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What Problem Are We Trying to Solve?

Abnormalities in genetic tumor suppression mechanisms enable cancer progression

- **CDKN2A** and/or **CDKN2B** abnormalities are widely found in many solid tumors

Use pharmacologic inhibitors acting in the p16 (**CDK2**) and/or p53 (**CDK9**) pathways to restore tumor suppression

Opportunities/Challenges:

- **CDK2** and **CDK9** versus CDK2 versus CDK9
- Single agent and/or combination
- Historical toxicities (mostly hematological) have limited clinical utility

CDKN2A/B Genetic Abnormalities & Fadra Mechanism of Action

CDKN2A and **CDKN2B** genes encode the body's own, innate, **tumor suppressors** (incl. p16^{INK4a}, p15^{INK4b} etc.)

They also disrupt degradation of p53 (a tumor suppressor master switch) by controlling levels of the MDM2 protein

There are no approved drugs to treat patients with **CDKN2A/B** genetic abnormalities

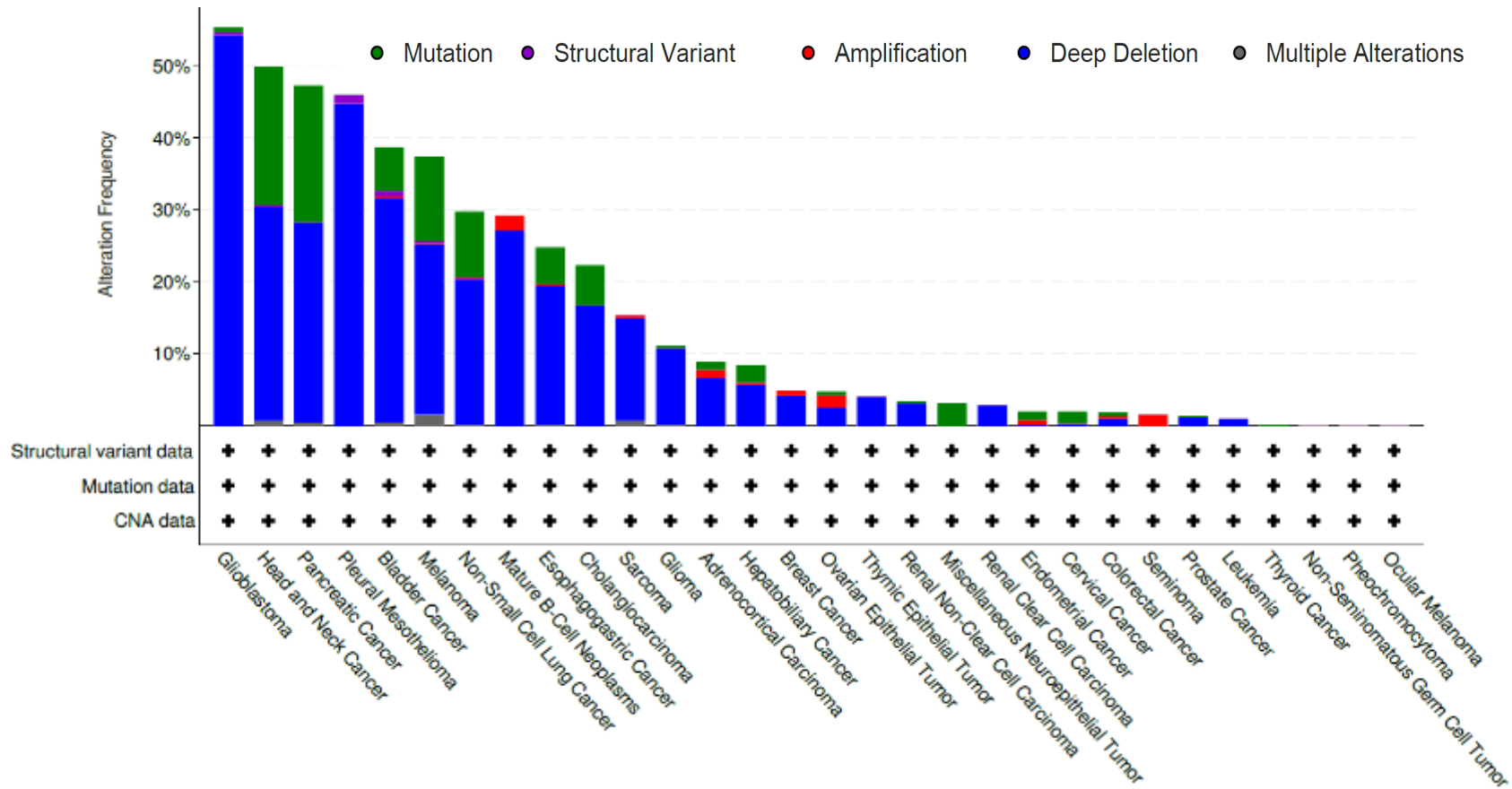
If these genes are **deleted** or **lose their ability to function**, cancer **progresses**. **Can drugs replace this loss of function?**

CDK4/6 inhibitors (palbociclib, abemaciclib and ribociclib) are approved for the major subtype of breast cancer

- Cumulative annual sales of **\$7-8 billion**, but:
- Activity of the **CDK2 enzyme** can **bypass** CDK4/6 inhibition and render these drugs ineffective¹
- Inhibition of the **CDK9 enzyme** suppresses MDM2 levels and can compensate for cancer resistance

Medicines inhibiting both **CDK2 and CDK9** may be well suited to address these mechanisms to control cancer

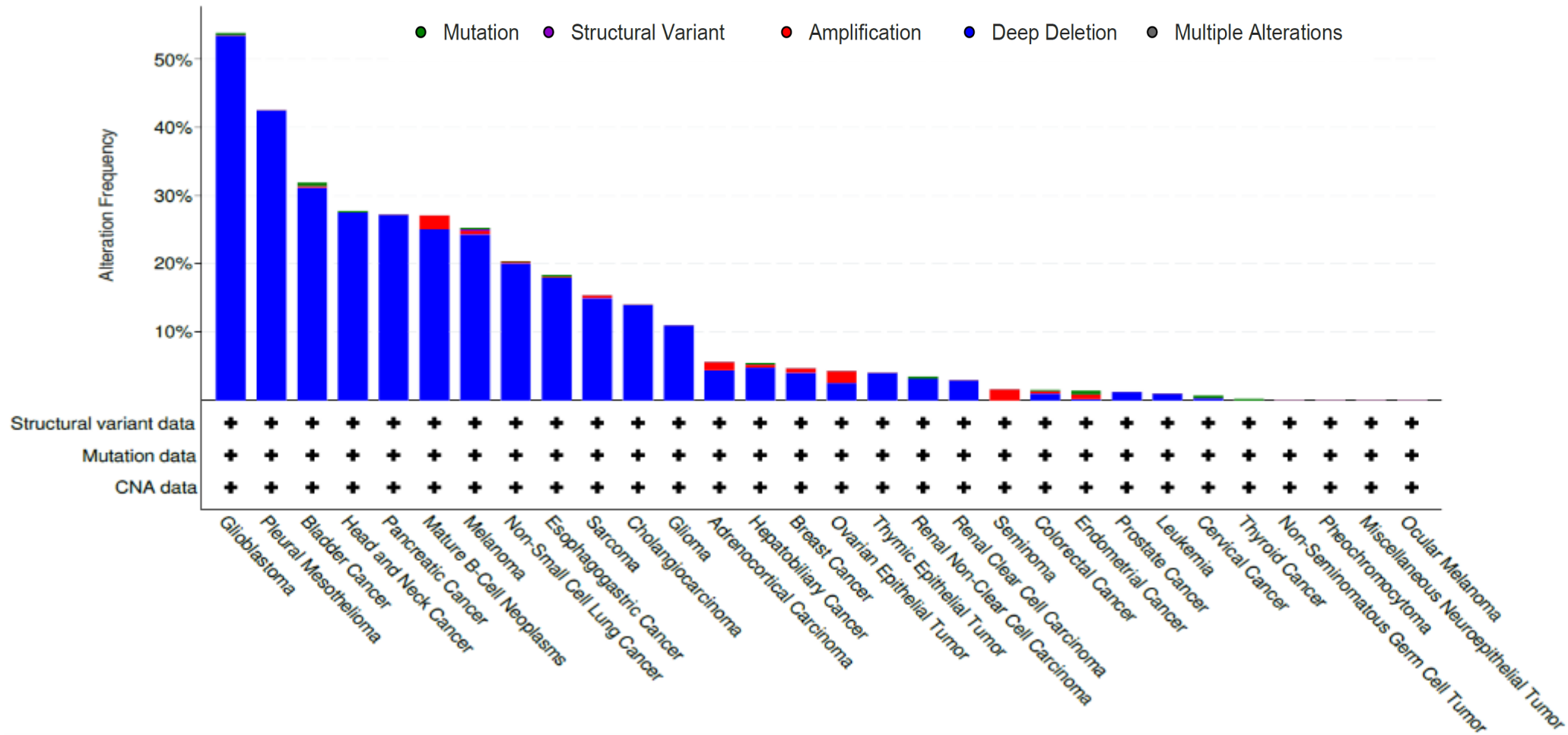
CDKN2A Alterations



Solid tumors >10%: GBM, H&N, pancreas, esophagus, lung, bladder, HCC/BTC, breast, melanoma, sarcoma

Lymphoma: CDKN2A deletions in 46% of PTCL-NOS patients.

CDKN2B Alterations



>10%: glioma, lung, bladder, H&N, pancreas, melanoma, esophagus, sarcoma, HCC/BTC, breast, ovarian

Fadra Phase 1 Patient Groups

- Two dose escalation studies:
 - 065-01 IV (n=52)
 - 20/52 had sequencing data
 - 6/20 had CDKN2A and/or CDKN2B alterations
 - 065-101 oral (n=47)
 - 21/47 had sequencing data
 - 5/21 had CDKN2A and/or CDKN2B alterations

Phase 1 Responder Profiles: CDKN2A/B Alterations *(retrospective review)*

Patient Study	Histology	Best Response (sum of target lesions)	Dose Level	Schedule	Mutation
38 iv 065-01	Endometrial	CR (-100%)	213mg QD	2d/wk 2/3 wks	CDKN2A, CDKN2B, MTAP loss, MCL1 amp
14 iv 065-01	Ovarian	SD (-2.5%)	192mg/m ²	1d/3 wks	CDKN2A, CCNE1, MYC gain
11 iv 065-01	Salivary gland	SD (0.8%)	128mg/m ²	1d/3 wks	CDKN2A mutation & gain CDKN2B gain
51 oral 065-101	NSCLC squamous	SD (-22%)	125mg BID	5d/wk 4/4 wks	CDKN2B loss
21 oral 065-101	PTCL angiimmunoblastic	PR (-16%)	100mg BID	5d/wk 4/4 wks	CDKN2A mutation
16 oral 065-101	Cholangio-carcinoma	SD (-5%)	75mg BID	5d/wk 4/4 wks	CDKN2A mutation
55 oral 065-101	Pancreatic	SD (4%)	125mg BID	5d/wk 4/4 wks	CDKN2A loss
62 oral 065-101	Sertoli germ cell testicular	SD (-12%)	150mg QD	7d/wk 4/4 wks	CDKN2A, CDKN2B, MTAP loss