CLAIMS

1. An *in vitro* method of detecting the presence of drug-tolerant persister (DTP) cells resistant to epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in a subject having EGFR-mutated non-small cell lung cancer (NSCLC), the method comprising:

(a) detecting an expression level of ALPP in a blood sample or tumour sample that has been obtained from the subject after the subject has received treatment with one or more EGFR-TKIs; and

(b) comparing the expression level of ALPP with a reference ALPP expression level, wherein the reference ALPP expression level is derived from a EGFR-TKI treatment naïve blood sample or tumour sample with a low to undetectable ALPP expression level,

wherein an increased expression level of ALPP in the blood sample or tumour sample relative to the reference ALPP expression level is indicative of the presence of the DTP cells in the subject's EGFR-mutated NSCLC.

2. The method of claim 1, wherein the one or more EGFR-TKIs have been administered to the subject on a continuous dosing schedule before the blood sample or tumour sample in step (a) has been obtained.

3. The method of claim 2, wherein the continuous dosing schedule is for at least 7 days.

4. The method of claim 1 or 2, wherein the EGFR-TKI treatment naïve blood sample or tumour sample has been obtained from the subject before receiving treatment with one or more EGFR-TKIs.

5. The method of any one of claims 1-4, wherein detecting the ALPP expression level comprises quantifying ALPP protein or an ALPP RNA transcript.

6. The method of any one of claims 1-5, wherein the increased expression level of ALPP comprises an increase of at least 10-fold or a log2 fold-change of at least 7 relative to the reference ALPP expression level.

7. The method of claim 1, wherein the one or more EGFR-TKIs have been administered to the subject on a continuous dosing schedule for 7 days before the blood sample or tumour sample has been obtained, and the method further comprises detecting a surface expression level of ALPP of cancer cells in the blood sample or tumour sample by fluorescence-activated cell sorting (FACS), wherein a high surface expression level of ALPP ($ALPP^{high}$) is indicative of DTP cells and a low surface expression level of ALPP ($ALPP^{low}$) is indicative of intrinsically resistant cells, wherein $ALPP^{high}$ is a fluorescence intensity of at least 10^4 arbitrary units and $ALPP^{low}$ is a fluorescence intensity below 10^3 arbitrary units.

8. The method of claim 1, wherein the one or more EGFR-TKIs have been administered to the subject on a continuous dosing schedule for more than 7 days before the blood sample or tumour sample has been obtained, and the method further comprises detecting a surface expression level of ALPP of cancer cells in the blood sample or tumour sample by fluorescence-activated cell sorting (FACS), wherein a low surface expression level of ALPP ($ALPP^{low}$) is indicative of fast-cycling drug-tolerant expanded persister (DTEP) cells, and a high surface expression level of ALPP ($ALPP^{high}$) is indicative of slow-cycling DTEP cells, wherein $ALPP^{high}$ is a fluorescence intensity of at least 10^4 arbitrary units and $ALPP^{low}$ is a fluorescence intensity below 10^3 arbitrary units.

9. The method of claim 7 or 8, further comprising isolating (i) the DTP cells and/or intrinsically resistant cells, or (ii) fast-cycling DTEP cells and/or slow-cycling DTEP cells, from the blood sample or tumour sample using fluorescence-activated cell sorting (FACS).

10. The method of any one of claims 1-9, further comprising classifying the likelihood of the subject being responsive or non-responsive to further EGFR-TKI treatment and/or an anti-ALPP therapy based on the presence of DTP cells in the blood sample or tumour sample.

11. The method of any one of claims 1-10, wherein the EGFR-mutated NSCLC is an EGFR-mutated lung adenocarcinoma (LUAD).

12. The method of any one of claims 1-11, wherein the one or more EGFR-TKIs comprise gefitinib and/or osimertinib.

13. An *in vitro* method of monitoring the efficacy of a EGFR-TKI treatment in a subject having EGFR-mutated NSCLC, the method comprising:

(a) detecting a reference ALPP expression level in a reference blood sample or tumour sample obtained from the subject before the EGFR-TKI treatment, wherein the reference ALPP expression level is low to undetectable;

(b) detecting an expression level of ALPP in a blood sample or tumour sample that has been obtained from the subject after the subject has received the EGFR-TKI treatment, wherein the EGFR-TKI treatment comprises one or more EGFR-TKIs having been administered to the subject; and

(c) comparing the expression level of ALPP with the reference ALPP expression level,

wherein an increased expression level of ALPP in the blood sample or tumour sample relative to the reference ALPP expression level is indicative of the presence and optionally the quantity, of the DTP cells in the subject's EGFR-mutated NSCLC,

wherein the presence of DTP cells in the blood sample or tumour sample is indicative of the efficacy of the EGFR-TKI treatment.

14. The method of claim 13, further comprising repeating steps (b) to (c) using a blood sample or tumour sample that has been obtained at two or more predetermined time points during and after

the EGFR-TKI treatment, wherein the detected presence or quantity of DTP cells at the two or more predetermined time points is compared to assess progression of the EGFR-mutated NSCLC and efficacy of the EGFR-TKI treatment.

15. The method of claim 13 or 14, further comprising selecting a EGFR-mutated NSCLC cancer treatment regimen for the subject comprising a EGFR-TKI treatment and/or an anti-ALPP therapy based on the presence, and optionally the quantity, of the DTP cells in the blood sample or tumour sample.

16. Use of an antibody-drug Conjugate (ADC) that specifically binds ALPP, in the manufacture of a medicament for treating EGFR-mutated NSCLC cancer in a subject, wherein the subject has previously received treatment with one or more EGFR-TKIs, and wherein cancer cells having a high surface expression level of ALPP ($ALPP^{high}$) have been detected in a blood sample or tumour sample that has been obtained from the subject after the subject has received the treatment with one or more EGFR-TKIs.