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The majority of patients who achieve a CR with first-line chemotherapy ultimately develop recurrent disease. These patients can be subdivided into platinum-sensitive or platinum-resistant groups.12 In platinum-sensitive patients, disease recurrence occurs more than 6 months after cessation of initial platinum-containing chemotherapy.12 Platinum-based therapies are typically used to retreat these patients, in light of clinically meaningful responses observed in these patients following a second platinum-based treatment. 13 Currently, there is no optimal treatment strategy for platinum-resistant patients whose disease recurs within 6 months of completing initial platinum-based chemotherapy.12,14 Despite a wide range of available treatments, prolonged survival has not been shown in this setting, and ORR is generally less than 20%.12,15 As resistant-disease is not curable, the goals of treatment for these patients include palliation of symptoms, prolonged survival and improvements in quality of life.13,15,16

Platinum-resistance is therefore a significant clinical problem for which improved treatment regimens are needed. In particular, bevacizumab (Avastin®), a monoclonal antibody targeted against the pro-angiogenic vascular endothelial growth factor (VEGF), holds significant therapeutic potential.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure contemplates a method of treating a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein said patient received two or fewer prior anti-cancer regimens, wherein said treatment prolongs said patient's median progression-free survival time as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. According to a first aspect, there is provided an anti-VEGF antibody for use in a method of treating a patient diagnosed with a platinum-resistant ovarian cancer, wherein the method comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein said patient received two or fewer prior anti-cancer regimens, wherein said chemotherapeutic is selected from the group consisting

of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD), wherein said treatment prolongs said patient's median progression-free survival time as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In one embodiment, the platinum-resistant ovarian cancer is an epithelial ovarian cancer (EOC), a fallopian tube carcinoma (FTC), or a primary peritoneal carcinoma (PPC). In another embodiment, the patient is not refractory to previous platinum

treatment and/or has measurable disease according to RECIST 1.0 or CA-125 assessable disease according to the GCIG criteria. In a further embodiment, the patient has an ECOG performance status of 0-2 and a life expectancy of at least 12 weeks.

The present ~~invention~~ disclosure contemplates a method of treating a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic as described above, where the chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD). In a further embodiment, the effective amount of said paclitaxel is administered at 80 mg/m2 as a 1 hour intravenous infusion on days 1, 8, 15 and 22 q4w.

In another embodiment in the method described above, the effective amount of said topotecan is administered at 4 mg/m2 as a 30 minute intravenous infusion on days 1, 8 and 15 q4w. In an alternative embodiment in the method described above, the effective amount of said topotecan is administered at 1.25 mg/m2 as a 30 minute intravenous infusion on days 1 to 5 every three weeks.

In another embodiment in the method described above, the effective amount of said PLD is administered at 40 mg/m2 as a 1 mg/min intravenous infusion on day 1 only, then as a 1 hour infusion thereafter, q4w.

In the present ~~invention~~ disclosure described above which contemplates a method of treating a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, the anti-VEGF antibody binds the A4.6.1 epitope. In a further embodiment, the anti-VEGF antibody is bevacizumab. In still a further embodiment, the anti-VEGF antibody comprises a variable heavy chain (VH) and a variable light chain (VL), wherein said VH has an amino acid sequence of SEQ ID NO:2 and said VL has an amino acid sequence of SEQ ID NO:1.

In the present disclosure ~~invention~~ described above which contemplates a method of treating a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, the effective amount of said anti-VEGF antibody is 10 mg/kg intravenously every two weeks and the effective amount of said anti-VEGF antibody is administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes. In a further embodiment, the effective amount of said anti-VEGF antibody is 15 mg/kg intravenously every three weeks, where the anti-VEGF antibody is administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes.

In the present disclosure ~~invention~~ described above, the anti-VEGF antibody is administered first to said patient at the first cycle and then subsequent administrations of said anti-VEGF antibody are either prior to or after said chemotherapeutic. In another embodiment, the anti-VEGF antibody is administered concurrently with said chemotherapeutic.

In the present disclosure ~~invention~~ described above which contemplates a method of treating a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, as described above, the median progression-free survival time is prolonged by about 3 months with a hazard ratio (HR) equal to 0.48, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In another embodiment, the median progression-free survival time is prolonged by at least 3 months or greater with a hazard ratio (HR) equal to 0.48, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In another embodiment, the median progression-free survival time is prolonged by at least 3 months or greater with a hazard ratio (HR) from about 0.32 to about 0.57, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In another embodiment, the median progression-free survival time is prolonged by about 3 months with a hazard ratio (HR) from about 0.32 to about 0.57, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In yet another embodiment, in the method described above, said chemotherapeutic is paclitaxel and said patient's median progression-free survival time is prolonged by at least 6 months or greater with a hazard ration (HR) of about 0.46 as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In yet another embodiment, in the method described above, said chemotherapeutic is pegylated liposomal doxorubicin (PLD) and said patient's median progression-free survival time is prolonged by at least 2 months or greater with a hazard ration of about 0.57 as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In yet another embodiment, in the method described above, said chemotherapeutic is topotecan and said patient's median progression-free survival time is prolonged by at least 3 months or greater with a hazard ratio (HR) of about 0.32 as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In yet another embodiment in the methods described above, the patient is less than 65 years old. In yet another embodiment in the methods described above, the patient is equal to or greater than 65 years old. In one embodiment in the methods described above, the patient has a platinum free interval (PFI) of less than 3 months. In an alternative embodiment in the methods described above, the patient has a PFI of 3 to 6 months.

In one embodiment in the methods described above, the patient has abdominal ascites. In an alternative embodiment in the methods described above, the patient does not have abdominal ascites.

In yet another embodiment, in the method described above, the treatment further improves said patient's objective response rate (ORR) as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In one embodiment, the ORR is improved by at least 1.5 fold or by at least 2 fold as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In yet another embodiment, the ORR is improved to about 30.9% as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In another embodiment, in the method described above, wherein the ORR is improved by at least 1.5 fold as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone, the chemotherapeutic is paclitaxel or pegylated liposomal doxorubicin (PLD) . In another embodiment, in the method described above, wherein the ORR is improved by at least 2 fold as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone, the chemotherapeutic is topotecan.

The present disclosure ~~invention~~ also contemplates a kit comprising an anti-VEGF antibody binding essentially to epitope A4.6.1, a chemotherapeutic and a package insert or label with instructions to treat a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein said patient received two or fewer prior anti-cancer regimens, wherein said treatment prolongs said patient's median progression-free survival time as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone. In one embodiment of the kit described above, the platinum-resistant ovarian cancer is an epithelial ovarian cancer (EOC), a fallopian tube carcinoma (FTC), or a primary peritoneal carcinoma (PPC). In another embodiment of the kit described above, the anti-VEGF antibody is bevacizumab and said chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD).

The present disclosure ~~invention~~ further contemplates a method of promoting administration of an anti-VEGF antibody binding essentially to epitope A4.6.1, and a chemotherapeutic to treat platinum-resistant ovarian cancer in a patient, wherein said promotion is by written material. In one embodiment to the promotional method described, the anti-VEGF antibody is bevacizumab, and said chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD). In another embodiment to the promotional method

described, the written material is a package insert or label that accompanies a commercial formulation of said anti-VEGF antibody and said chemotherapeutic.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the two-arm Phase III study design treatment sequence as disclosed in more detail in Example 1. In both Arms 1 and 2, there is a choice of chemotherapeutic, eitherpaclitaxel, topotecan or PLD. In Arm 2, for bevacizumab, the alternative dose is 15 mg/kg every three weeks if the chemotherapeutic topotecan is selected and administered at a dose of 1.25 mg/m2 on a 1-5/every three weeks schedule.

Figure 2 shows patient stratification analysis of the progression-free survival (PFS) results from the phase III AURELIA trial which subdivides the patients in subgroups based on different risk factors and compares in which patient subgroup the bevacizumab and chemotherapy combination treatment resulted in a better PFS outcome versus chemotherapy treatment alone. CT = chemotherapy; BEV + CT = bevacizumab + chemotherapy; HR = unadjusted hazard ratio; PFI = platinum-free interval as measured in months, where a total of 8 patients' information is missing.

Figure 3 shows a summary of best overall response rates (ORR), as measured by a two-sided chi-square test with Schouten correction, comparing the percent of patients who were measured by RECIST and/or CA-125 responders, RECIST responders alone, and CA-125 responders alone as between the two treatment arms, chemotherapy alone (CT) as shown in each case as the grey-stippeled bars, versus bevacizumab and chemotherapy combination (BEV + CT) as shown in each case as the grey bars. N shows the number of patients in each tested group.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

DEFINITIONS

An "anti-angiogenesis agent" or "angiogenesis inhibitor" refers to a small molecular weight substance, a polynucleotide, a polypeptide, an isolated protein, a recombinant protein, an antibody, or conjugates or fusion proteins thereof, that inhibits angiogenesis, vasculogenesis, or undesirable vascular permeability, either directly or indirectly. It should be understood that the anti-angiogenesis agent includes those agents that bind and block the angiogenic activity of the angiogenic factor or its receptor. For example, an anti-angiogenesis agent is an antibody or other antagonist to an angiogenic agent as defined throughout the specification or known in the art, e.g., but are not limited to, antibodies to VEGF-A or to the VEGF-A receptor (e.g., KDR receptor or

We claim:

1. An anti-VEGF antibody for use in a~~A~~ method of treating a patient diagnosed with a platinum-resistant ovarian cancer, wherein the method comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein said patient received two or fewer prior anti-cancer regimens, wherein said chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD), wherein said treatment prolongs said patient's median progression-free survival time as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.
2. The anti-VEGF antibody~~The method~~ of claim 1, wherein said platinum-resistant ovarian cancer is an epithelial ovarian cancer (EOC), a fallopian tube carcinoma (FTC), or a primary peritoneal carcinoma (PPC).
3. The anti-VEGF antibody~~The method~~ of claim 1, wherein said patient is not refractory to previous platinum treatment.
4. The anti-VEGF antibody~~The method~~ of claim 1, wherein said patient has measurable disease according to RECIST 1.0 or CA-125 assessable disease according to the GCIG criteria.
5. The anti-VEGF antibody~~The method~~ of claim 1, wherein said patient has an ECOG performance status of 0-2 and a life expectancy of at least 12 weeks.

~~6. The method of claim 1, wherein said patient has a life expectancy of at least 12 weeks.~~

~~7. The method of claim 1, wherein said chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD).~~

~~8.~~6. The anti-VEGF antibody~~The method~~ of claim 1~~7~~, wherein said effective amount of said paclitaxel is administered at 80 mg/m2 as a 1 hour intravenous infusion on days 1, 8, 15 and 22 q4w.

~~9.~~7. The anti-VEGF antibody~~The method~~ of claim 1~~7~~, wherein said effective amount of said topotecan is administered at 4 mg/m2 as a 30 minute intravenous infusion on days 1, 8 and 15 q4w or at 1.25 mg/m2 as a 30 minute intravenous infusion on days 1 to 5 every three weeks.

~~10. The method of claim 7, wherein said effective amount of said topotecan is administered at 1.25 mg/m2 as a 30 minute intravenous infusion on days 1 to 5 every three weeks.~~

~~11.~~8. The anti-VEGF antibody~~The method~~ of claim 1~~7~~, wherein said effective amount of said PLD is administered at 40 mg/m2 as a 1 mg/min intravenous infusion on day 1 only, then as a 1 hour infusion thereafter, q4w.

~~12.~~9. The anti-VEGF antibody~~The method~~ of claim 1, wherein said anti-VEGF antibody binds the A4.6.1 epitope.

~~13.~~10. The anti-VEGF antibody~~The method~~ of claim 1, wherein said anti-VEGF antibody is bevacizumab.

~~14.~~11. The anti-VEGF antibody~~The method~~ of claim 1, wherein said anti-VEGF antibody comprises a variable heavy chain (VH) and a variable light chain (VL), wherein said VH has an amino acid sequence of SEQ ID NO:2 and said VL has an amino acid sequence of SEQ ID NO:1.

~~15.~~12. The anti-VEGF antibody~~The method~~ of claim 1, wherein said effective amount of said anti-VEGF antibody is 10 mg/kg intravenously every two weeks or 15 mg/kg intravenously every three weeks.

~~16. The method of claim 10, wherein said effective amount of said anti-VEGF antibody is 15 mg/kg intravenously every three weeks.~~

~~17.~~13. The anti-VEGF antibody~~The method~~ of claim 12~~15~~, wherein said effective amount of said anti-VEGF antibody is administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes.

~~18. The method of claim 16, wherein said effective amount of said anti-VEGF antibody is administered initially intravenously over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes.~~

~~19. The method of claim 1, wherein said anti-VEGF antibody is administered first to said patient at the first cycle.~~

~~20. The method of claim 19, wherein subsequent administrations of said anti-VEGF antibody are either prior to or after said chemotherapeutic.~~

~~21. The method of claim 1, wherein said anti-VEGF antibody is administered concurrently with said chemotherapeutic.~~

~~22. The method of claim 1, wherein said median progression-free survival time is prolonged by about 3 months with a hazard ratio (HR) equal to 0.48, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~23. The method of claim 1, wherein said median progression-free survival time is prolonged by at least 3 months or greater with a hazard ratio (HR) equal to 0.48, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~24. The method of claim 1, wherein said median progression-free survival time is prolonged by about 3 months with a hazard ratio (HR) from about 0.32 to about 0.57, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~25. The method of claim 1, wherein said median progression-free survival time is prolonged by at least 3 months or greater with a hazard ratio (HR) from about 0.32 to about 0.57, as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~26. The method of claim 22, 23, 24 or 25, wherein said patient is less than 65 years old.~~

~~27. The method of claim 22, 23, 24 or 25, wherein said patient is equal to or greater than 65 years old.~~

~~28.~~14. The anti-VEGF antibody~~The method~~ of claim ~~122, 23, 24 or 25~~, wherein said patient has a platinum free interval (PFI) of less than 3 months.

~~29. The method of claim 22, 23, 24 or 25, wherein said patient has a PFI of 3 to 6 months.~~

~~30.~~15. The anti-VEGF antibody~~The method~~ of claim ~~122, 23, 24 or 25~~, wherein said patient has abdominal ascites.

~~31. The method of claim 22, 23, 24 or 25, wherein said patient does not have abdominal ascites.~~

~~32.~~16. The anti-VEGF antibody~~The method~~ of claim 1, wherein said treatment further improves said patient's objective response rate (ORR) as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.

~~33. The method of claim 32, wherein said ORR is improved by at least 1.5 fold as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~34. The method of claim 32, wherein said ORR is improved by at least 2 fold as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~35. The method of claim 32, wherein said ORR is improved to about 30.9% as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~36. The method of claim 25, wherein said chemotherapeutic is paclitaxel and further wherein said patient's median progression-free survival time is prolonged by at least 6 months or greater with a hazard ration (HR) of about 0.46 as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~37. The method of claim 24, wherein said chemotherapeutic is pegylated liposomal doxorubicin (PLD) and further wherein said patient's median progression-free survival time is prolonged by at least 2 months or greater with a hazard ration of about 0.57 as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~38. The method of claim 25, wherein said chemotherapeutic is topotecan and further wherein said patient's median progression-free survival time is prolonged by at least 3 months or greater with a hazard ratio (HR) of about 0.32 as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.~~

~~39. The method of claim 33, wherein said chemotherapeutic is paclitaxel.~~

~~40. The method of claim 33, wherein said chemotherapeutic is pegylated liposomal doxorubicin (PLD).~~

~~41. The method of claim 34, wherein said chemotherapeutic is topotecan.~~

42. A kit comprising an anti-VEGF antibody binding essentially to epitope A4.6.1, a chemotherapeutic and a package insert or label with instructions to treat a patient diagnosed with a platinum-resistant ovarian cancer comprising administering to said patient an effective amount of an anti-VEGF antibody and a chemotherapeutic, wherein said patient received two or fewer prior anti-cancer regimens, wherein said treatment prolongs said patient's median progression-free survival time as compared to a platinum-resistant ovarian cancer patient receiving said chemotherapeutic alone.

43. The kit of claim 42, wherein said platinum-resistant ovarian cancer is an epithelial ovarian cancer (EOC), a fallopian tube carcinoma (FTC), or a primary peritoneal carcinoma (PPC).

44. The kit in claim 42, wherein said anti-VEGF antibody is bevacizumab and said chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD).

45. A method of promoting administration of an anti-VEGF antibody binding essentially to epitope A4.6.1, and a chemotherapeutic to treat platinum-resistant ovarian cancer in a patient, wherein said promotion is by written material.

46. The method of claim 45, wherein said anti-VEGF antibody is bevacizumab, and said chemotherapeutic is selected from the group consisting of paclitaxel, topotecan or a pegylated liposomal doxorubicin (PLD).

47. The method of claim 45, wherein said written material is a package insert or label that accompanies a commercial formulation of said anti-VEGF antibody and said chemotherapeutic.