**Supplementary Figure S26. Validation of mass spectrometry and inhibitors’ activity**

### a. Quantitative Mass Spectrometry of PTM

#### T0 Components

- Latency
- Dormancy
- Awakening
- TEPs

#### PCA Analysis

**PCA: MCF7**

- Component 2 (21.6%)

**PCA: T47D**

- Component 2 (21.6%)

### b. Mass spectrometry validation

**MCF7 - H3K27me3**

- T0
- 14d

**MCF7 - H3K9me3**

- T0
- 14d

**Densitometric analysis**

- T0
- 30d
- E2
- AI
- Vehicle

### c. T47D - H3K9me3

- T0
- 30d
- E2
- AI
- Vehicle

**Densitometric analysis**

- T0
- 30d
- E2
- AI
- Vehicle

### d. Inhibitors’ validation

**G9ai (HKMTi-1-005)**

- MCF7
- T47D

**Densitometric analysis**

- +E2
- -E2

**H3K9me2**

- Vehicle
- G9ai

### e. EZH2i (GSK343)

- MCF7
- T47D

**Densitometric analysis**

- +E2
- -E2

### f. KMT5B/Ci (A-196)

- MCF7
- T47D

**Densitometric analysis**

- A-196 (µM)
- 0
- 0.5
- 1
- EZH2i

- +E2
- -E2
Supplementary Figure S26. Validation of mass spectrometry and inhibitors’ activity. a) PCA plots for super-SILAC mass spectrometry of post-translational histone modifications in TRADITIOM dataset for MCF7 and T47D from T0 to TEPs (late progression). b) Mass spectrometry validation of TRADITIOM MCF7 dataset was done with ELISA for H3K27me3 (2 biological and 2 technical replicates) and with Western blotting for H3K9me2. Densitometric analysis (normalized over total H3) is shown in the bar plot. c) Mass spectrometry data of TRADITIOM T47D dataset were validated via Western blotting for H3K9me2 and H4K20me3. Densitometric analyses (normalized over total H4) are shown in bar plots. d) The effective inhibition by G9a inhibitor (HKMTi-1-005) was validated via Western blotting for both MCF7 (1mM, left panel) and T47D (1.5mM, right panel) in either oestrogen supplemented (+E2) or oestrogen deprived conditions (-E2). Densitometric analysis (normalized over total H3) is shown in bar plots. e) The effective inhibition by EZH2 inhibitor (GSK343) was validated via ELISA on two biological replicates for both MCF7 (1mM, left panel) and T47D (1.5mM, right panel) in either oestrogen supplemented (+E2) or oestrogen deprived conditions (-E2). f) The effective inhibition by KMT5B/C inhibitor (A-196) was validated via Western blotting for MCF7 cells (H4K20me1/me2/me3) in either oestrogen supplemented (+E2) or oestrogen deprived conditions (-E2). Densitometric analysis for target H4K20me3 modification is shown in bar plots.