Tips about TP53 and P53 in Breast Cancer

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What Is p53 and Where Is the Gene Located?

- While commonly known as p53, the official name of this gene is **Tumor Protein p53** and its official symbol is **TP53**. TheTP53 gene codes for the TP53 (**p53) protein** which acts as a tumor suppressor and works in response to DNA damage to orchestrate the **repair of damaged DNA.** If the DNA cannot be repaired, the p53 protein prevents the cell from dividing and signals it to undergo apoptosis (programmed cell death).
- **The name p53 is due to protein's 53 kilo-Dalton molecular mass**. The gene which codes for this protein is located on the short (p) arm of chromosome **17 at position 13.1 (17p13.1)**. The gene begins at base pair 7,571,719 and ends at base pair 7, 590,862 making it **19,143 base pairs long**

What Does the p53 Gene Look Like When Translated Into Protein?

The TP53 gene spans **20 kb on** chromosome 17p13 and has **11 exons** and a very large **10 kb intron between exons 1 and 2**.

In humans, **exon 1 is non-coding** and it has been shown that this region could form a stable stem-loop structure which binds tightly to normal p53 but not to mutant p53 proteins

The TP53 gene provides the base pair sequence from which to code for the tumor protein p53, which is **393 amino acids** long. The gene codes for a protein which contains several different domains which include:

TP53 domains

- a) A transactivation domain at the amino (N) - terminus which activates transcription followed by a proline-rich segment.
- b) The proline-rich domain mediates the p53 response to DNA damage through apoptosis. A common polymorphism is the substitution of an **arginine for a proline** at codon #72 but it isn't clear if this substitution is related to cancer or not.
- c) The core domain is the **DNA-binding domain** and is the section of the protein that recognizes specific DNA sequences so it can bind to the DNA

- d) It is followed by the **tetramerization** domain and consists of a **beta-strand**, which interacts with another p53 monomer to form a **dimer**. This dimer formation is followed by an **alpha-helix** which mediates the dimerization of two p53 dimers to form a **tetramer** which is essential for activating p53
- e) The carboxyl (C) -terminus acts in a **regulatory role** recognizing damaged DNA, such as misaligned base pairs or single-stranded DNA

How Does the p53 Protein Function?

- Tumor protein p53 acts as a **tumor suppressor** and was identified in **1979 by Arnold Levine** at **Princeton University**, **David Lane at Dundee University (UK), and William Old at Sloan-Kettering Memorial Hospital**.
- The **p53 phosphoprotein** is located in the nucleus of each cell and works to in response to DNA damage to orchestrate the **repair of the damaged DNA**. If the DNA cannot be repaired, the p53 protein prevents the cell from **dividing and signals it to undergo apoptosis.**

- p53 plays a central role in the coordination of cellular response to stress, such as exposure to **UV radiation and reactive oxygen species** (ROS). ROS are chemically reactive molecules containing oxygen, such as oxygen ions and peroxides.
- Other examples of stress **are heat shock, viral infection, and nutrient depletion.**

- The **MDM2 gene is the target gene of the transcription factor p53 protein**. The encoded MDM2 protein is a nuclear phosphoprotein that binds and **inhibits transactivation by the p53 protein**, as part of an auto-regulatory negative feedback loop. If MDM2 gene is overexpressed, it can result in the excessive inactivation of the p53 protein and thus diminishing its functions.

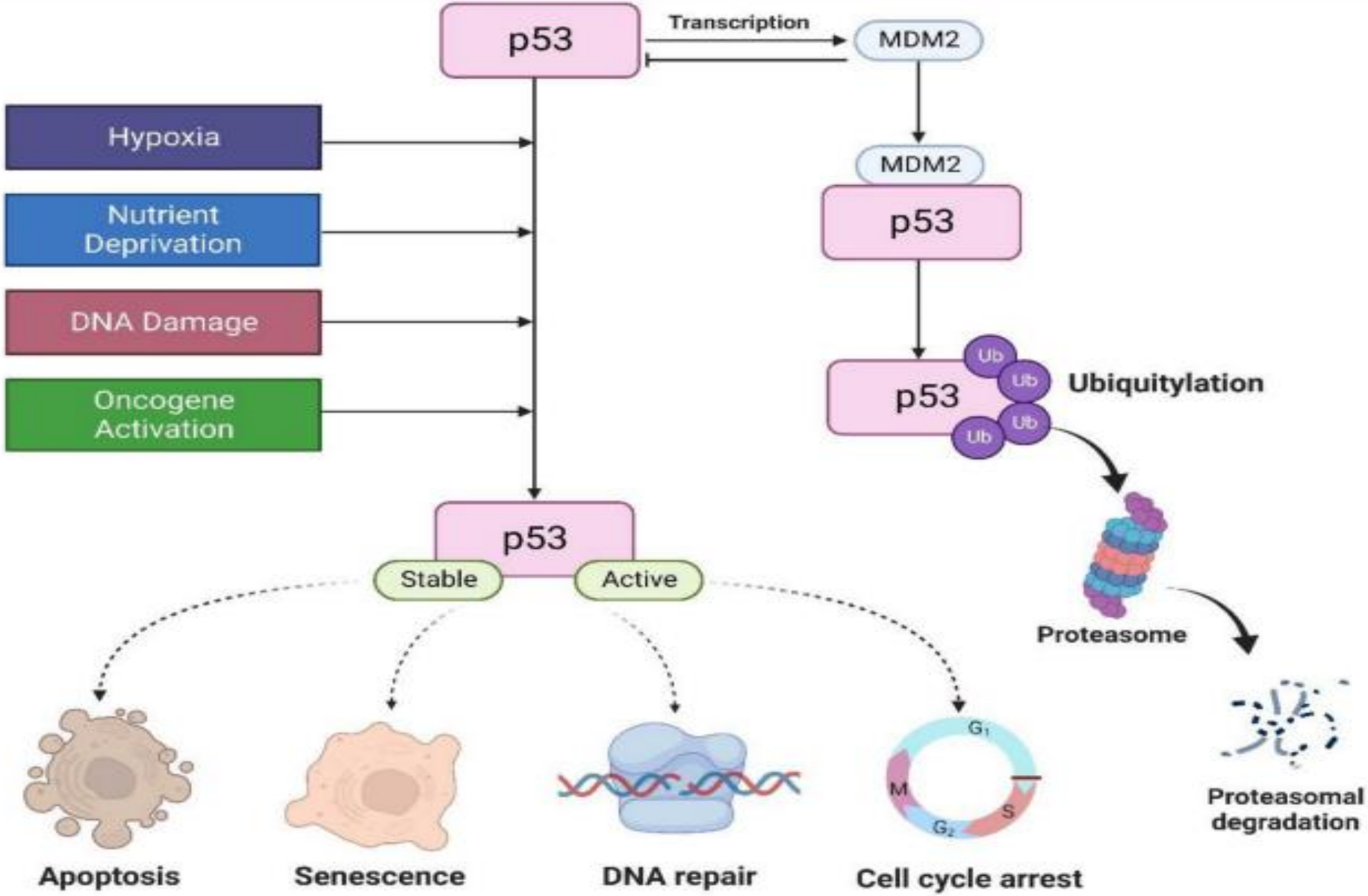
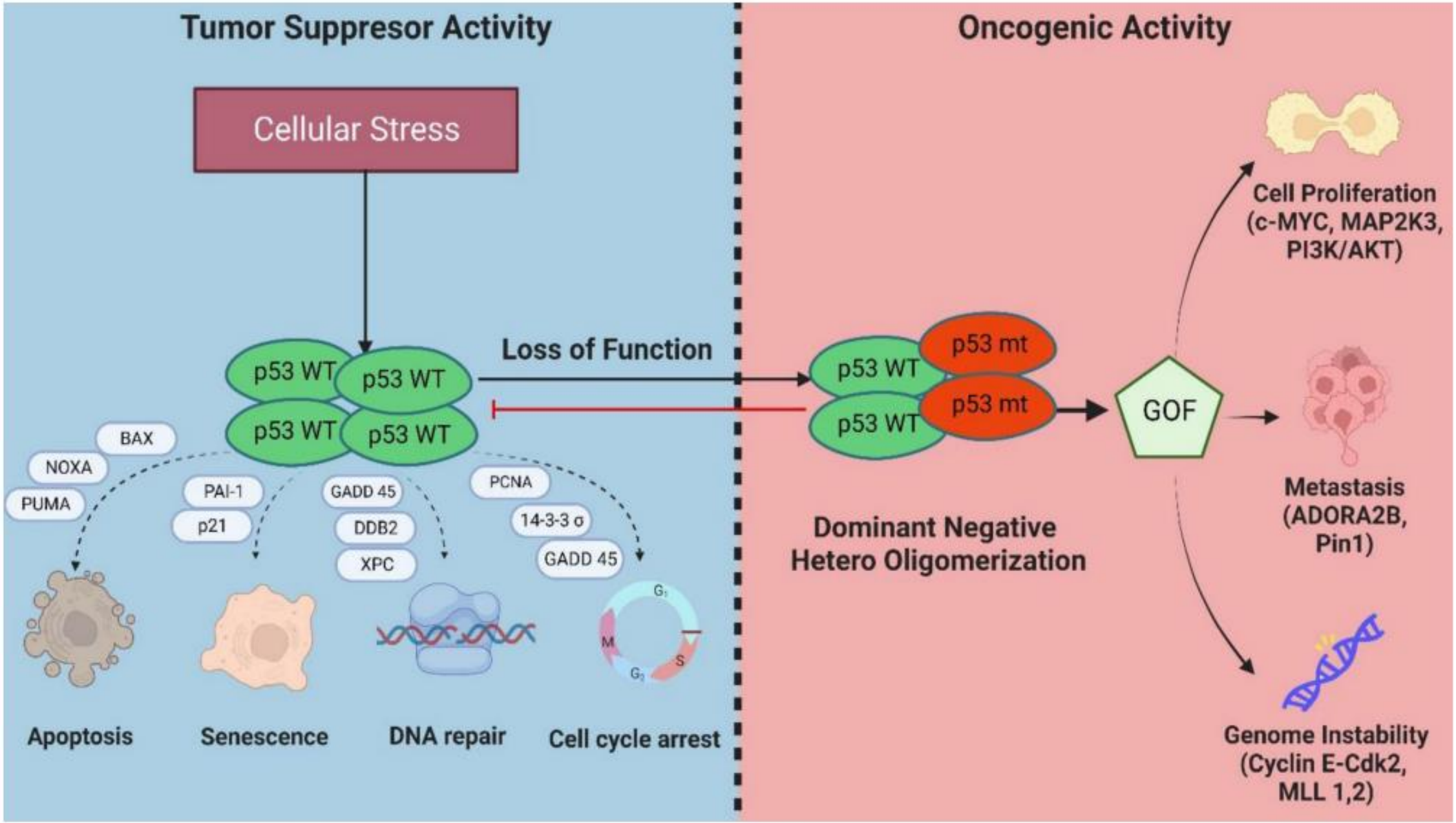


Figure 1. Under normal conditions, MDM2 regulates p53 protein. P53 is activated by hypoxia, activation of oncogenes, DNA damage, and nutrient deprivation to regulate cell cycle, apoptosis, DNA repair, and senescence.



ure 4. Mechanisms of inactivation of the tumor suppressive activity of wild-type p53 and GOF activities in mutant p53-bearing breast tumors.

outline

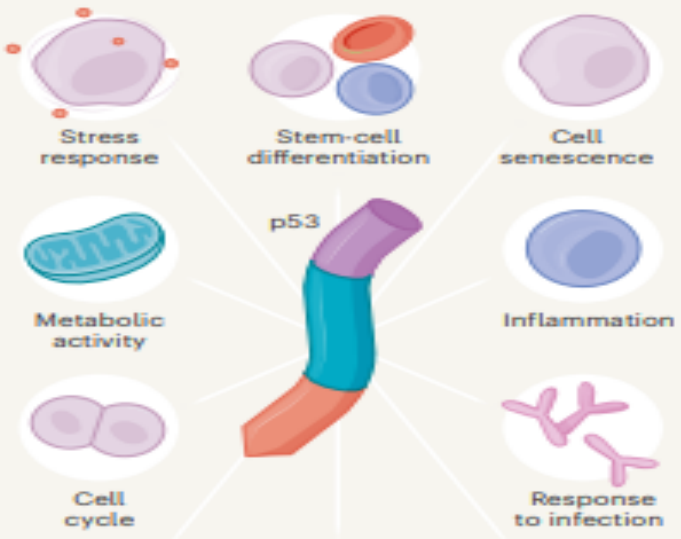
RESTORING PROTECTION

Many tumours exhibit dysfunction of the p53 protein, a crucial suppressor of cancer. But, because the cause of this dysfunction varies, so, too, must potential treatments.
By **Michael Eisenstein**; *infographic by* **Lucy Reading-Ikkanda**

p53 THE VIP

The p53 protein is involved in a dizzying array of healthy physiological functions. In many cases, p53 controls these functions by regulating gene expression.

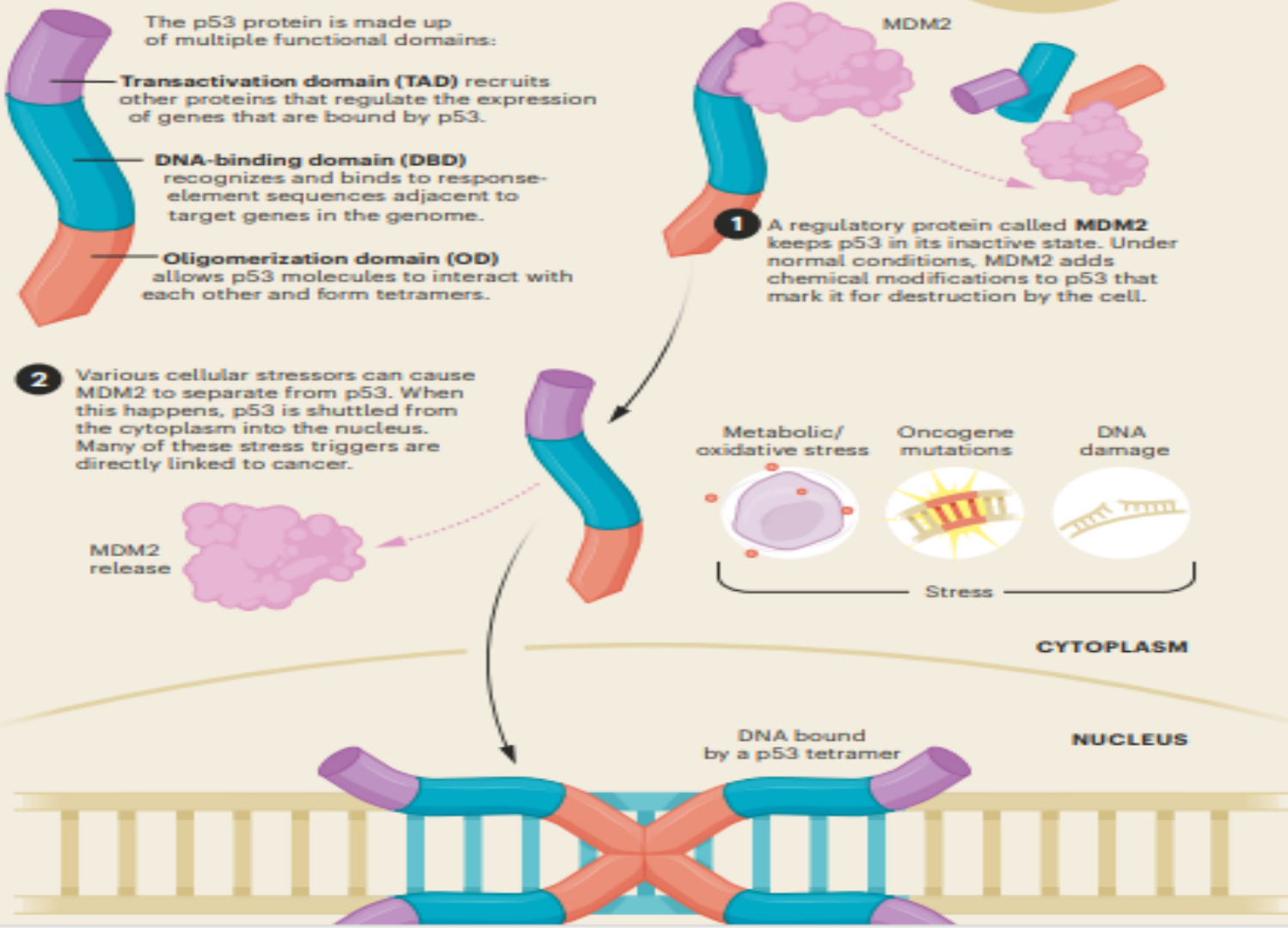
p53 directly regulates more than **300 GENES** with many more indirectly affected[1].

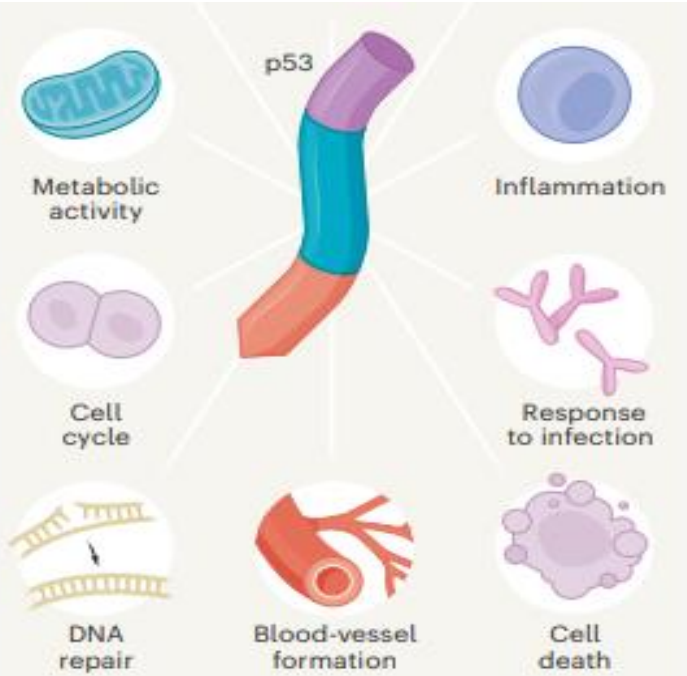


A HEALTHY FUNCTION

Healthy cells express low levels of p53. The protein is normally trapped in an inhibited state, and these inactive p53 molecules are swiftly broken down.

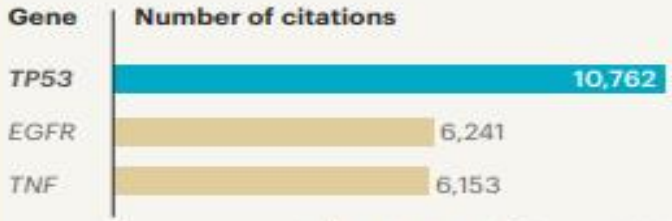
Inactive p53 molecules have an average half-life of just **9 MINUTES**[2].



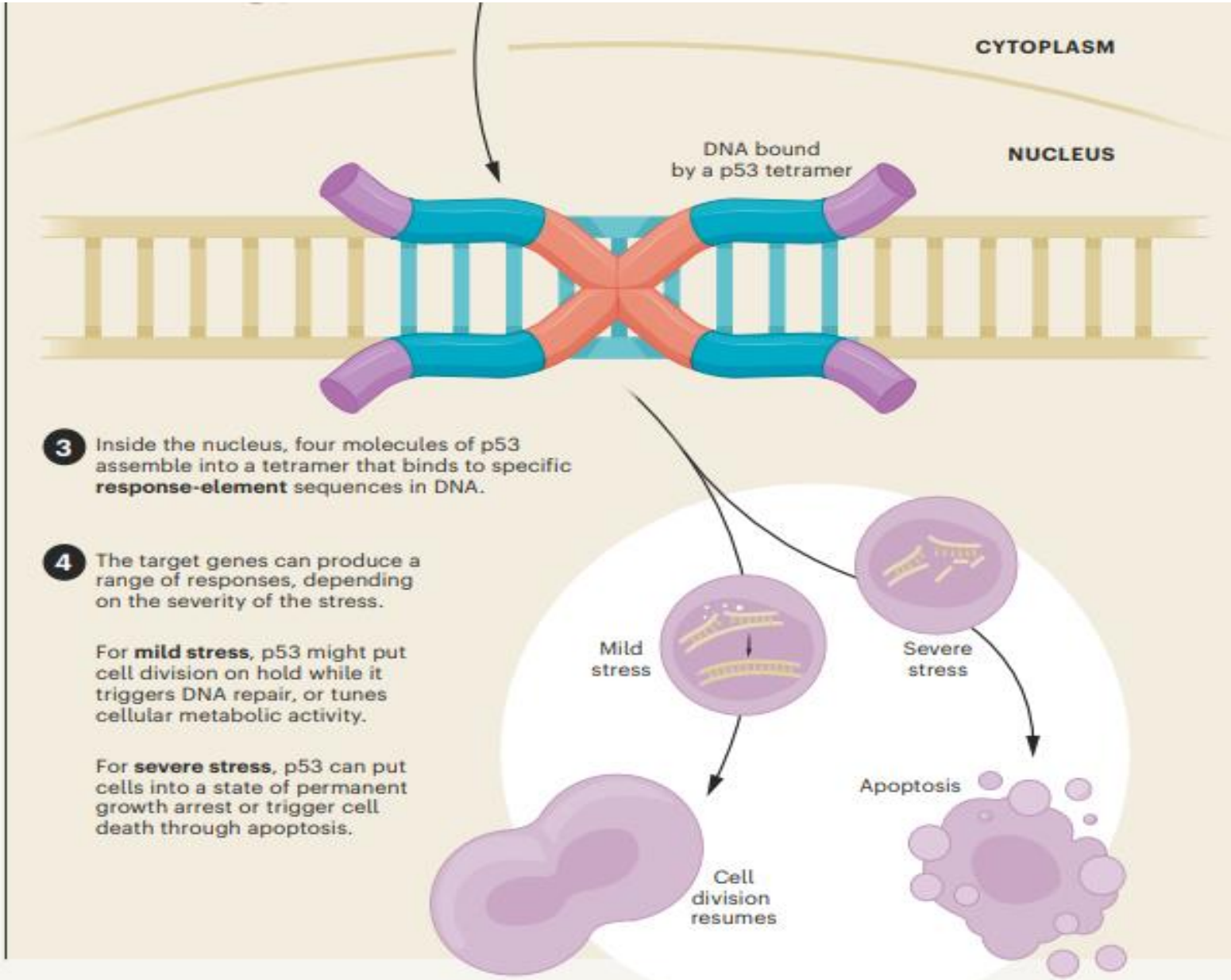


CENTRE OF ATTENTION

The gene that produces p53 (known as *TP53*) is the most well-studied gene in the human genome, having been cited in more than 10,000 papers since its discovery in 1979 (ref. 2).



Data from NCBI-NLM as of 25 January 2022.



Watch an animation at go.nature.com/collections/p53-outline

BROKEN OR BLOCKED

The function of p53 can be lost owing to mutations in the *TP53* gene, or because of the dysfunction of proteins that regulate p53. In either case, these problems give cancer the green light to progress.

The *TP53* gene is mutated in more than **50%** of tumours[1].

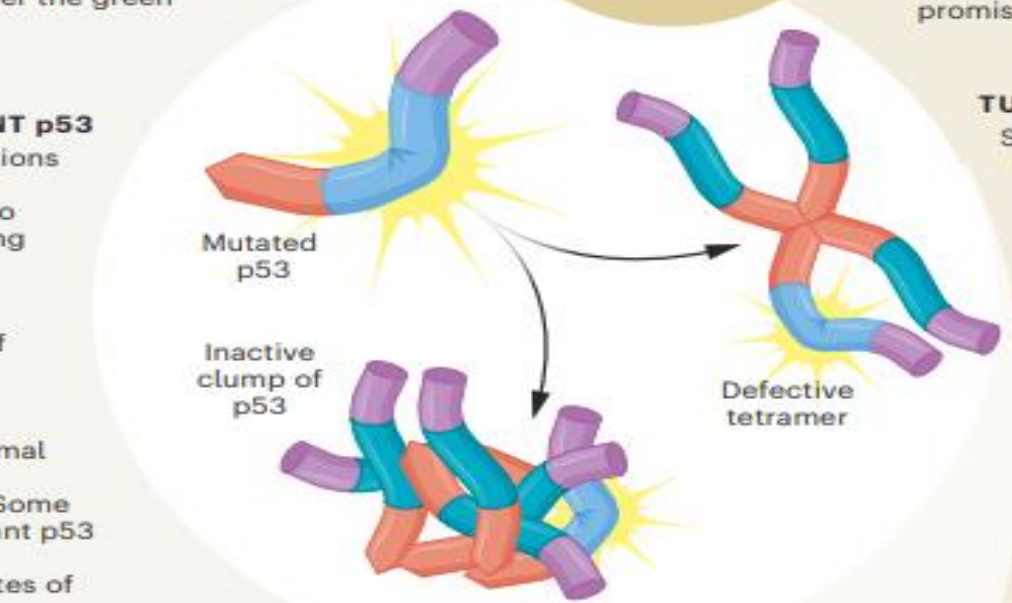
TUMOURS WITH MUTANT p53

Around 80% of p53 mutations affect amino acids in the protein's DBD, causing it to misfold and also interfering with the recognition of target genes[4].

Even one mutated copy of *TP53* can fuel tumour formation, given that a defective p53 protein combined with other, normal p53 proteins will form a non-functional tetramer. Some studies suggest that mutant p53 also inflicts damage by accumulating as aggregates of misfolded proteins[5].

TUMOURS WITH WILD-TYPE p53

Even if *TP53* is not mutated, p53 function can still be disrupted. For example, some tumours produce excessive MDM2 that keeps p53 trapped in an inactive state.



A CHANCE OF TREATMENT

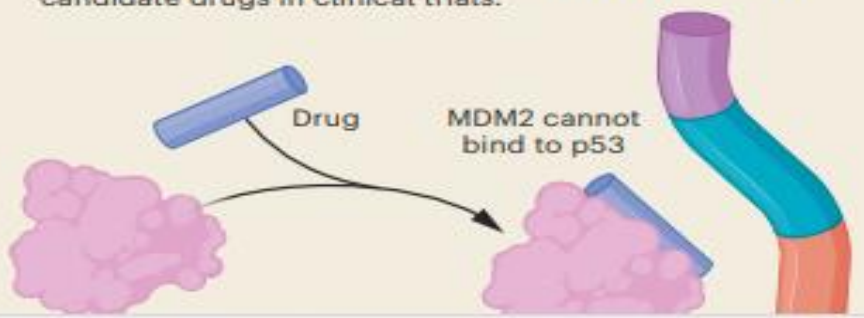
Even after 40 years of research, clinicians still lack drugs that can specifically target tumours with p53 dysfunction. But several promising therapeutic strategies are now undergoing trials.

TUMOURS WITH MUTANT p53

Some small-molecule drugs can bind mutant p53 in a way that restores normal folding. Several such drugs are now in preclinical or early-stage clinical development[6]. However, this approach requires therapy to be tailored to each patient's particular *TP53* mutation.

TUMOURS WITH WILD-TYPE p53

Drugs that block MDM2's ability to inhibit p53 might offer a solution for tumours that produce an excess of MDM2 (ref. 7). Multiple companies currently have such candidate drugs in clinical trials.



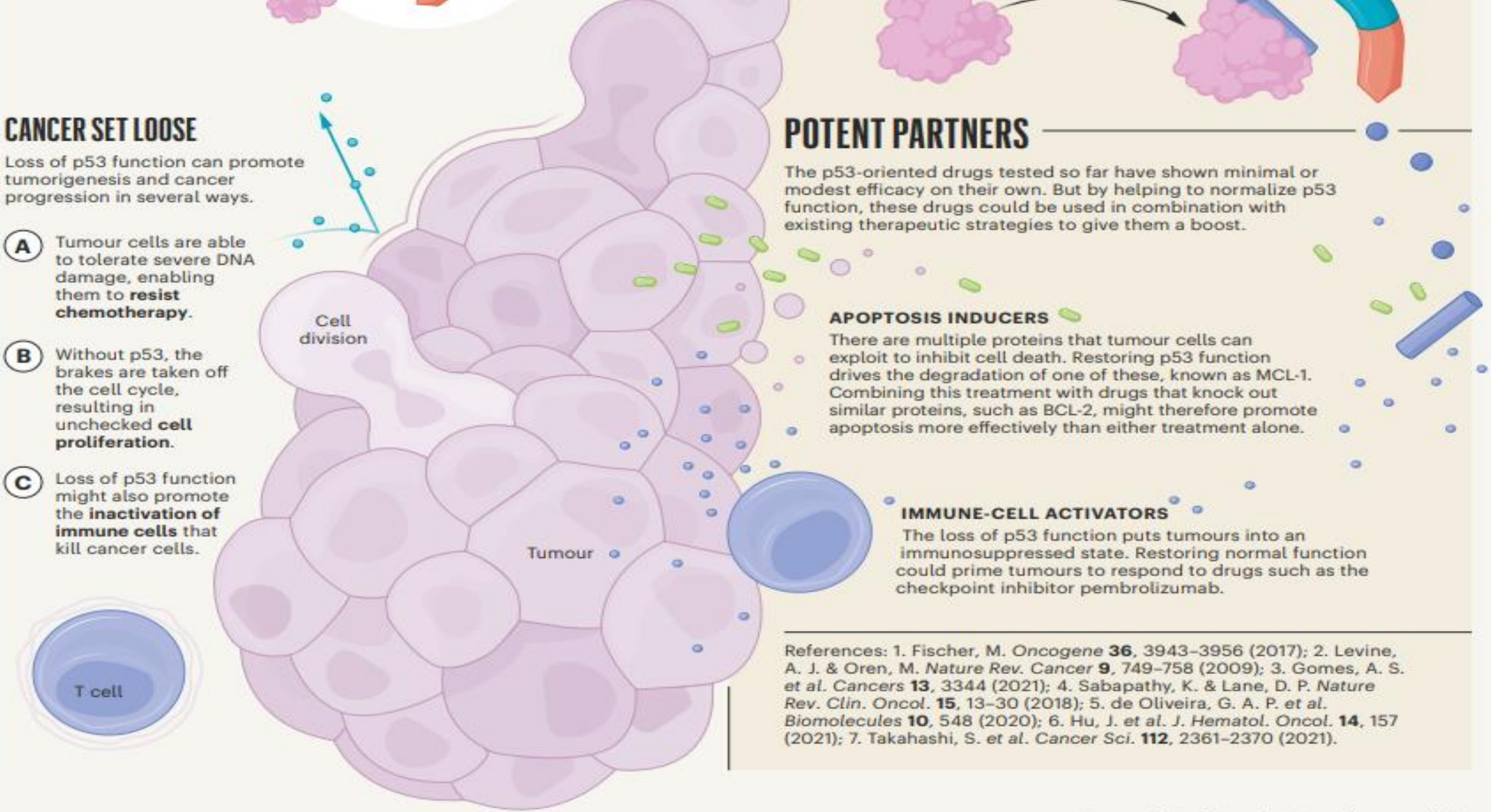
CANCER SET LOOSE

Loss of p53 function can promote tumorigenesis and cancer progression in several ways.

A Tumour cells are able to tolerate severe DNA damage, enabling them to **resist chemotherapy**.

B Without p53, the brakes are taken off the cell cycle, resulting in unchecked **cell proliferation**.

C Loss of p53 function might also promote the **inactivation of immune cells** that kill cancer cells.



POTENT PARTNERS

The p53-oriented drugs tested so far have shown minimal or modest efficacy on their own. But by helping to normalize p53 function, these drugs could be used in combination with existing therapeutic strategies to give them a boost.

APOPTOSIS INDUCERS

There are multiple proteins that tumour cells can exploit to inhibit cell death. Restoring p53 function drives the degradation of one of these, known as MCL-1. Combining this treatment with drugs that knock out similar proteins, such as BCL-2, might therefore promote apoptosis more effectively than either treatment alone.

IMMUNE-CELL ACTIVATORS

The loss of p53 function puts tumours into an immunosuppressed state. Restoring normal function could prime tumours to respond to drugs such as the checkpoint inhibitor pembrolizumab.

References: 1. Fischer, M. *Oncogene* **36**, 3943–3956 (2017); 2. Levine, A. J. & Oren, M. *Nature Rev. Cancer* **9**, 749–758 (2009); 3. Gomes, A. S. *et al. Cancers* **13**, 3344 (2021); 4. Sabapathy, K. & Lane, D. P. *Nature Rev. Clin. Oncol.* **15**, 13–30 (2018); 5. de Oliveira, G. A. P. *et al. Biomolecules* **10**, 548 (2020); 6. Hu, J. *et al. J. Hematol. Oncol.* **14**, 157 (2021); 7. Takahashi, S. *et al. Cancer Sci.* **112**, 2361–2370 (2021).

What Role Do Mutations in the p53 Gene Play in Causing Cancer?

- About **50% of the cases of adult human cancers** contain a mutation in the p53 gene. This includes **point mutations (missense and nonsense) and insertions/deletions in the DNA of the gene**. Changes in the DNA mean a transcription into mRNA and translation of that mRNA into a protein which is different than normal p53. With a different sequence of amino acids in this new protein, it will potentially **fold improperly and function abnormally or not at all.**

- About **20%** of the mutations in p53 are concentrated at **'hot-spot'** codons, such as **arginine (A) 175, 248, 249, 273, and 282 and glycine (G) 245, mostly in the DNA-binding domain.**
- **The most common mutation occurs at arginine 248** which normally forms a strong stabilizing interaction with DNA by fitting into the minor groove. With changes in amino acids at the DNA-binding sites, it means that the p53 protein won’t be able to bind to the DNA to initiate repairs of damaged DNA and more importantly, won’t be able to initiate apoptosis in cells with mutated or damaged DNA. There also will be no regulation of arresting cell division in the cells with mutated or damaged DNA.

- In patients in New England, **90% of squamous cell carcinomas and more than 50% of basal cell carcinomas contained UV-like mutations in the p53 tumor suppressor gene**. These somatic mutations are differently encountered within the body. In some cases, differences in frequencies of mutations at a specific site may reflect an enhanced growth 3 advantage for a tumor in a particular tissue. For example, **the mutation of p53 at amino acid 175 is common in colon cancer but is rarely seen in lung cancer**

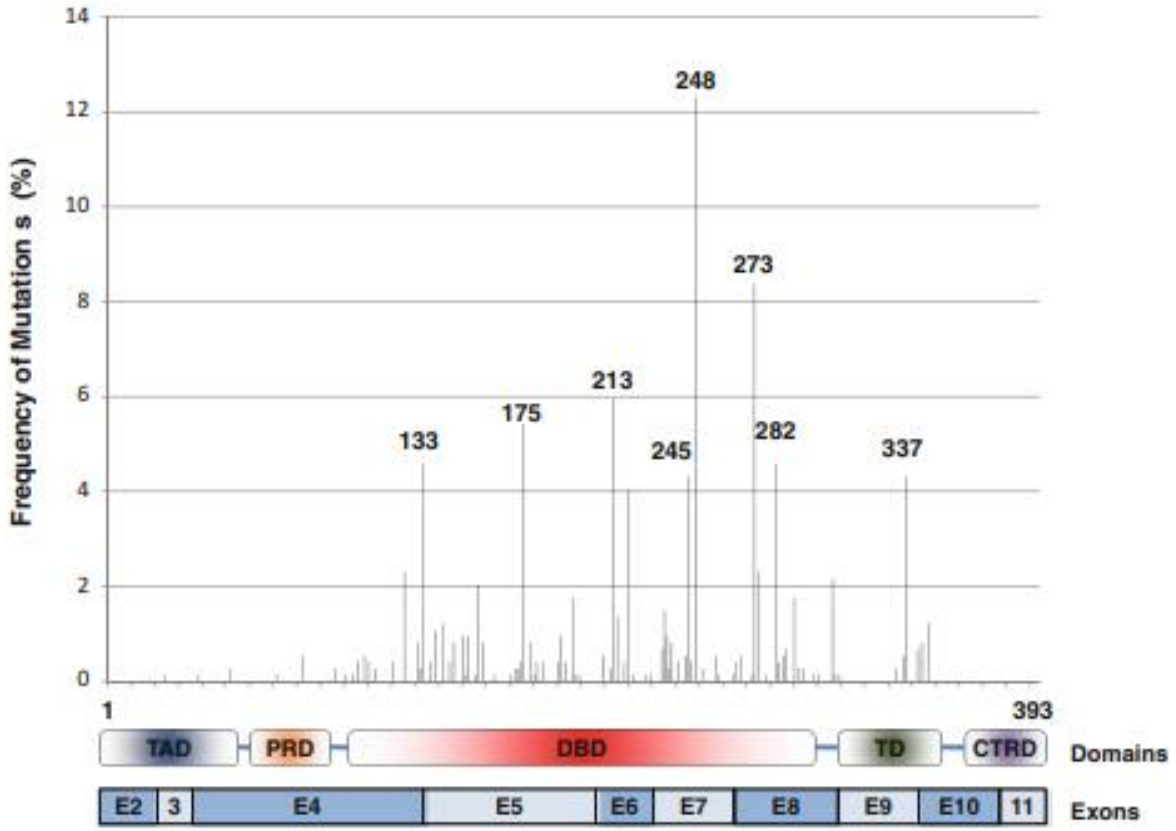


Figure 28.2 Structural organization of the coding exons of the *TP53* gene and functional domains of TP53 are illustrated at the *bottom* of the figure. Relative frequencies and codon positions of germline *TP53* mutations found in LFS and LFL families are *plotted*. Only single base substitutions and insertions/deletions in the codons are listed. Adapted

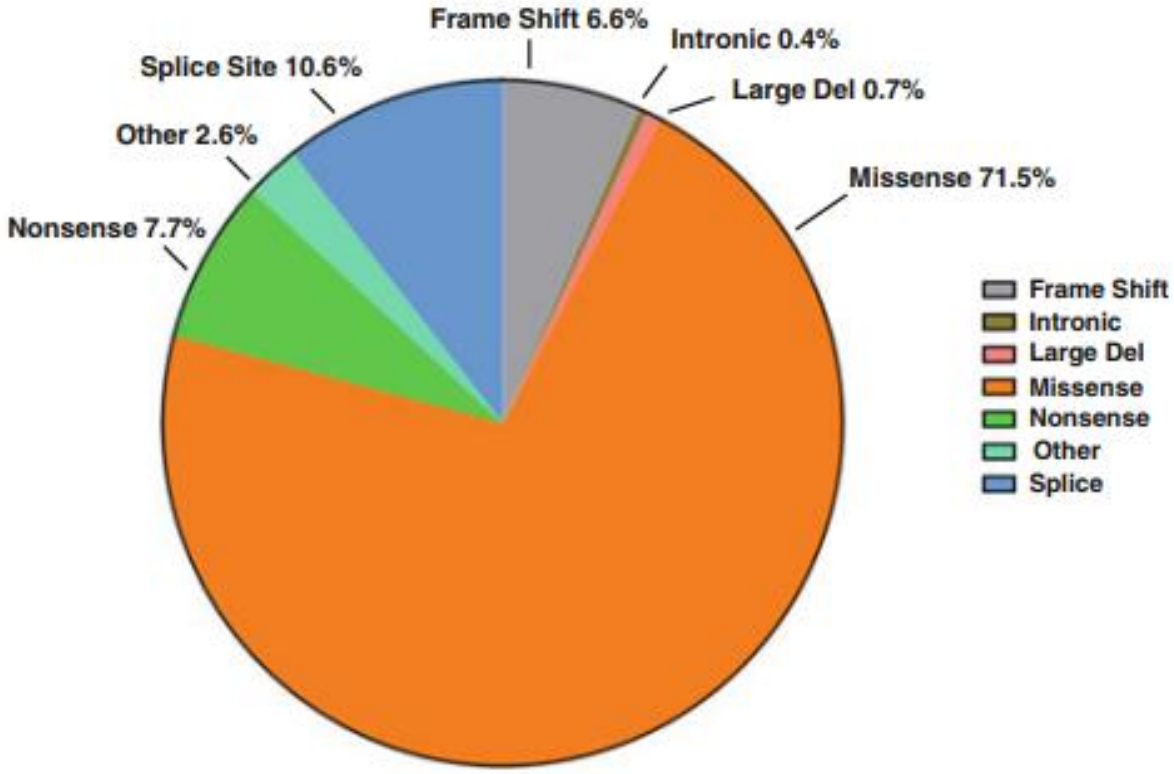


Figure 28.3 Types of germline mutations in the *TP53* gene found in LFS and LFL cases. *Pie chart* shows the percentage of the different types of observed mutations. Adapted from the International Association for Research on Cancer (IARC) database (R17, November 2013, http://p53.iarc.fr/)

Li-Fraumeni

- Li-Fraumeni syndrome appears to be the **only inherited syndrome associated with mutations in the p53 gene. There are more than 60 different mutations that have been identified in individuals** with this syndrome. Since the mutation(s) is inherited from a parent, it appears in all of the body's cells, unlike someone who develops a somatic mutation in the p53 gene in a specific organ of the body. Inheritance is autosomally dominant so a person who inherits a PP or Pp genotype would be affected and a person who inherits the pp genotype would be normal. (P = mutated p53 gene and p = normal p53 gene). **This syndrome was named after two physicians, Li and Fraumeni, who studied the pedigrees of families with cases of childhood sarcomas.** They identified this syndrome in those families where one individual had a sarcoma, at least two immediate relatives had cancer before age 45, and multiple cancers, such as breast, brain, and leukemia, were found elsewhere in the family.

Cancer patients who should be tested for germline disease-causing *TP53*[a]

Recommendation 1	All patients who meet the modified 'Chompret Criteria' should be tested for germline *TP53* variants: • *Familial presentation*: proband with a *TP53* core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma) before 46 years AND at least one first- or second-degree relative with a core tumour before 56 years; *or* • *Multiple primitive tumours*: proband with multiple tumours, including 2 *TP53* core tumours, the first of which occurred before 46 years, irrespective of family history; *or* • *Rare tumours*: patient with adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; *or* • *Very early-onset breast cancer*: Breast cancer before 31 years, irrespective of family history
Recommendation 2	Children and adolescents should be tested for germline *TP53* variants if presenting with: • Hypodiploid acute lymphoblastic leukaemia (ALL); *or* • Otherwise unexplained *sonic hedgehog*-driven medulloblastoma; *or* • Jaw osteosarcoma

Table (continued)

Recommendation 3	Patients who develop a second primary tumour, within the radiotherapy field of a first core *TP53* tumour which occurred before 46 years, should be tested for germline *TP53* variants
Recommendation 4	a. Patients older than 46 years presenting with breast cancer without personal or familial history fulfilling the 'Chompret Criteria' should not be tested for germline *TP53* variants
	b. Any patient presenting with isolated breast cancer and not fulfilling the 'Chompret Criteria', in whom a disease-causing *TP53* variant has been identified, should be referred to an expert multi-disciplinary team for discussion
Recommendation 5	Children with any cancer from southern and south-eastern Brazilian families should be tested for the p.R337H Brazilian founder germline *TP53* variant

[a]Testing for disease-causing *TP53* variants should be performed before starting treatment in order to avoid in variant carriers, if possible, radiotherapy and genotoxic chemotherapy and to prioritise surgical treatments.

Available Assays

- Sequencing (first NGS and then Sanger especially for confirmation)
- IHC
- SSCP

Sequencing

- Exons 2-11
- Hot spot mutations in exons 5-8 (75%)

IHC

- In summary, IHC for p53 identifies TP53- mutated luminal BCs with high specificity and accuracy. Optimal cutoffs are 35% and 25% for treatment-naïve and endocrine-pretreated patients, respectively.

- p53 Expression in Luminal Breast Cancer Correlates With TP53 Mutation and Primary Endocrine Resistance

p53 protein expression patterns associated with *TP53* mutations in breast carcinoma

Sarah A. Anderson[1] · Brooke B. Bartow[1] · Shuko Harada[1] · Gene P. Siegal[1] · Shi Wei[1] · Valeria L. Dal Zotto[1] · Xiao Huang[1]

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Abstract

Purpose The importance of a *TP53* mutation has been demonstrated in several tumor types, including breast cancer (BC). However, the accuracy of p53 protein expression as a predictor of gene mutation has not been well studied in BC. Therefore, we evaluated p53 protein expression associated with *TP53* mutations in breast cancers from 64 patients.

Methods *TP53* mutation was examined using next-generation sequencing (NGS). p53 protein expression was examined using immunohistochemistry (IHC).

Results Among the 64 BCs, 55% demonstrated abnormal expression patterns including 27% overexpression, 22% null, 6% equivocal with 45% having a wild-type pattern. A *TP53* mutation was present in 53% (34/64) of tumors including 30% (19/64) demonstrating a missense mutation, 11% (7/64) with a frameshift mutation, 11% (7/64) with a nonsense mutation, and 3% (1/64) with a splice site mutation. Abnormal expression of p53 protein was present in 33 of 34 (97%) tumors carrying a *TP53* mutation; conversely, a wild-type pattern was present in 28 of 30 (93%) tumors without a detectable mutation ($p < 0.0001$). The majority of BCs with a p53 IHC overexpression pattern (15/17, 88%) contained a missense *TP53* mutation; while the majority of BCs with a null pattern (12/14, 86%) contained a truncating mutation ($p < 0.0001$). The BCs with a null pattern are associated with a high Nottingham histological grade and a triple-negative phenotype when compared to those demonstrating overexpression ($p < 0.05$).

Conclusion These findings suggest that p53 IHC can be a potential surrogate for *TP53* mutations in BC. Different p53 expression patterns may correlate with specific *TP53* genetic mutations in BC.

Keywords p53 immunohistochemistry · *TP53* mutation · Breast carcinoma

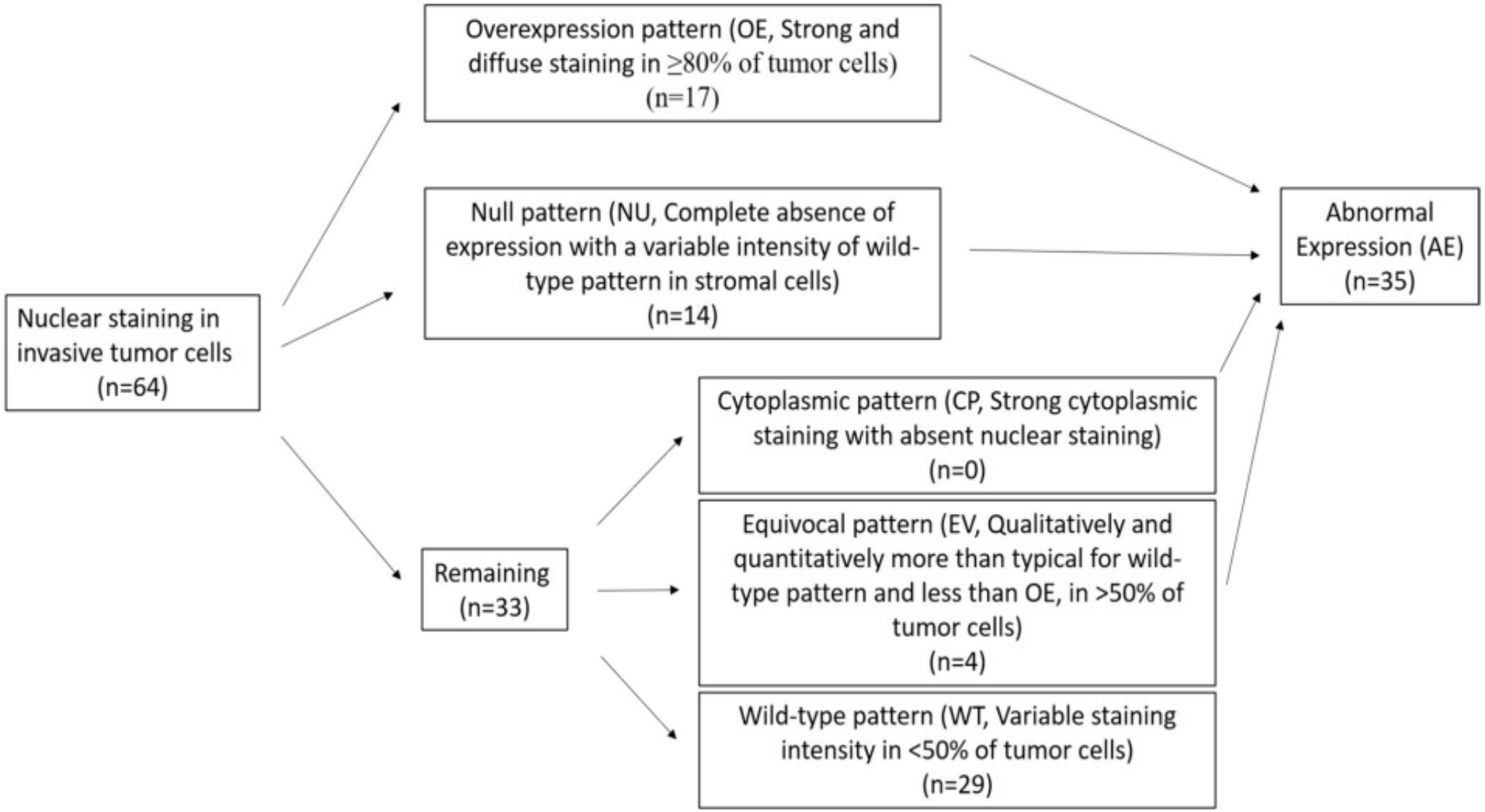
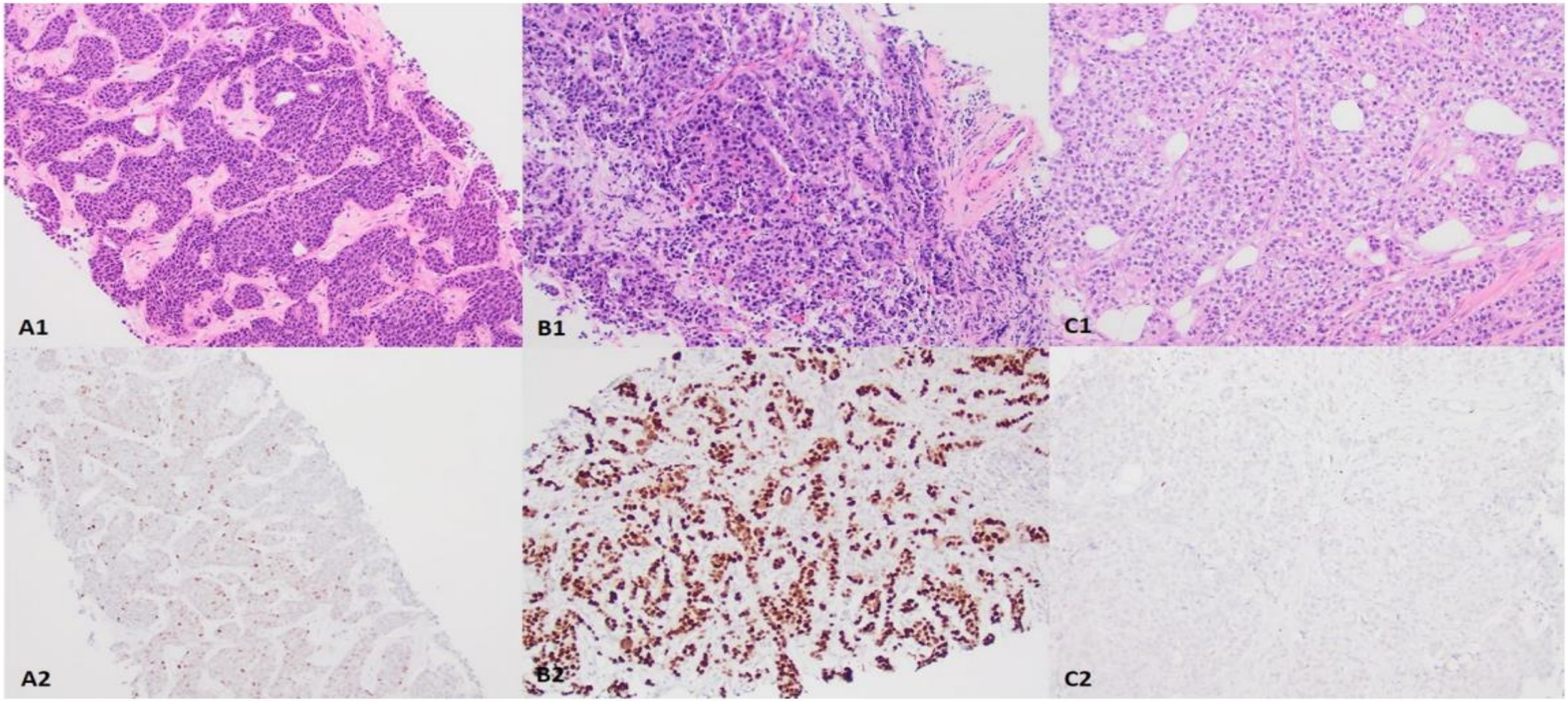


Fig. 1 Algorithm for p53 immunohistochemistry interpretation



A wild-type pattern. B overexpression pattern. C null pattern

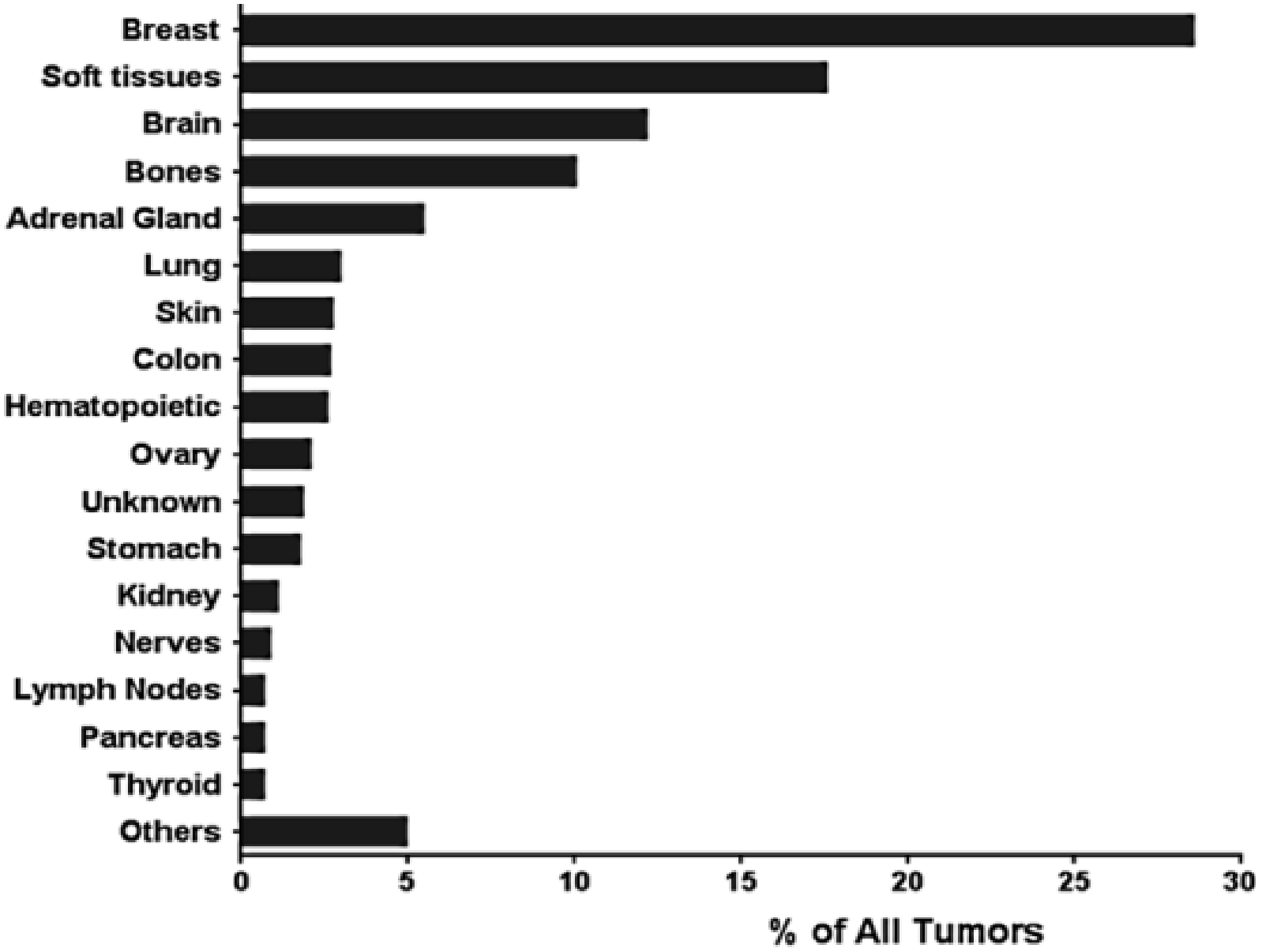


Figure 28.1 Tumor spectrum in individuals affected with LFS or LFL. The proportion of specific types of tumors among a total of 822 tumors reported in patients with LFS or LFL features is illustrated in the *bar graph*. Adapted from the International Association for Research on Cancer (IARC) database (R17, November 2013, http://p53.iarc.fr/)

Cancer Types with TP53 Mutations ?

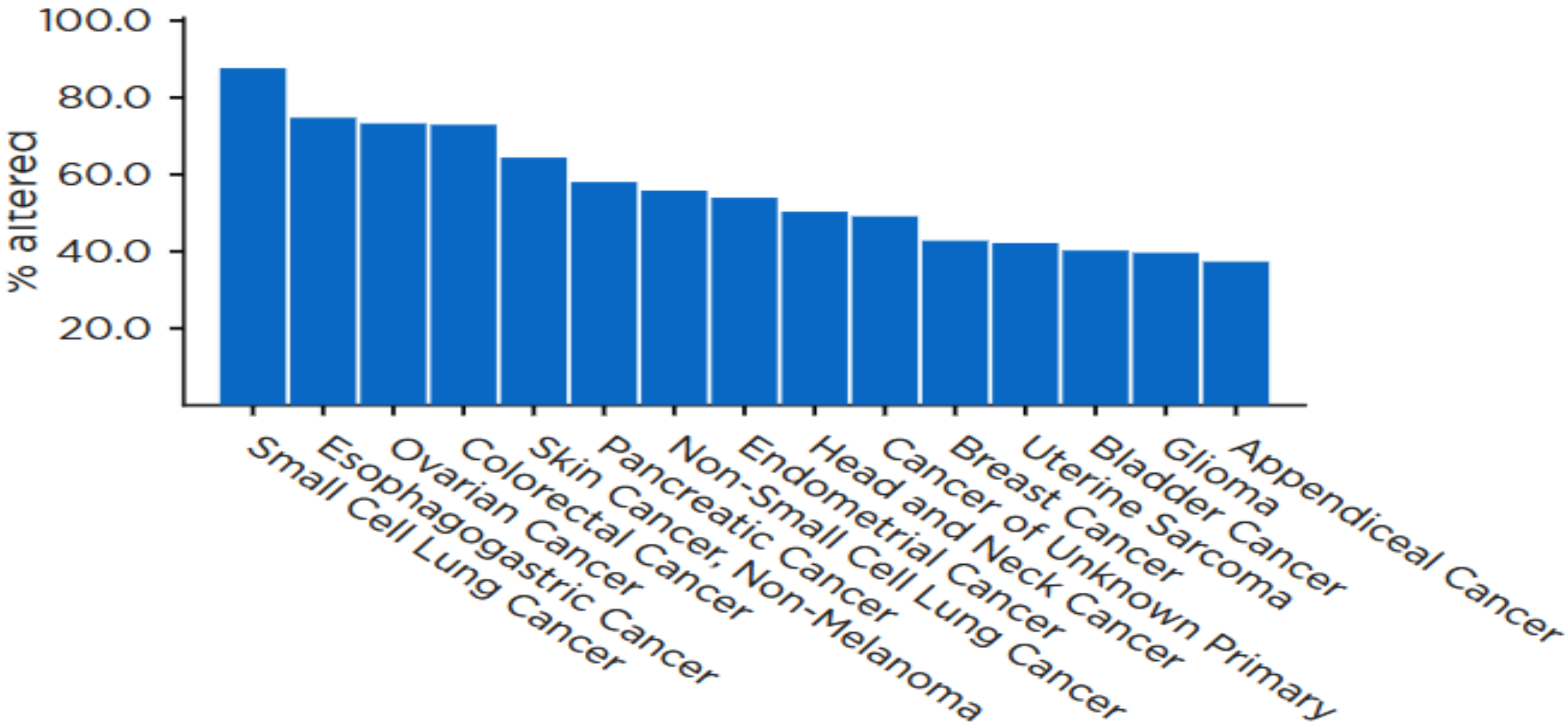


Table 3 Cancer screening recommendations for patients with LFS

	NCCN	NICE	eviQ
	USA	**UK**	**Australia**
Breast	• Clinical exam every 6–12 months, starting at age 20–25 years • Age 20–29 years, annual MRI with contrast or mammogram if MRI unavailable • Age 30–75 years, annual mammogram and breast MRI with contrast • Age >75 years, management on individual basis • Discuss risk-reducing mastectomy	• 20–49 years, annual breast MRI • 50–70 years, consider annual breast MRI	• 20–50 years, annual breast MRI. Mammogram/ultrasound should be considered only if unable to access MRI
Colon	• Colonoscopy every 2–5 years starting at age 25 years or 5 years before earliest colon cancer in the family		• Colonoscopy every 2–5 years from age 25 years or younger if there is a family history of bowel cancer
Other cancers	• Address limitations of screening for many cancers associated with LFS • Annual comprehensive H&P (including neurologic examination) • Annual dermatologic examination • Annual whole-body MRI (or equivalent), preferably in the context of a clinical trial • Brain MRI		• Annual H&P • Further investigations if clinically indicated

Abbreviations: eviQ, eviQ cancer treatments online; H&P, history and physical exam; LFS, Li–Fraumeni syndrome; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence.

Clinical Relevance of TP53 Status in Breast Cancer

- The impact of the TP53 tumor suppressor gene in cancer development has been demonstrated through various approaches, in particular by the important observation of TP53 knockout mice developing various tumors (Donehower et al. 1992) . Li–Fraumeni Syndrome (LFS) patients carrying a germline mutation in TP53 are frequently hit by cancer at young age, and one of the organs most commonly affected is the breast, suggesting a crucial role for TP53 in breast cancer development.
- Overall, one in four breast cancer patients has a somatic mutation in the TP53 gene, and this is significantly associated with an aggressive cancer with a poor prognosis and development of metastasis. TP53 mutations also have been observed as an early event in tumor development, found in premalignant hyperplasia and in situ stages of breast cancer (Chitemerere et al. 1996 ; Zhou et al. 2009). **TP53 may play an important role in the origin of certain breast cancer subtypes, such as the basal-like**

- HER2-enriched groups described previously in this chapter. A very intriguing finding is **that the majority of breast cancers arising in LFS patients are HER2 +** (83 %) (Wilson et al. 2010) , suggesting that a TP53 mutation may be an event prior to HER2 amplification/overexpression in sporadic breast tumors

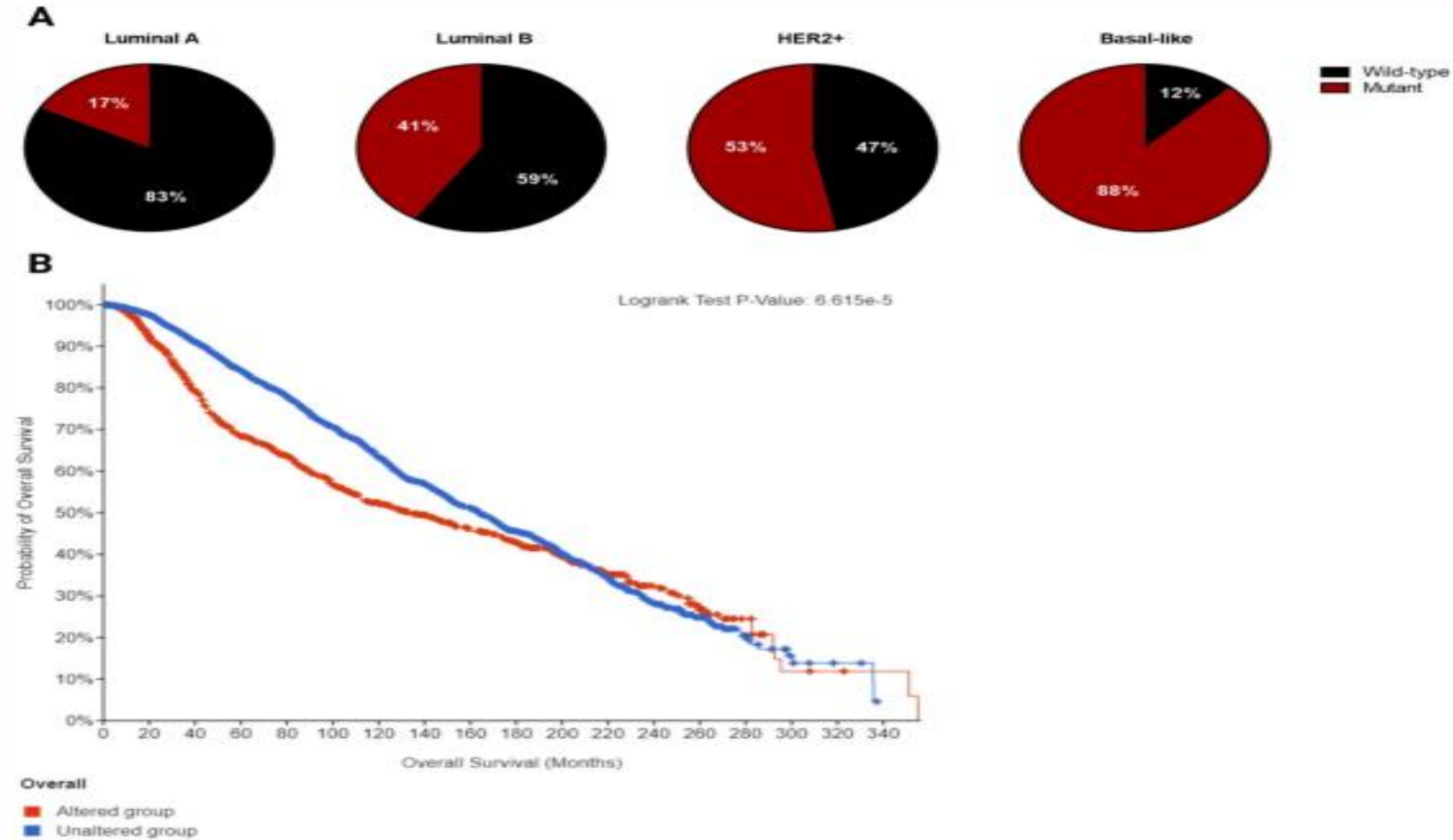


Figure 3. A. Frequency of p53 mutation in different breast cancer subtypes. B. Overall survival curve of altered (mutant p53, n=1018) versus unaltered (wild-type p53, n=2047) among breast cancer patients plotted using cBioPortal. Data were pooled from TCGA and METABRIC datasets (Total n= 3065). Median overall survival of patients with mutant p53 and wild-type p53 is 133.23 (95% confidence interval: 111.97 - 159.07) and 164.03 (95% confidence interval: 152.07 – 173.03) in months respectively (p=0.000114).

- Measuring a pure prognostic or predictive effect of tumor markers is difficult in an ethical perspective. The original definition of a prognostic biomarker is a biomarker that provides information on the likely course of the cancer disease in an untreated individual. Since the majority of breast cancer patients receive adjuvant treatment, most studies of prognostic markers will today include patients who received systemic treatment, influencing the natural course of the disease. **A prognostic marker may, however, be extremely valuable in selecting early stage patients for the appropriate adjuvant systemic treatment.**
- The term **predictive biomarker is defined as a marker which can be used to identify subpopulations of patients who are most likely to respond to a given therapy**. Predictive markers are the basis of personalized medicine, and in breast cancer patients, estrogen and progesterone receptors are used to predict sensitivity to endocrine therapy, whereas HER2 is used to predict sensitivity to Herceptin treatment

- The data supporting a prognostic power of TP53 mutation status in breast cancer are rather convincing, as the majority of studies show association between **mutant TP53 and poor prognosis** (Petitjean et al. 2007) . As discussed in Chap. 8, the predictive value of TP53 status remains uncertain because of the lack of study replication. Indeed, available studies are heterogeneous in the type, dosage and combination of drugs used, the methods used to assess TP53 status and treatment response, and the type of tumor included**.**
- **TP53 mutations seems to confer resistance to single-agent anthracyclines (Aas et al. 1996 ; Chrisanthar et al. 2011) , but to predict response to dose intense combined anthracycline/cyclophosphamide treatment (Bertheau et al. 2007) or to a regimen of docetaxel-capecitabine ± trastuzumab (Glück et al. 2011).**

- **A recent phase III clinical trial showed no impact of TP53 status on response to taxanes** (Bonnefoi et al. 2011) . Many large clinical trials have unfortunately not included TP53 mutation analysis in their study design, but based on promising results as prognostic and predictive marker, we encourage including TP53 gene mutation analysis in all relevant clinical trials to resolve these important issues. Breast cancer on the molecular bases appears to be several different diseases with seemingly different origin, progression, and outcome, and the significance of TP53 as a marker should be evaluated in the different subtypes of breast cancer.

Current Guidelines and Future Perspectives

- Despite many reports on somatic TP53 mutation status as a strong prognostic and also predictive marker of breast cancer, analysis of TP53 mutations in tumor tissue is generally not routinely performed in clinical practice for breast cancer patients. In a guideline from the American Society of Clinical Oncology (ASCO) concerning the use of tumor markers in breast cancer, they concluded that the present data in 2007 were insufficient to recommend use of TP53 measurements for management of patients with breast cancer (Harris et al. 2007) , referring to diagnosis, staging, prognosis, surveillance, or monitoring treatment of patients with breast cancer. They acknowledge TP53 gene mutations as associated with poor prognosis, as shown, e.g., in a study of almost 1,800 breast cancer patients (Olivier et al. 2006) . **Based on this study they also suggested that TP53 status may, if confirmed, be used to select patients that will benefit from systemic adjuvant therapy in node-negative, ER-positive patients.**

Systemic Therapy Considerations

Mutation (Li-Fraumeni Syndrome) p53 is a critical tumor suppressor gene and a germline mutation in p53 is associated with a high risk of malignancy. **One study estimated that the prevalence of a germline p53 mutation among women with early-onset breast cancer and no family history was 5–8%** [121]. Studies have suggested that patients with germline mutations in p53 are **less susceptible to DNA-damaging cytotoxic agents** [122, 123]. **Novel therapeutic approaches** may include MK-8776, a novel chk-1 kinase inhibitor found to radio-sensitize p53-deficient cancer cells [124], and MK-1775, a Wee1-kinase inhibitor found to sensitize p53- deficient cells to DNA-damaging agents [125]

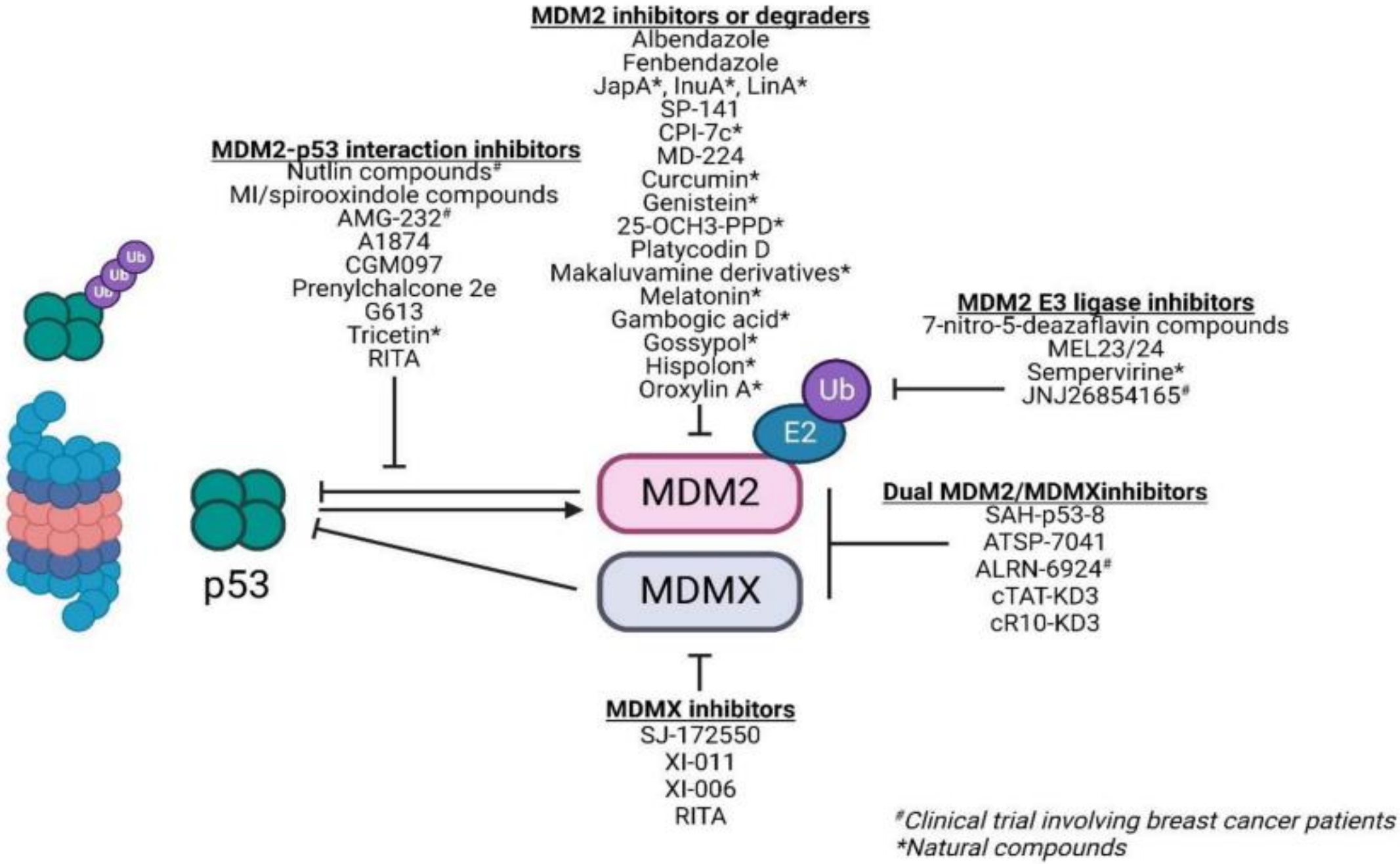


Figure 5. Compounds against wild-type p53 tumors that have been evaluated in breast cancer

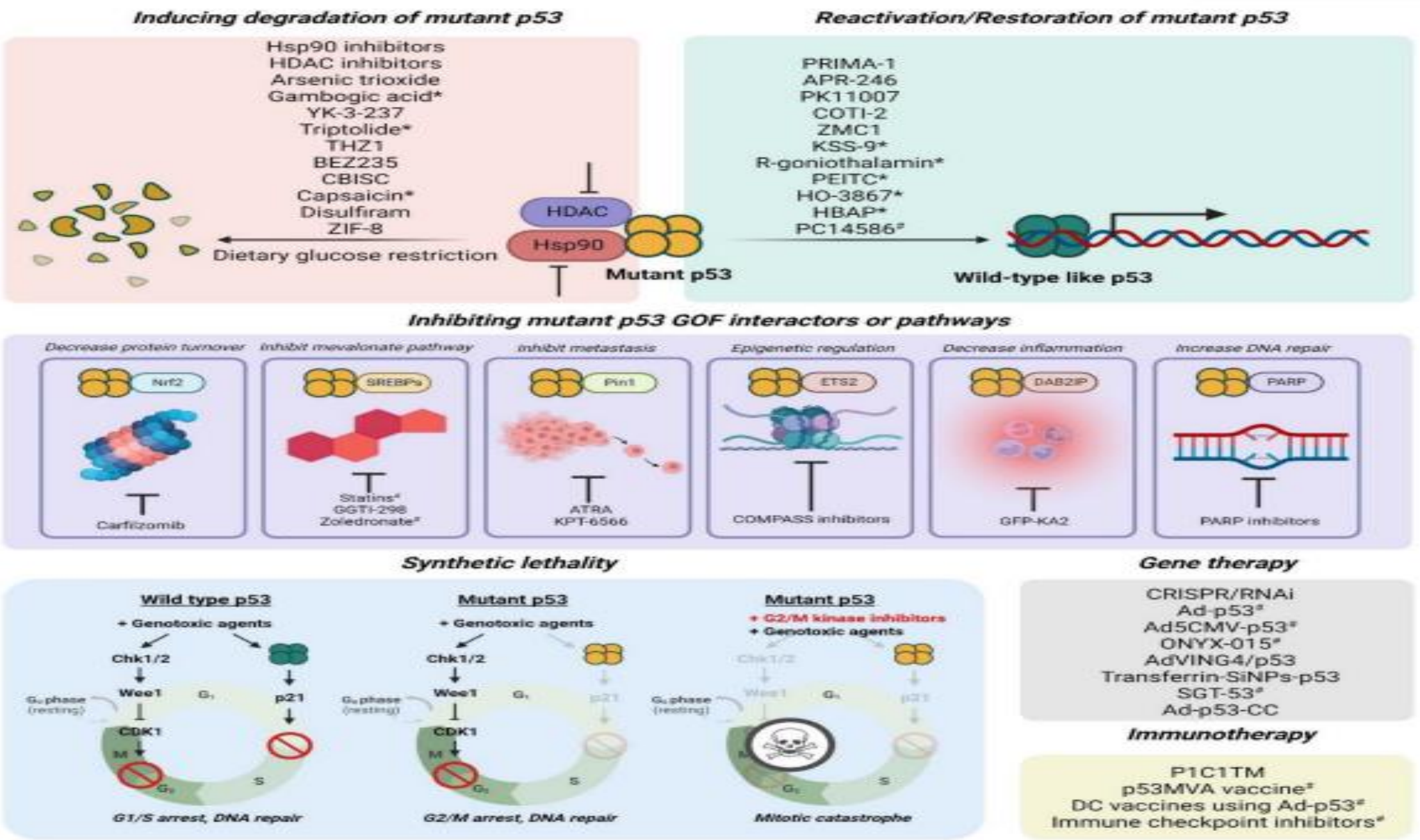


Figure 6. Strategies to treat mutant p53 tumors that have been evaluated in breast cancer

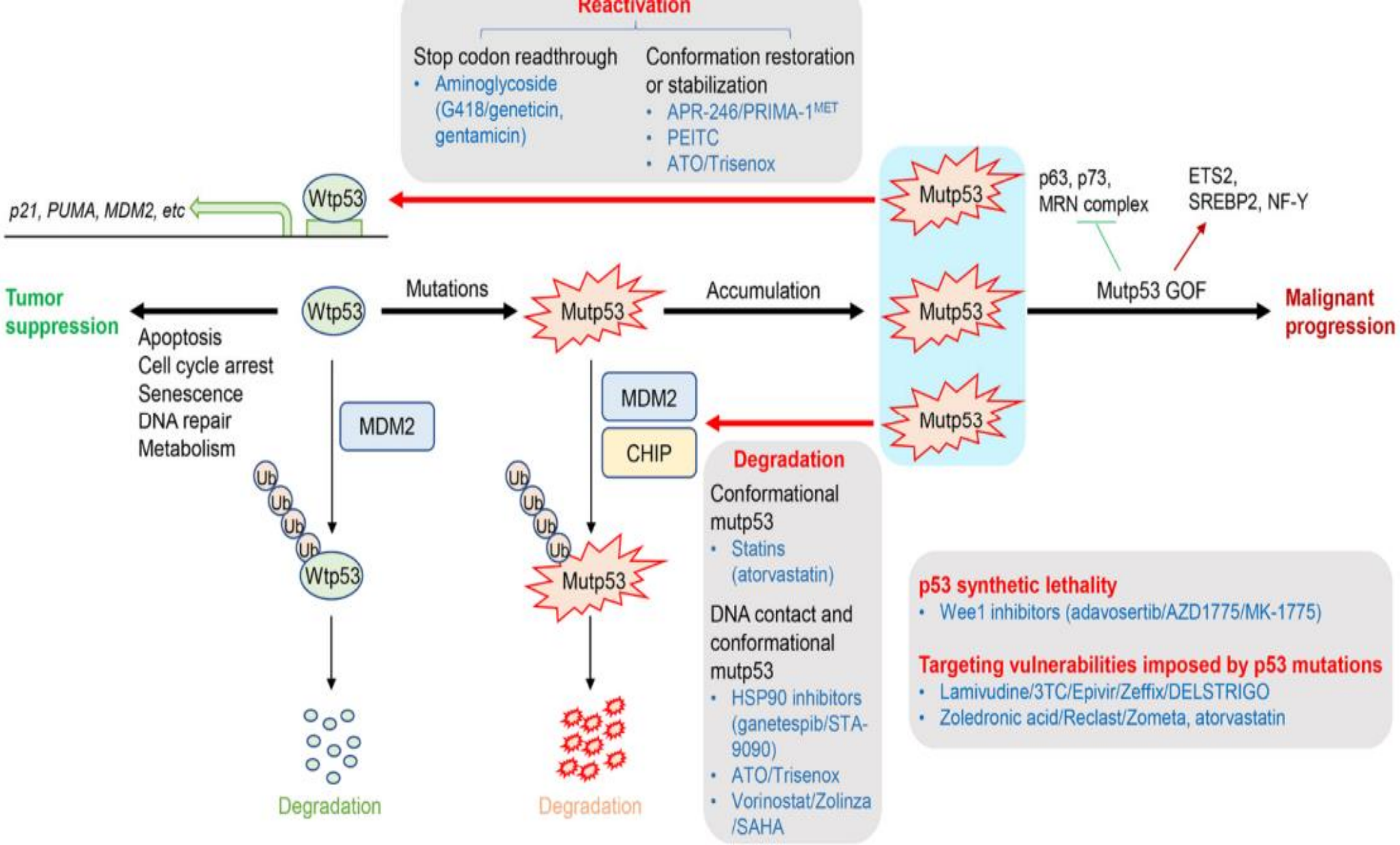
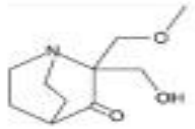
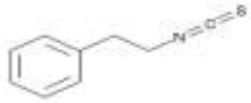
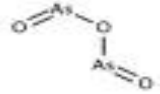
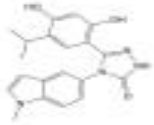
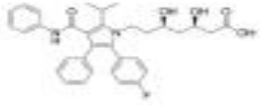
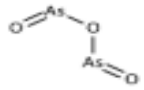
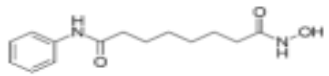
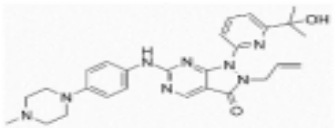
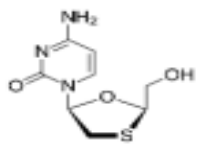
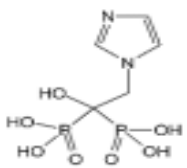


Figure 1. Function of wtp53, mutp53 GOF, and strategies to target p53 mutations.

Table 1. Summary of drugs targeting p53 mutations.

Drug	Chemical Structure	Action on p53	Trial Identifier	Cancer Type	Reference	Brief Summary/Current Status
APR-246 (eprenetapopt, PRIMA-1^{MET})		Mutp53 reactivation	NCT04383938	Advanced solid tumor (bladder, gastric, NSCLC, urothelial)	[23]	Well tolerated for the combination with pembrolizumab
			NCT03072043	MDS/oligoblastic AML	[24]	Favorable outcomes with response rates for MDS (73%) and oligoblastic AML (64%)
			NCT03588078	AML/MDS	[25]	Favorable outcomes with response rates for MDS (62%) and AML (33%)
			NCT03931291	AML/MDS in post-HCT maintenance therapy	[26]	Improved RFS
			NCT03745716	MDS	NA	NR, trial completed
			NCT02098343	Platinum-sensitive recurrent HGSOC	NA	NR, trial completed
			NCT03268382	Platinum-resistant recurrent HGSOC	NA	NR, trial completed
			NCT04214860	Myeloid malignancies	NA	NR, trial completed
PEITC (phenethyl isothio-cyanate)		Mutp53 reactivation	NCT01790204	Oral cancer	NA	NR, trial completed
ATO (arsenic triox-ide/Trisenox)		Mutp53 reactivation	NCT03855371	AML/MDS	NA	NR, recruiting patients
			NCT04869475	Refractory solid tumors	NA	NR, recruiting patients
			NCT04489706	Recurrent and metastatic ovarian and endometrial cancer	NA	NR, recruiting patients
			NCT04695223	Refractory solid tumors	NA	NR, recruiting patients
HSP90 inhibitor (ganetespib/STA-9090)		Mutp53 degradation	NCT02012192	High-grade platinum-resistant ovarian cancer	[27]	Confirm safe use of the combination
Atorvastatin		Mutp53 degradation	NCT04767984	Longstanding ulcerative colitis	NA	NR, recruiting patients
			NCT03560882	Solid tumor and relapsed AML	NA	NR, recruiting patients

Drug	Chemical Structure	Action on p53	Trial Identifier	Cancer Type	Reference	Brief Summary/Current Status
ATO/Trisenox		Mutp53 degradation	NCT03381781	AML	NA	NR, not recruiting yet
			NCT03377725	MDS	NA	NR, not recruiting yet
Vorinostat /Zolinza/SAHA		Mutp53 degradation	NCT02042989	Advanced malignancies	[28]	Limited effects
			NCT01339871	Advanced malignancies	[29]	Extended PFS
Wee1 inhibitor (adavosertib/ AZD1775/MK-1775)		Synthetic lethality to p53	NCT01164995	Refractory and resistant ovarian cancer	[30]	Enhance carboplatin efficacy
			NCT01357161	Platinum-sensitive ovarian tumors	[31]	Modest clinical benefit with improved PFS
			NCT02272790	Platinum-resistant ovarian cancer	[32]	Some promising outcomes with carboplatin
			FOCUS4-C	Metastatic colorectal cancer with RAS	[33]	Improved PFS
			NCT03668340	Recurrent uterine serous carcinoma	[34]	Significant activity (but p53 deficiency alone is not sufficient)
			NCT02688907	Relapsed SCLC with CDKN2A	NA	NR, trial terminated
			NCT02593019	Relapsed SCLC with CDKN2A	NA	NR, trial completed
			NCT02087241	Untreated stage IV NSCLC	NA	NR, trial terminated
			NCT02087176	NSCLC	NA	NR, trial terminated
Lamivudine (3TC/Epivir/ Zeffix/DELSTRIGO)		Inhibition of LINE-1 upregulated by p53 loss	NCT03144804	Metastatic colorectal cancer	[35]	SD in 8 out of 32 cases
Zoledronic acid (ZA/ Reclast/Zometa) and atorvastatin	 ZA	Inhibition of YPA/TAZ activity enhanced by mutp53	NCT03358017	Triple negative breast cancer	NA	NR, recruiting patients

Treatment

- Bilateral mastectomy rather than lumpectomy is often recommended in those with LFS-related breast cancer to reduce the risk of a second primary breast cancer and to avoid radiation therapy [Siegel et al 2022].

- It has been indicated that treating LFS with radiation therapy and alkylating agents can damage DNA and increase the risk of secondary cancer onset. Therefore, when LFS is suspected in patients with cancer, it is highly significant to determine whether the subject has the germline TP53 pathogenic variant

Thanks for your attention