CLAIMS

~~1. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for treating rapamycin insensitive prostate cancer in a patient having rapamycin insensitive prostate cancer,~~

~~wherein the rapamycin insensitive prostate cancer is not E-twenty six overexpressing castration-resistant prostate cancer.~~

~~2. The use of claim 1, wherein the rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated.~~

~~3. The use of claim 2, wherein the rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.~~

~~4. The use of claim 1, wherein said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof is to be administered to a patient in a unit dosage form comprising 0.25 mg, 1.0 mg, or 5.0 mg of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.~~

~~5. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for improving a condition according to the Prostate-Specific Antigen Working Group 2 (PSAWG2) Criteria for rapamycin insensitive prostate cancer of a patient having rapamycin insensitive prostate cancer,~~

~~wherein the rapamycin insensitive prostate cancer is not E-twenty six overexpressing castration-resistant prostate cancer.~~

~~6. The use of claim 5, wherein the rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated.~~

~~7. The use of claim 6, wherein the rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.~~

~~8. An *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having rapamycin insensitive prostate cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof .~~

~~9. The method of claim 8, wherein the rapamycin insensitive prostate cancer is not E-twenty six overexpressing castration-resistant prostate cancer and the prostate cancer is that in which the PI3K/mTOR pathway is activated.~~

~~10. The method of claim 9, wherein the rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.~~

~~11. An *in vitro* method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having rapamycin insensitive prostate cancer, comprising measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample of said patient who was administered an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to~~

~~administration of an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(trans-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof .~~

~~12. The method of claim 11, wherein the rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated.~~

~~13. The method of claim 12, wherein rapamycin insensitive prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.~~

1. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for treating prostate cancer, wherein the prostate cancer is not ETS overexpressing castration-resistant prostate cancer.

2. The use of claim 1, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

3. The use of claim 2, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

4. The use of claim 1, wherein said patient is to be administered about 0.5 mg/day to about 128 mg/day of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

5. The use of claim 4, wherein said patient is to be administered 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, 120

mg/day or 128 mg/day of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

6. The use of claim 1, wherein said patient is to be administered a unit dosage form comprising 0.25 mg, 1.0 mg, 5.0 mg, 25 mg, 45 mg or 50 mg of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

7. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for improving the Prostate-Specific Antigen Working Group 2 (PSAWG2) Criteria for prostate cancer of a patient, wherein the prostate cancer is not ETS overexpressing castration-resistant prostate cancer.

8. The use of claim 7, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

9. The use of claim 8, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

10. A method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having prostate cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of said patient which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, measuring the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of said patient which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or

tautomer thereof, and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological samples , wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof indicates inhibition.

11. The method of claim 10, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

12. The method of claim 11, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

13. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a patient having prostate cancer.

14. Use according to claim 13, wherein inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having prostate cancer is measured by measuring the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of said patient which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, measuring the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of said patient which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or

tautomer thereof, and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological samples , wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof indicates inhibition.

15. The use of claim 13 or 14, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

16. The use of claim 15, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

17. A method for measuring inhibition of DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having prostate cancer, comprising measuring the amount of phosphorylated DNA-PK in a biological sample of said patient which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, measuring the amount of phosphorylated DNA-PK in a biological sample of said patient which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing the amount of phosphorylated DNA-PK in said biological samples, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said 7-(6-

(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4 dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof indicates inhibition.

18. The method of claim 17, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

19. The method of claim 18, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

20. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having prostate cancer.

21. Use according to claim 20, wherein inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having prostate cancer is measured by measuring the amount of phosphorylated DNA-PK in a biological sample of said patient which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, measuring the amount of phosphorylated DNA-PK in a biological sample of said patient which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing the amount of phosphorylated DNA-PK in said biological samples, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4 dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-

b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof indicates inhibition.

22. The use of claim 20 or 21, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

23. The use of claim 22, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

24. A method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having prostate cancer, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in a biological sample of said patient which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in a biological sample of said patient which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT in said biological samples.

25. The method of claim 24, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

26. The method of claim 25, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

27. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or

tautomer thereof in the manufacture of a medicament for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having prostate cancer.

28. Use according to claim 27, wherein measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having prostate cancer comprises measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in a biological sample of said patient which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in a biological sample of said patient which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT in said biological samples.

29. The use of claim 27 or 28, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

30. The use of claim 29, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

31. A method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having prostate cancer, comprising measuring the amount of phosphorylated DNA-PK S2056 present in said skin sample which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in a skin sample which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically

acceptable salt, stereoisomer or tautomer thereof to said patient, and comparing said amount of phosphorylated DNA-PK S2056 in said skin samples.

32. The method of claim 31, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

33. The method of claim 32, wherein prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

34. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a medicament for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having prostate cancer.

35. Use according to claim 34, wherein inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having prostate cancer is measured by measuring the amount of phosphorylated DNA-PK S2056 present in said skin sample which was obtained after administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in a skin sample which was obtained prior to administration of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof to said patient, and comparing said amount of phosphorylated DNA-PK S2056 in said skin samples.

36. The use of claim 34 or 35, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated.

37. The use of claim 36, wherein the prostate cancer is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

38. A kit comprising 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and means for monitoring inhibition of phosphorylation of DNA-PK in a biological sample of a patient, wherein said patient has prostate cancer.

39. Use of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and means for monitoring patient response to administration of said 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in the manufacture of a kit, wherein said patient has prostate cancer.