Supplemental Figure Legends

Figure. S1. DNMT1 overexpression was associated with p53 mutation and poor prognosis in TNBC

(**A - E**) Exploration of the effectiveness of antibodies for IHC. Antibodies selected for TMA staining are marked in blue.

(**A - D**) H1299 cancer cell line was treated with decitabine to downregulate DNMTs and 5mC, followed by paraffin embedding and IHC staining using the indicated antibodies. Since DNMT3B was expressed at extremely low level in H1299 cells, they were transfected with a plasmid expressing DNMT3B as a positive control.

(**E**) The p53-null cancer cell line H1299 was transfected with empty vector or a vector expressing wild-type p53. Cells were harvested, followed by paraffin embedding and IHC staining. p53 was stained by the indicated antibodies.

(**F**) Representative DO1 staining patterns in TNBC TMA, absent (0%), scattered (1-40%) and diffuse (41-100%).

(**G**) Analysis of p53 antibodies for staining sensitivity and accuracy. Bars showing the p53 Sanger sequencing results and DO1 and E47 staining patterns in 20 fresh tumor tissues from the TMA cohort.

(**H**) Representative IHC staining images of DNMT1, DNMT3A, DNMT3B and 5mC in tumors with different p53 IHC patterns.

(**I**) Bar graphs demonstrating the correlations between DNMT1, DNMT3A, DNMT3B, 5mC expression levels, p53 IHC patterns and clinicopathological characteristics.

(**J**) Forest plot of univariate Cox regression models predicting the RFS and OS using biomarkers and clinicopathological features. Statistically significant features are marked in red.

(**K**) Kaplan-Meier plots of RFS and OS stratified by DNMT3A, DNMT3B, 5mC

expression level and p53 IHC patterns (* $P < 0.05$, ** $P < 0.01$). HR, hazard ratio. CI, confidence interval.

(**L**) Kaplan-Meier plots of RFS and OS for the 29 p53-wild-type patients stratified by DNMT1 expression levels.

(**M**) Table showing the patient number, RFS events and OS events in total cohort, p53-mutant sub-cohort and p53-wild-type sub-cohort stratified by different clinicopathological features.

Figure. S2. Response and adverse events in the DETECT trial

(**A**) Radiological evaluation of targeted lesions of the indicated patients during treatment.

(**B** and **C**) Kaplan-Meier plots showing the PFS and OS stratified by response. The median survival of each subgroup is shown.

(**D**) Hematological adverse events before and after administration of G-CSF observed in the first 6 enrolled patients.

(**E**) Changes of ALT and AST levels in the 4 patients receiving more than 3 cycles of decitabine treatment.

Figure. S3. Correlation between p53 mutation and response in the DETECT trial

(**A**) Raw TP53 Sanger sequencing profiles of the DNA samples from the indicated patients.

(**B**) Summary of adverse events of patients with different p53 mutation status.

(**C**) Representative IHC staining images of DNMT1 in the 9 patients with available tumor samples before treatment in DETECT.

Figure. S4 Decitabine preferentially inhibited isogenic TNBC cell lines harboring DETECT-derived p53 mutations

(**A**) Box plot of mRNA expression level of *DNMT1* in TNBC and non-TNBC patients in the METABRIC cohort.

(**B**) Box plot of mRNA expression levels of *DNMT1*, *CDKN1A* and *ACTIN* in p53 wild-type (WT) and p53-mutated (MUT) TNBC patients in METABRIC.

(**C**) Immunoblotting of DNMT1, DNMT3A and DNMT3B after treatment of decitabine in concentration gradient in TNBC cell line BT549.

(**D**) Micrographs of the isogenic HCC1937 cell lines infected with the DETECT-derived p53 variants. In the lower panel, fluorescence of the co-infected GFP expression was used to evaluate the infection efficiency.

(**E**) The indicated TNBC cell lines were treated with the indicated concentrations of DAC for 5 days and/or sequential 1.5 μg/ml cisplatin for 1 day, followed by cell viability determination. CI, combination index.

Figure. S5 Decitabine potently induced IRF7-medaited immunity response in p53-deficient TNBC.

(**A**) Bar plots showing the frequency of p53 mutation, mRNA levels of *DNMT1* and *CDKN1A* in tumor samples harboring p53-R282W and p53-G266V in TCGA pan-cancer cohort.

(**B**) Bar plots showing the frequency of p53 mutations R282W and G266V in MSKCC breast cancer cohort.

(**C**) Enrichment assays based on the UP-KEYWORDs analysis for the 870 decitabine-upregulated DEGs. Asterisks represent items involved in immune response.

(**D**) Enrichment assays based on KEGG pathway analysis for the IRGs in the interested cluster in Fig. 5F.

(**E**) PPI network for the decitabine-upregulated IRGs in THP-1 cell based on STRING database.

(**F**) Scatter plots of immune cell infiltration score for the indicated immune cell types against mRNA level of *IRF7* in TCGA TNBC cohort.

Supplementary Tables

Table S1. Baseline characteristics of patients contributing samples to the tissue microarray (TMA)

Characteristics	N	%
Age (years)		
Median	54	
Range	28 - 84	
<= 55	70	53.0
> 55	62	47.0
Menstrual status		
Pre-/peri-	51	38.6
post-	81	61.4
Family history		
No	127	96.2
Yes	5	3.8
Comorbidity		
No	84	63.6
Yes	48	36.4
Breast surgery		
BCS	34	25.8
MX	98	74.2

Axillary surgery			
SLNB	35		26.5
ALND	97		73.5
Tumor size			
Median		2.5	
Range		0 - 13	
<= 2 cm	59		44.7
> 2 cm	73		55.3
Lymph node metastasis			
0	88		66.7
1 - 3	27		20.5
4 - 9	8		6.1
> 9	9		6.8
Pathological type			
IDC	116		87.9
non-IDC	16		12.1
Tumor grade			
I - II	47		35.6
III	65		49.2
NA	20		15.2
LVI			
No	123		93.2

Yes	9	6.8
Ki67 index (%)		
<= 30	37	28.0
> 30	94	71.2
NA	1	0.1

Abbreviations: BCS, breast-conserving surgery; MX, mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; IDC, invasive ductal carcinoma; NA, not available; LVI, lymphovascular invasion.