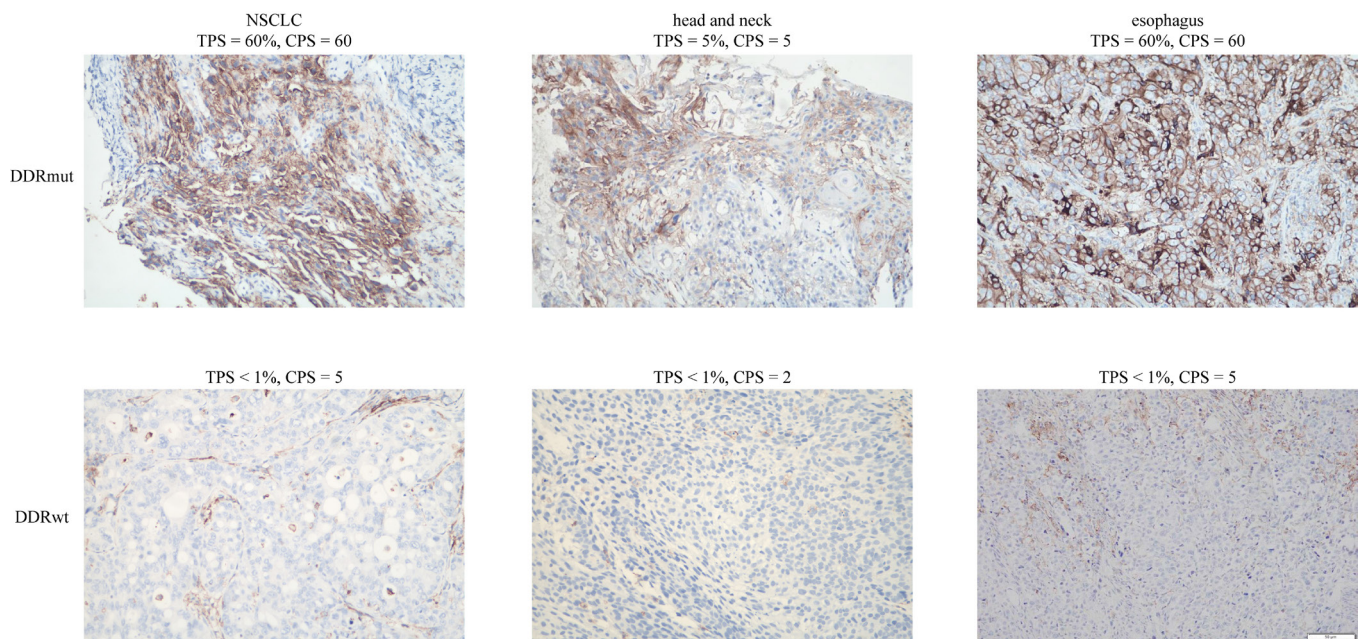
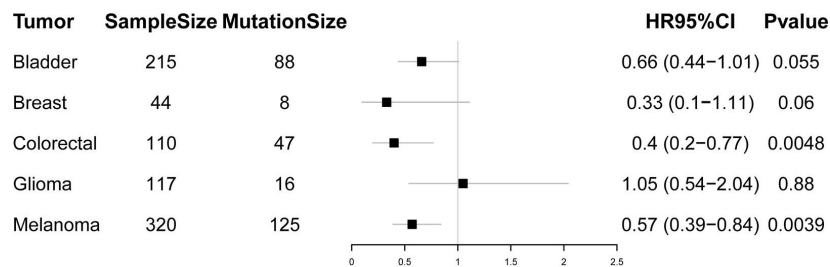


**Figure S1** Analysis of germline DDR gene alterations in pan cancer. (A) Germline DDR gene alterations are frequent and non-uniformly distributed by type and frequency across cancer types. (B) Germline DDR pathway alterations are frequent and non-uniformly distributed by type and frequency across cancer types. (C) Mutual exclusion of germline mutations in different DDR pathways. DDR, DNA damage repair; BER, base excision repair; NER, nucleotide excision repair; MMR, mismatch repair; DS, damage sensor; FA, Fanconi anemia; HR, homology-dependent recombination; NHEJ, non-homologous end joining.



**Figure S2** The representative images of PD-L1 IHC in different cancers with or without DDR mutation. PD-L1, programmed cell death-ligand 1; IHC, immunohistochemistry; DDR, DNA damage repair; NSCLC, non-small cell lung cancer; TPS, tumor proportion score; CPS, combined positive score.



**Figure S3** The result of survival analysis for del-sDDRmut in pan-cancer immunotherapy cohorts. del-sDDRmut, deleterious somatic DDR mutation; DDR, DNA damage repair.

**Table S1** Annotation of 31 DDR genes to specific DDR pathways

Entrez gene ID	Gene description								DDR pathway membership						
	Gene symbol	Gene description	Alias (selected)	Additional comments	Approved sy	Approved name	HGNC ID	Location	BER	NER	MMR	FA	HR	NHEJ	DS
4361	<i>MRE11A</i>	MRE11 homolog A, double strand break repair nuclease			<i>MRE11</i>	MRE11 homolog, double strand break repair nuclease	HGNC:723 0	11q21					MRE11A	MRE11A	
5591	<i>PRKDC</i>	Protein kinase, DNA-activated, catalytic polypeptid			<i>PRKDC</i>	protein kinase, DNA-activated, catalytic polypeptide	HGNC:941 3	8q11.21						PRKDC	
10111	<i>RAD50</i>	RAD50 double strand break repair protein			<i>RAD50</i>	RAD50 double strand break repair protein	HGNC:981 6	5q31.1					RAD50	RAD50	
4292	<i>MLH1</i>	mutL homolog 1			<i>MLH1</i>	mutL homolog 1	HGNC:712 7	3p22.2			MLH1				
4436	<i>MSH2</i>	mutS homolog 2			<i>MSH2</i>	mutS homolog 2	HGNC:732 5	2p21-p16.3			MSH2				
2956	<i>MSH6</i>	mutS homolog 6			<i>MSH6</i>	mutS homolog 6	HGNC:732 9	2p16.3			MSH6				
5395	<i>PMS2</i>	PMS1 homolog 2, mismatch repair system component			<i>PMS2</i>	PMS1 homolog 2, mismatch repair system component	HGNC:912 2	7p22.1			PMS2				
5424	<i>POLD1</i>	Polymerase (DNA directed), delta 1, catalytic subunit		Replication	<i>POLD1</i>	DNA polymerase delta 1, catalytic subunit	HGNC:917 5	19q13.3	POLD1	POLD1	POLD1		POLD1		
472	<i>ATM</i>	ATM serine/threonine kinase			<i>ATM</i>	ATM serine/threonine kinase	HGNC:795	11q22.3							ATM
545	<i>ATR</i>	ATR serine/threonine kinase			<i>ATR</i>	ATR serine/threonine kinase	HGNC:882	3q23							ATR
580	<i>BARD1</i>	BRCA1 associated RING domain 1			<i>BARD1</i>	BRCA1 associated RING domain 1	HGNC:952	2q35				BARD1	BARD1		
641	<i>BLM</i>	Bloom syndrome, RecQ helicase-like			<i>BLM</i>	Bloom syndrome RecQ like helicase	HGNC:105 8	15q26.1				BLM	BLM		
672	<i>BRCA1</i>	Breast cancer 1, early onset			<i>BRCA1</i>	BRCA1, DNA repair associated	HGNC:110 0	17q21.31				BRCA1	BRCA1		
675	<i>BRCA2</i>	Breast cancer 2, early onset			<i>BRCA2</i>	BRCA2, DNA repair associated	HGNC:1101	13q13.1				BRCA2	BRCA2		
83990	<i>BRIP1</i>	BRCA1 interacting protein C-terminal helicase 1	BACH1, FANCI, OF		<i>BRIP1</i>	BRCA1 interacting protein C-terminal helicase 1	HGNC:204 73	17q23.2				BRIP1	BRIP1		
1111	<i>CHEK1</i>	Checkpoint kinase 1			<i>CHEK1</i>	Checkpoint kinase 1	HGNC:192 5	11q24.2							CHEK1
11200	<i>CHEK2</i>	Checkpoint kinase 2			<i>CHEK2</i>	Checkpoint kinase 2	HGNC:166 27	22q12.1							CHEK2
8452	<i>CUL3</i>	Cullin 3			<i>CUL3</i>	Cullin 3	HGNC:255 3	2q36.2		CUL3					
2067	<i>ERCC1</i>	Excision repair cross-complementation group 1			<i>ERCC1</i>	ERCC excision repair 1, endonuclease non-catalytic subunit	HGNC:343 3	19q13.32		ERCC1		ERCC1	ERCC1		
2175	<i>FANCA</i>	Fanconi anemia, complementation group A			<i>FANCA</i>	Fanconi anemia complementation group A	HGNC:358 2	16q24.3				FANCA			
2176	<i>FANCC</i>	Fanconi anemia, complementation group C			<i>FANCC</i>	Fanconi anemia complementation group C	HGNC:358 4	9q22.32				FANCC			
2177	<i>FANCD2</i>	Fanconi anemia, complementation group D2			<i>FANCD2</i>	Fanconi anemia complementation group D2	HGNC:358 5	3p25.3				FANCD2			
2178	<i>FANCE</i>	Fanconi anemia, complementation group E			<i>FANCE</i>	Fanconi anemia complementation group E	HGNC:358 6	6p21.31				FANCE			
2188	<i>FANCF</i>	Fanconi anemia, complementation group F			<i>FANCF</i>	Fanconi anemia complementation group F	HGNC:358 7	11p14.3				FANCF			
2189	<i>FANCG</i>	Fanconi anemia, complementation group G			<i>FANCG</i>	Fanconi anemia complementation group G	HGNC:358 8	9p13.3				FANCG			
55120	<i>FANCL</i>	Fanconi anemia, complementation group L			<i>FANCL</i>	Fanconi anemia complementation group L	HGNC:207 48	2p16.1				FANCL			
4595	<i>MUTYH</i>	mutY DNA glycosylase			<i>MUTYH</i>	mutY DNA glycosylase	HGNC:752 7	1p34.1	MUTYH						
79728	<i>PALB2</i>	Partner and localizer of BRCA2	FANCN		<i>PALB2</i>	Partner and localizer of BRCA2	HGNC:261 44	16p12.2				PALB2	PALB2		
5426	<i>POLE</i>	Polymerase (DNA directed), epsilon, catalytic subunit		Replication	<i>POLE</i>	DNA polymerase epsilon, catalytic subunit	HGNC:917 7	12q24.33	POLE	POLE					
5888	<i>RAD51</i>	RAD51 recombinase	FANCR		<i>RAD51</i>	RAD51 recombinase	HGNC:981 7	15q15.1				RAD51	RAD51		
7465	<i>WEE1</i>	WEE1 G2 checkpoint kinase			<i>WEE1</i>	WEE1 G2 checkpoint kinase	HGNC:127 61	11p15.4							WEE1

DDR, DNA damage repair; BER, base excision repair; NER, nucleotide excision repair; MMR, mismatch repair; DS, damage sensor; FA, Fanconi anemia; HR, homology-dependent recombination; NHEJ, non-homologous end joining.

**Table S2** The baseline clinical of the 10,284 patients

Characteristics	Overall, n=10,284	Biliary tract, n=8,501	Bladder/urinary tract, n=2,261	Breast, n=3,321	Cervix, n=1,691	Colorectum, n=1,0971	Endometrium, n=1,061	Esophagus, n=1,461	GIST, n=571	Head neck, n=2,201	Intestine, n=1,191	Kidney, n=4,581	Liver, n=1,2371	Lung, n=2,8761	Lung (SCLC), n=831	Mediastinal tumor, n=271	Melanoma, n=1,431	Neuroendocrine, n=791	Other, n=2,641	Ovary, n=2,611	Pancreas, n=5,121	Prostate, n=681	Sarcoma, n=2,841	Stomach, n=6,381	Thyroid, n=321	DDR <sup>wt</sup> , n=9,0661	DDR <sup>mut</sup> , n=1,2181	P value	
Age, n [%]																													0.7
<60	5,407 [53]	399 [47]	67 [30]	268 [81]	130 [77]	588 [54]	55 [52]	64 [44]	36 [63]	125 [57]	66 [55]	287 [63]	862 [70]	1,167 [41]	25 [30]	18 [67]	78 [55]	52 [66]	171 [65]	162 [62]	250 [49]	14 [21]	196 [69]	305 [48]	22 [69]	4,774 [53]	633 [52]		
≥60	4,877 [47]	451 [53]	159 [70]	64 [19]	39 [23]	509 [46]	51 [48]	82 [56]	21 [37]	95 [43]	53 [45]	171 [37]	375 [30]	1,709 [59]	58 [70]	9 [33]	65 [45]	27 [34]	93 [35]	99 [38]	262 [51]	54 [79]	88 [31]	333 [52]	10 [31]	4,292 [47]	585 [48]		
Sex, n [%]																													0.066
Female	4,062 [39]	388 [46]	61 [27]	328 [99]	169 [100]	463 [42]	106 [100]	26 [18]	21 [37]	53 [24]	48 [40]	129 [28]	157 [13]	1,026 [36]	16 [19]	12 [44]	69 [48]	26 [33]	109 [41]	260 [100]	196 [38]	0 [0]	147 [52]	236 [37]	16 [50]	3,551 [39]	511 [42]		
Male	6,222 [61]	462 [54]	165 [73]	4 [1.2]	0 [0]	634 [58]	0 [0]	120 [82]	36 [63]	167 [76]	71 [60]	329 [72]	1,080 [87]	1,850 [64]	67 [81]	15 [56]	74 [52]	53 [67]	155 [59]	1 [0.4]	316 [62]	68 [100]	137 [48]	402 [63]	16 [50]	5,515 [61]	707 [58]		
MSS type, n [%]																													<0.001
MSI-H	220 [2.2]	19 [2.4]	5 [2.3]	0 [0]	7 [4.4]	71 [6.8]	24 [24]	0 [0]	1 [1.8]	2 [1.0]	7 [6.3]	5 [1.1]	9 [0.8]	19 [0.7]	0 [0]	0 [0]	1 [0.7]	1 [1.4]	2 [0.8]	6 [2.5]	5 [1.0]	3 [4.6]	0 [0]	33 [5.4]	0 [0]	55 [0.6]	165 [14]		
MSI-L	20 [0.2]	1 [0.1]	1 [0.5]	2 [0.7]	0 [0]	1 [<0.1]	0 [0]	0 [0]	0 [0]	1 [0.5]	0 [0]	0 [0]	1 [<0.1]	9 [0.3]	0 [0]	0 [0]	1 [0.7]	1 [1.4]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 [0.2]	1 [3.2]	15 [0.2]	5 [0.4]		
MSS	9,555 [98]	760 [97]	211 [97]	300 [99]	151 [96]	979 [93]	78 [76]	138 [100]	54 [98]	204 [99]	104 [94]	441 [99]	1,136 [99]	2,794 [99]	80 [100]	25 [100]	138 [99]	70 [97]	251 [99]	234 [98]	477 [99]	62 [95]	259 [100]	579 [94]	30 [97]	8,558 [99]	997 [85]		
PD-L1, n [%]																													0.039
<1%	4,384 [59]	387 [59]	112 [65]	152 [69]	62 [45]	575 [78]	68 [73]	46 [37]	22 [61]	60 [36]	62 [70]	192 [67]	550 [65]	891 [44]	55 [86]	3 [13]	46 [39]	49 [84]	116 [61]	112 [53]	263 [64]	44 [85]	149 [80]	362 [72]	6 [35]	3,868 [60]	516 [56]		
≥1%	3,036 [41]	265 [41]	59 [35]	67 [31]	76 [55]	165 [22]	25 [27]	79 [63]	14 [39]	107 [64]	26 [30]	96 [33]	291 [35]	1,139 [56]	9 [14]	20 [87]	71 [61]	9 [16]	75 [39]	99 [47]	146 [36]	8 [15]	38 [20]	141 [28]	11 [65]	2,629 [40]	407 [44]		
TMB (mut/Mb), median [IQR]	6 [4, 10]	6 [4, 9]	10 [6, 17]	6 [4, 9]	6 [4, 14]	8 [6, 10]	8 [6, 22]	8 [6, 11]	3 [2, 4]	6 [4, 9]	6 [4, 9]	5 [3, 7]	6 [5, 9]	7 [4, 13]	11 [8, 16]	5 [2, 6]	4 [3, 6]	5 [3, 7]	4 [2, 7]	6 [3, 7]	5 [3, 6]	5 [2, 6]	3 [2, 5]	6 [4, 10]	2 [2, 6]	6 [4, 9]	9 [6, 21]	<0.001	
TMB group, n [%]																													<0.001
< Median	5,027 [52]	415 [54]	107 [50]	159 [53]	78 [50]	561 [54]	57 [56]	72 [53]	28 [51]	111 [54]	61 [55]	232 [52]	576 [51]	1,388 [50]	40 [51]	14 [56]	67 [50]	36 [51]	128 [51]	132 [56]	256 [54]	40 [62]	137 [53]	316 [52]	16 [52]	4,637 [54]	390 [34]		
≥ Median	4,650 [48]	359 [46]	107 [50]	140 [47]	78 [50]	483 [46]	45 [44]	63 [47]	27 [49]	96 [46]	50 [45]	213 [48]	564 [49]	1,375 [50]	39 [49]	11 [44]	66 [50]	35 [49]	123 [49]	104 [44]	221 [46]	25 [38]	120 [47]	291 [48]	15 [48]	3,880 [46]	770 [66]		

GIST, gastrointestinal stromal tumor; SCLC, small cell lung cancer; DDR, DNA damage repair; MSS, microsatellite stability; MSI, microsatellite instability; MSI-H, MSI-high; MSI-L, MSI-low; PD-L1, programmed cell death-ligand 1; TMB, tumor mutational burden; mut/Mb, mutations/Mb.