CLAIMS

We claim:

1. Use of tipifarnib ~~a composition~~ in the manufacture of a medicament that is to be administered in combination with a therapeutically effective amount of PI3K-α inhibitor BYL719 for a method of treating a head and neck squamous cell carcinoma (HNSCC) in a subject, wherein the HNSCC is a wild-type H-Ras-overexpressing HNSCC ~~the composition comprising a farnesyltransferase inhibitor (FTI), wherein the medicament is to be administered to said subject that has H-Ras overexpressing SCC~~.

~~2. The use of claim 1, wherein said subject has a H-Ras expression that is at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 10 fold, at least 15 fold, or at least 20 fold greater than a reference level.~~

2.~~3.~~ The use of claim 1 ~~or claim 2~~, wherein the HNSCC has wild-type H-Ras overexpression that is greater than a ~~reference level is the~~ median expression level of wild-type H-Ras in corresponding tissue in a population of healthy subjects.

3.~~4.~~ The use of claim 1 ~~or claim 2~~, wherein the HNSCC has wild-type H-Ras overexpression that is greater than a ~~reference level is the~~ median expression level of wild-type H-Ras in corresponding tissue in a population of subjects having HNSCC.

~~5. Use of a composition in the manufacture of a medicament for a method of treating a SCC in a subject, the composition comprising a FTI, wherein said subject has a higher ratio of H-Ras expression to K-Ras expression than a reference ratio.~~

~~6. Use of a composition in the manufacture of a medicament for a method of treating a SCC in a subject, the composition comprising a FTI, wherein said subject has a higher ratio of H-Ras expression to N-Ras expression than a reference ratio.~~

~~7. Use of a composition in the manufacture of a medicament for a method of treating a SCC in a subject, the composition comprising a FTI, wherein said subject has a higher ratio of H-Ras expression to the combined expression of K-Ras and N-Ras than a reference ratio.~~

~~8. The use of any one of claims 5 to 7, wherein the reference ratio is the median ratio in a population of healthy subjects.~~

~~9. The use of any one of claims 5 to 7, wherein the reference level is the median ratio in a population of subjects having SCC.~~

~~10. The use of any one of claims 5 to 7, wherein the reference ratio is 1/10, 1/9, 1/8, 1/7, 1/6, 1/5, 1/4, 1/3, 1/2, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.~~

~~11. The use of any one of claims 1 to 10, wherein said SCC has an H-Ras mutation.~~

~~12. The use of claim 11, wherein said H-Ras mutation is or comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from a group consisting of G12, G13, Q61, Q22, K117, A146, and any combination thereof, in the corresponding mutant H-Ras protein.~~

~~13. The use of any one of claims 1 to 12, wherein the SCC is head and neck SCC (HNSCC), lung SCC (LSCC), thyroid SCC (TSCC), esophagus SCC (ESCC), bladder SCC (BSCC), or urothelial carcinoma (UC).~~

~~14. The use of claim 13, wherein the SCC is HNSCC.~~

4. The use of any one of claims 1-3, wherein the HNSCC expresses wild-type PI3K-α protein.

5. The use of any one of claims 1-4, wherein the HNSCC has amplified wild-type PIK3CA gene.

6. The use of any one of claims 1-5, wherein the HNSCC expresses mutant PI3K-α protein.

7. The use of any one of claims 1-6, wherein the HNSCC has a PIK3CA gene mutation.

8. The use of claim 7, wherein the PIK3CA gene mutation comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from a group consisting of G118, E545, and a combination thereof, in the corresponding wild-type PI3K-α protein.

9. The use of any one of claims 1-8, wherein the HNSCC has amplified mutant PI3K-α protein.

10.~~15.~~ The use of any one of claims 1-9 ~~claim 14~~, wherein said HNSCC is HNSCC of the trachea, HNSCC of the maxilla, or HNSCC of the oral cavity.

11.~~16.~~ The use of any one of claims 1-10 ~~claims 1-15~~, wherein said HNSCC is human papillomavirus (HPV)-negative.

12.~~17.~~ The use of any one of claims 1-11 ~~claims 1-15~~, wherein said HNSCC is at an advanced stage, relapsed, or refractory ~~or metastatic~~.

13.~~18.~~ The use of any one of claims 1-12 ~~claims 1-15~~, wherein said HNSCC is metastatic ~~relapsed~~.

~~19. The use of any one of claims 1-15, wherein said SCC is refractory.~~

~~20. The use of any one of claims 1-15 or 16-19, wherein the H-Ras expression level in a sample from said subject is analyzed before administration of the medicament to the subject.~~

~~21. The use of claim 20, wherein the K-Ras expression level, N-Ras expression level, or both in the sample are further analyzed.~~

~~22. The use of claim 20 or 21, wherein the protein level of H-Ras, K-Ras, N-Ras, or any combination thereof are measured.~~

~~23. The use of claim 22, wherein the protein level is determined using a immunohistochemistry (IHC) approach, an immunoblotting assay, flow cytometry (FACS), or ELISA.~~

~~24. The use of claim 20 or 21, wherein the mRNA level of H-Ras, K-Ras, N-Ras, or any combination thereof are measured.~~

~~25. The use of claim 24, wherein the mRNA level is measured using qPCR, RT-PCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH.~~

~~26. The use of any one of claims 20 to 25, wherein the mutation status of H-Ras in the sample is further determined.~~

~~27. The use of any one of claims 20 to 26, wherein said sample is a tissue biopsy, a tumor biopsy, or isolated cells.~~

~~28. The use of any one of claims 1-15 or 16-27, wherein the FTI is selected from the group consisting of tipifarnib, lonafarnib, arglabin, perrilyl alcohol, L778123, L739749, FTI-277, L744832, CP-609,754, R208176, AZD3409, and BMS-214662.~~

~~29. The use of claim 28, wherein the FTI is tipifarnib.~~

~~30. The use of claim 29, wherein tipifarnib is to be administered at a dose of 0.05-500 mg/kg body weight.~~

14.~~31~~. The use of any one of claims 1-13 ~~claim 29~~, wherein the tipifarnib is to be administered twice a day.

15.~~32.~~ The use of any one of claims 1-14 ~~claim 29~~, wherein the tipifarnib is to be administered at a dose of 100-1200 mg twice a day.

16.~~33.~~ The use of any one of claims 1-15 ~~claim 29~~, wherein the tipifarnib is to be administered at a dose of 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, 900 mg or 1200 mg twice a day.

17.~~34.~~ The use of any one of claims 1-16 ~~claim 29~~, wherein the tipifarnib is to be administered on days 1-7 and 15-21 of a 28-day treatment cycle, days 1-21 of a 28-day treatment cycle, or days 1-7 of a 28-day treatment cycle.

18.~~35.~~ The use of claim 17 ~~claim 34~~, wherein the tipifarnib is to be administered for at least 1 cycle.

19.~~36.~~ The use of claim 18 ~~claim 35~~, wherein the tipifarnib is to be administered for at least 3 cycles, 6 cycles, 9 cycles, or 12 cycles.

20.~~37.~~ The use of any one of claims 1-19 ~~claims 29, 30-34, or 35-36~~, wherein the tipifarnib is to be administered before, during, or after radiation.

~~38. The use of any one of claims 1-15, 16-17, 18-29, 30-34, or 35-37, wherein the medicament is to be administered with a second active agent.~~

21.~~39.~~ The use of any one of claims 1-20 ~~claim 38~~, wherein the tipifarnib is to be administered before, during, or after the administration of the PI3K-α inhibitor BYL719 ~~said second active agent~~.

~~40. The use of claim 38 to 39, wherein said second active agent is selected from the group consisting of a DNA-hypomethylating agent, an alkylating agent, a topoisomerase inhibitor, a therapeutic antibody that specifically binds to a cancer antigen, a hematopoietic growth factor, a cytokine, an antibiotic, a cox-2 inhibitor, a CDK inhibitor, a PI3K-α inhibitor, an AKT inhibitor an MTOR 1/2 inhibitor, an immunomodulatory agent, an anti-thymocyte globulin, an immunosuppressive agent, and a corticosteroid or a pharmacological derivative thereof.~~

~~41. The use of claim 38 to 39, wherein said second active agent is an EGFR inhibitor.~~

~~42. The use of claim 41, wherein said EGFR inhibitor is cetuximab.~~

~~43. The use of claim 38 to 39, wherein said second active agent is an alkylating agent.~~

~~44. The use of claim 43, wherein said alkylating agent is cisplatin.~~

~~45. The use of claim 38 to 39, wherein said second active agent is a CDK inhibitor.~~

~~46. The use of claim 45, wherein said CDK inhibitor is palbociclib.~~

~~47. The use of claim 38 to 39, wherein said second active agent is a PI3K-α inhibitor.~~

~~48. The use of claim 47, wherein said PI3K-α inhibitor is BYL719.~~

~~49. The use of claim 38 to 39, wherein said second active agent is an AKT inhibitor.~~

~~50. The use of claim 49, wherein said AKT inhibitor is GSK2141795.~~

~~51. The use of claim 38 to 39, wherein said second active agent is an MTOR 1/2 inhibitor.~~

~~52. The use of claim 51, wherein said MTOR 1/2 inhibitor is INK-128.~~

~~53. The use of claim 38 to 39, wherein said second active agent is an anti-PD1 antibody, an anti-PDL1 antibody, or an anti-CTLA-4 antibody.~~

22.~~54.~~ The use of any one of claims 1-21 ~~claims 1-15, 16-27, 28-29, 30-34, or 35-37~~, wherein the medicament is to be administered with a support care therapy.