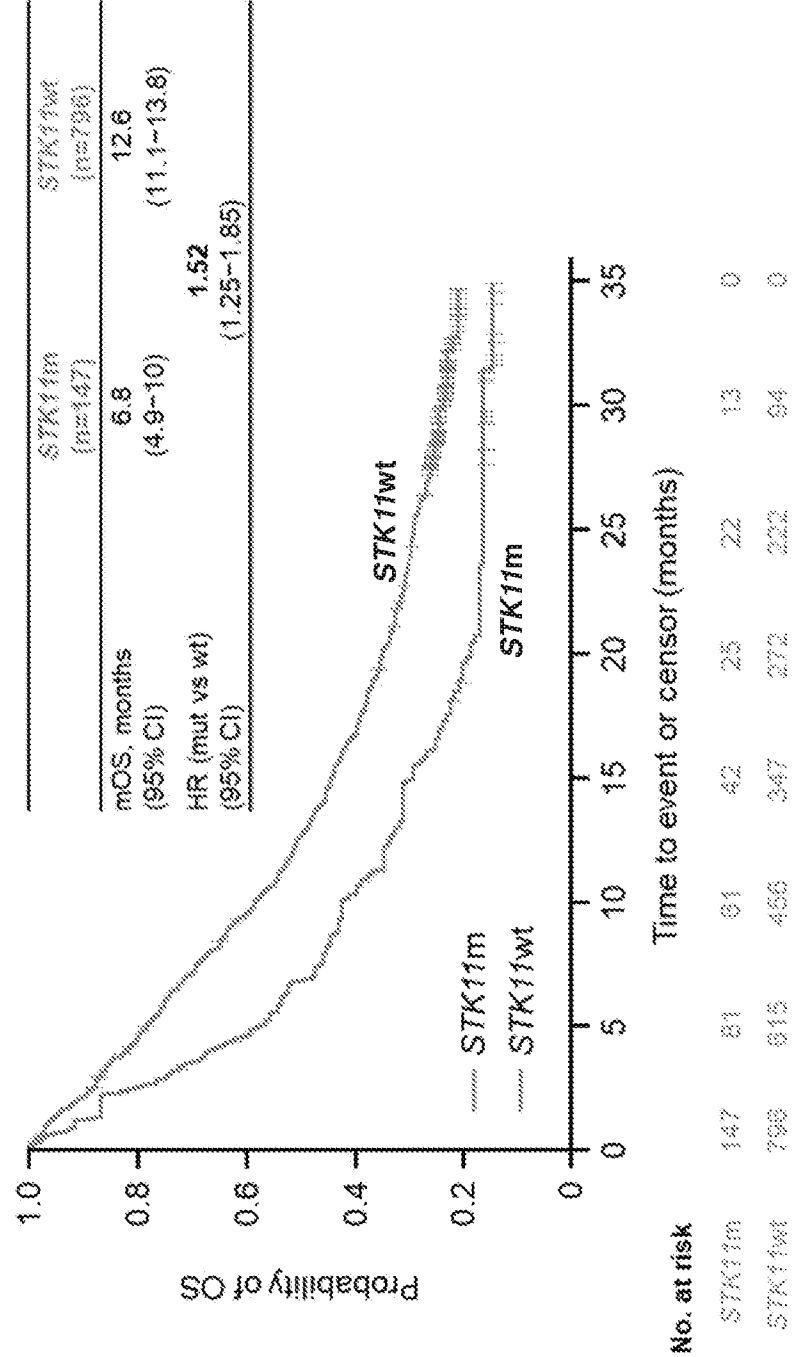


Figure 26

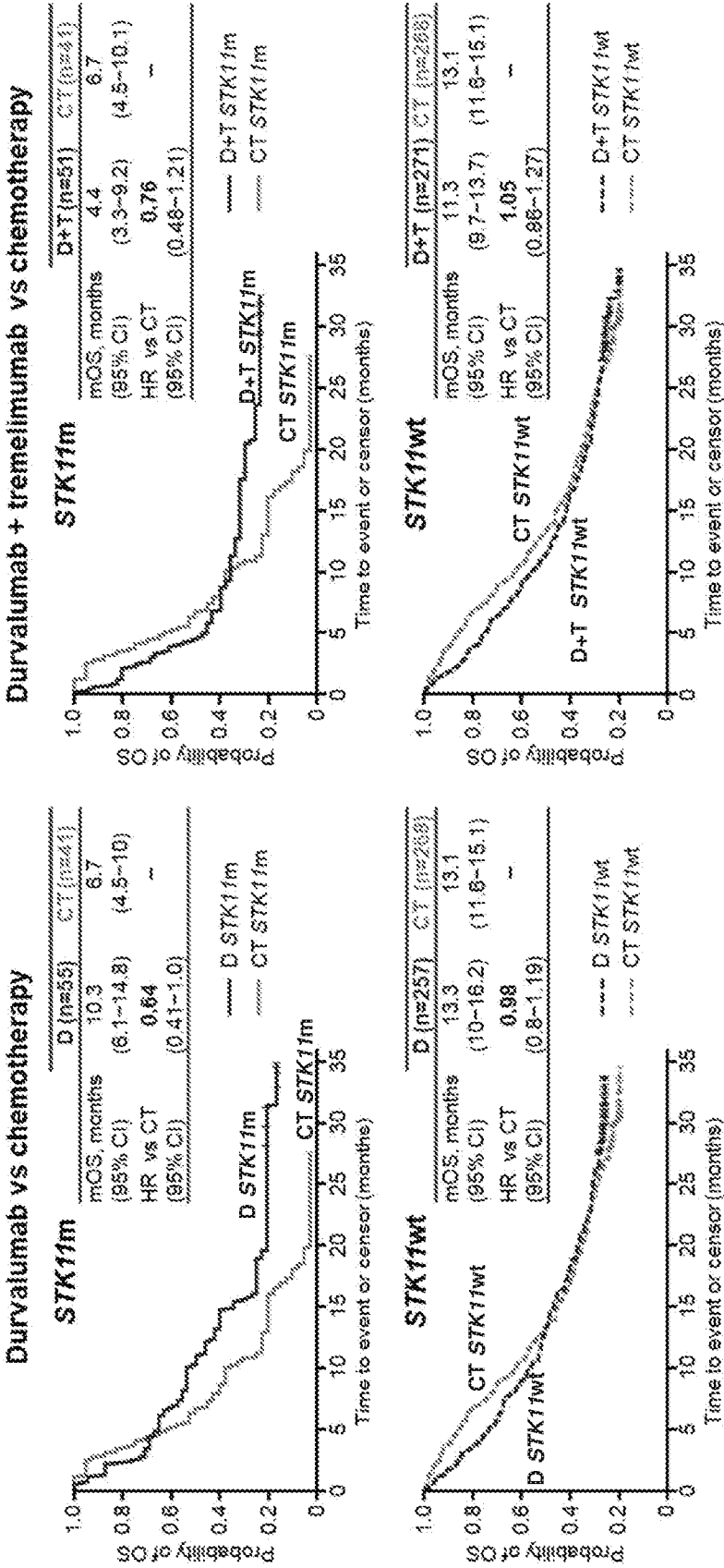


Figure 27

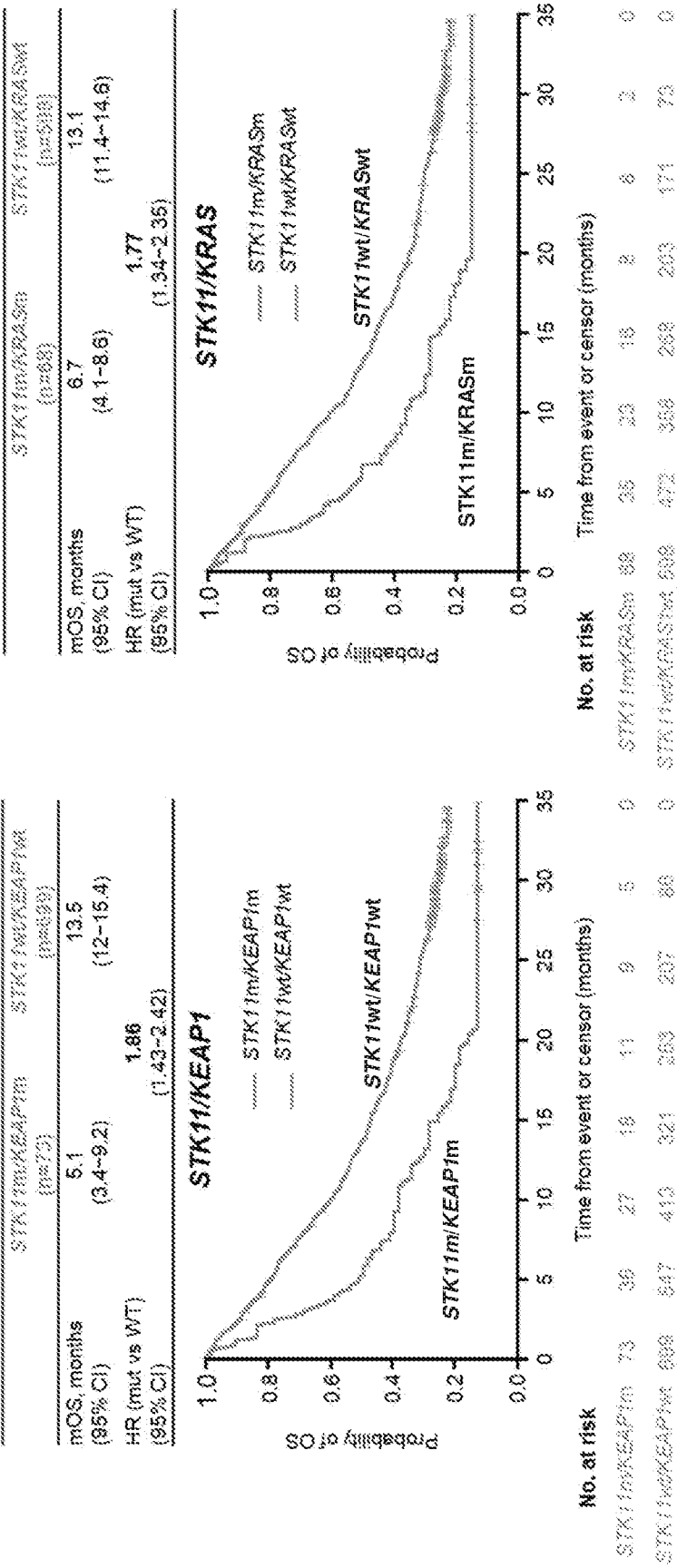


Figure 28

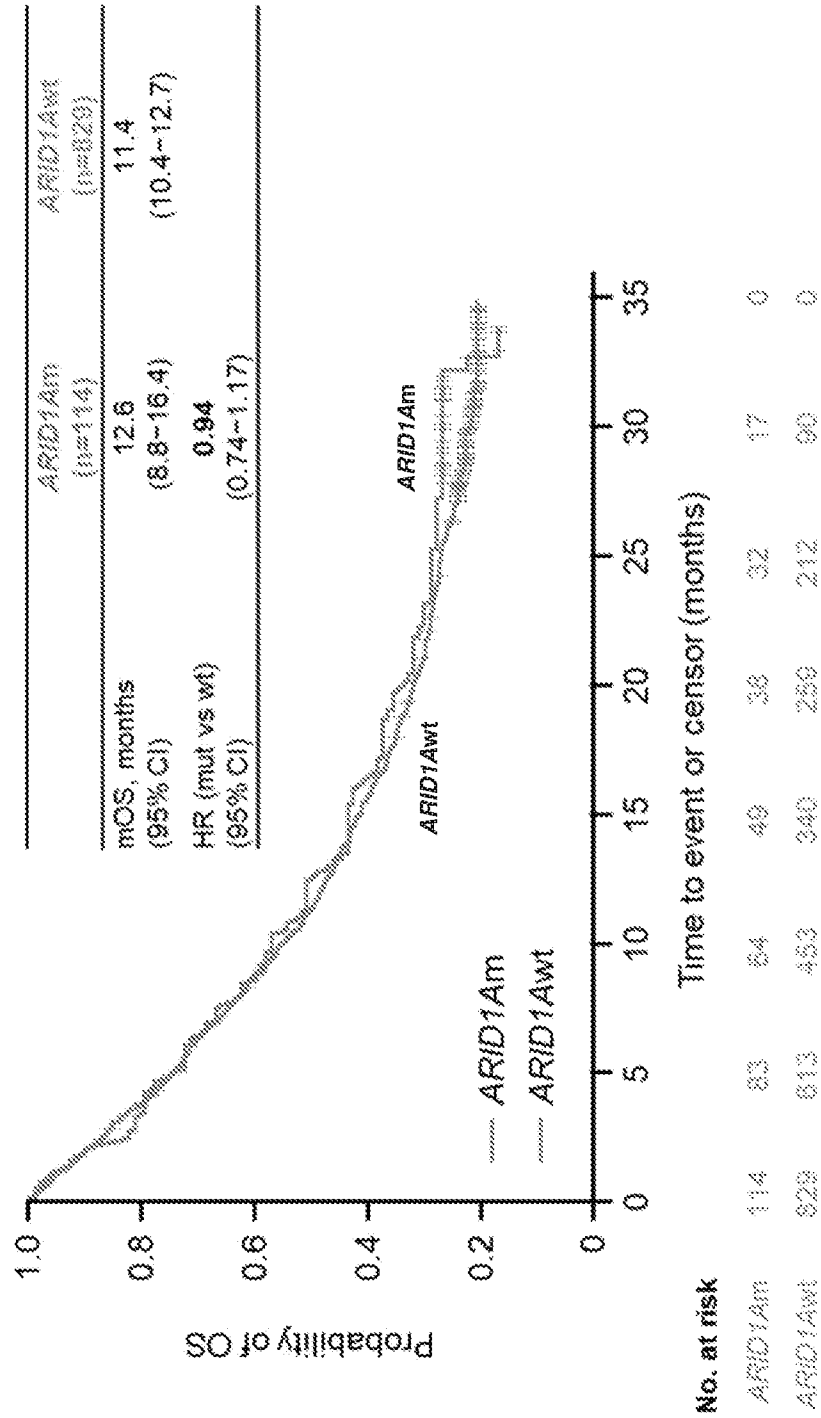
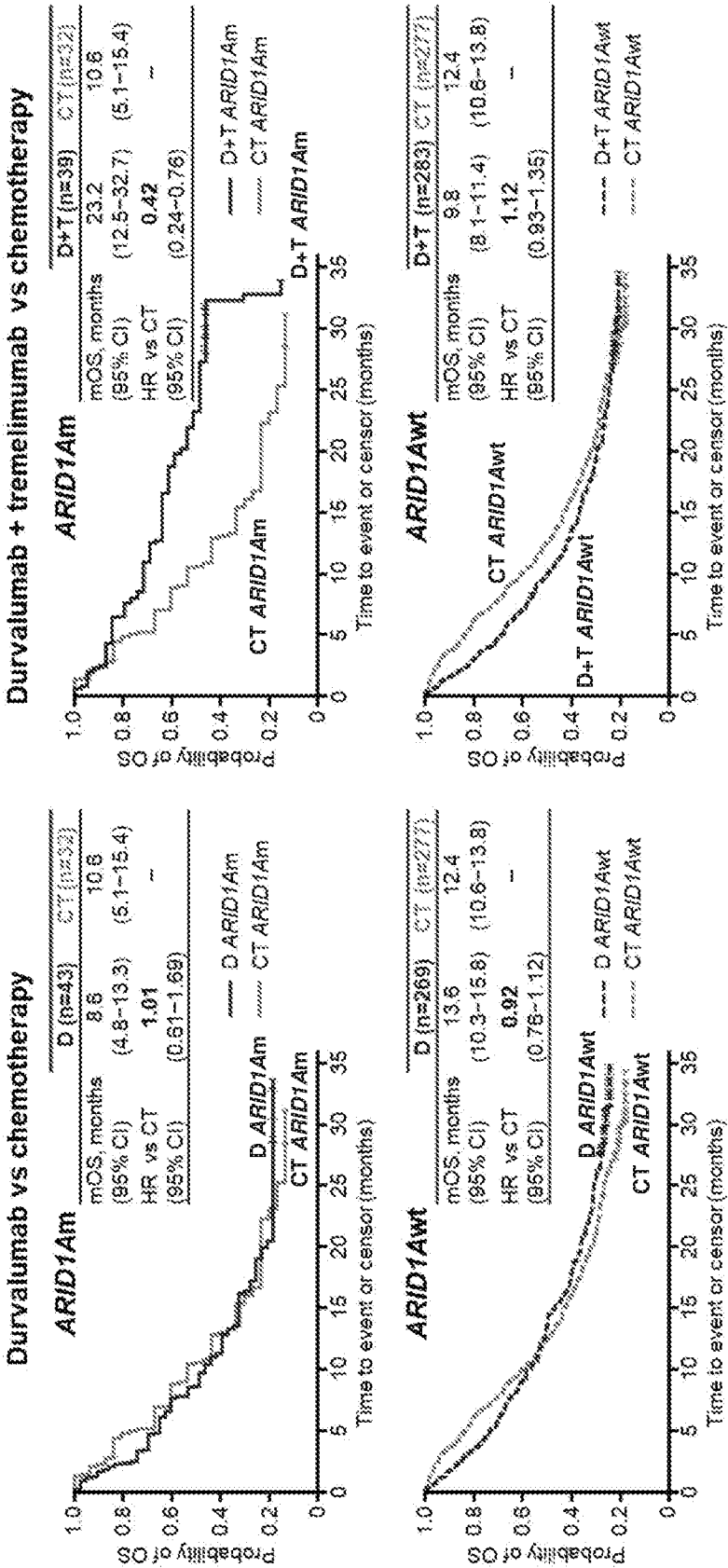


Figure 29



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/060676

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395; C12N 15/12; C12Q 1/68; C12Q 1/6827; C12Q 1/6886 (2020.01)

CPC - A61K 2039/505; A61P 35/00; C07K 2317/76; C12Q 1/68; C12Q 1/6827; C12Q 1/6886; C12Q 2600/106; C12Q 2600/118; C12Q 2600/156; G01N 2800/52 (2020.02)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/130.1; 435/6; 435/375; 536/23.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                           | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2018/183928 A1 (BRISTOL-MYERS SQUIBB COMPANY) 04 October 2018 (04.10.2018) entire document                                                                                                                                                                                | 1-29                  |
| A         | WO 2017/151524 A1 (FOUNDATION MEDICINE, INC. et al) 08 September 2017 (08.09.2017) entire document                                                                                                                                                                           | 1-29                  |
| A         | WO 2017/151502 A1 (GENENTECH, INC. et al) 08 September 2017 (08.09.2017) entire document                                                                                                                                                                                     | 1-29                  |
| A         | HIGGS et al. "Interferon Gamma Messenger RNA Signature in Tumor Biopsies Predicts Outcomes in Patients with Non-Small Cell Lung Carcinoma or Urothelial Cancer Treated with Durvalumab," Clin Cancer Res, 01 May 2018 (01.05.2018), Vol. 24, Pgs. 3857-3866. entire document | 1-29                  |
| A         | US 2018/0282417 A1 (MEDIMMUNE, LLC) 04 October 2018 (04.10.2018) entire document                                                                                                                                                                                             | 1-29                  |
| A         | US 2018/0291074 A1 (MEMORIAL SLOAN KETTERING CANCER CENTER) 11 October 2018 (11.10.2018) entire document                                                                                                                                                                     | 1-29                  |
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☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Name and mailing address of the ISA/US  
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, VA 22313-1450  
Facsimile No. 571-273-8300

Authorized officer  
Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300  
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