Diffuse mid-line glioma with H3K27M mutation

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Learning objectives

- Case discussion
- Diffuse mid-line glioma with H3K27M mutation.
- Molecular biology.
- Potential targeted treatment options: Histone deacetylase inhibitors (HDACi).

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Chief complaint

“ Gradual weakness of bilateral upper and lower extremities”.

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Case description – Part A

- Ms X is a 50 year-old-female who presented with numbness and weakness of her right upper extremity (RUE) progressing to right lower extremity(RLE), numbness around her trunk, and urinary hesitance/incontinence over a period of 9 months.
- Medical history: none
- Surgical history: none
- Family history: no significant familial/medical history
- Social history: a small business owner, non-smoker, non-drinker, lives with her parents and 4 sisters.
- ROS: negative except as above.

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Case description – Part A (contd)

- Labs: Unremarkable
- Physical examination:
- Hemodynamically stable
- Neurological examination: awake, alert and oriented to time, place and person; motor strength - 3/5 RUE, 2/5 RLE; right hand contractures, sensation intact bilaterally, standing with assistance.

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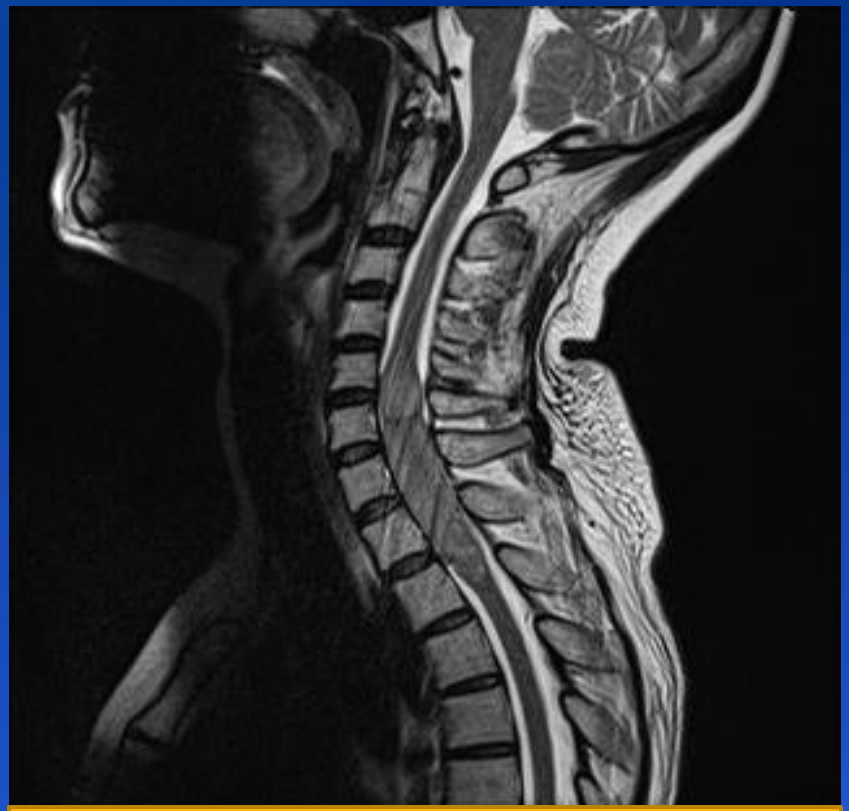
Diagnosis and management – Part A



SAG T2 on presentation

- Surgery: Cervical laminectomy C4-T3 and subtotal resection of intradural intramedullary spinal cord tumor C5-T2.
- Pathology : spinal cord pilocytic astrocytoma IDH-1 negative and MIB-1 10%.

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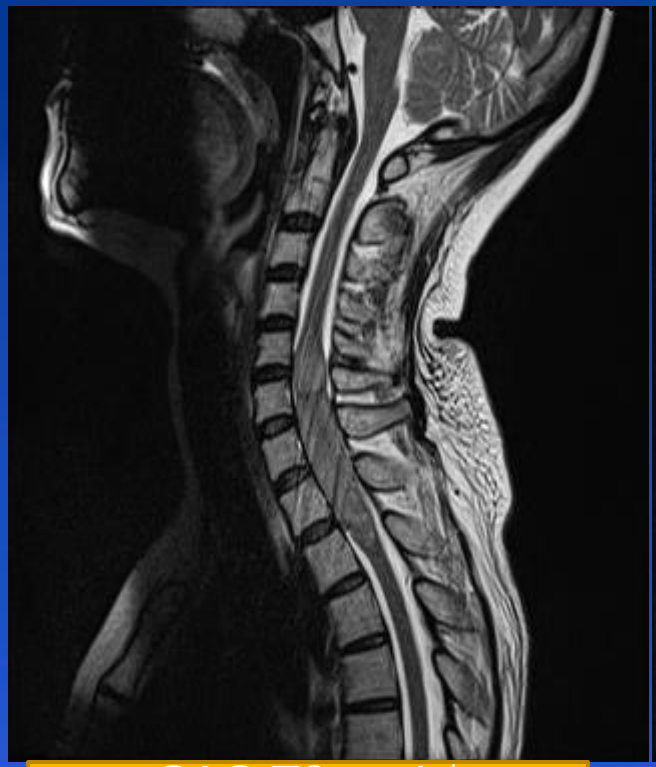
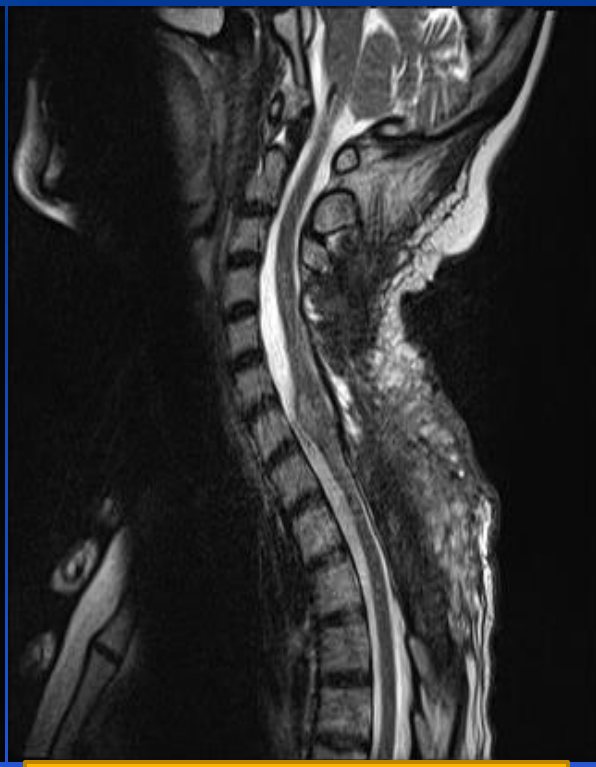
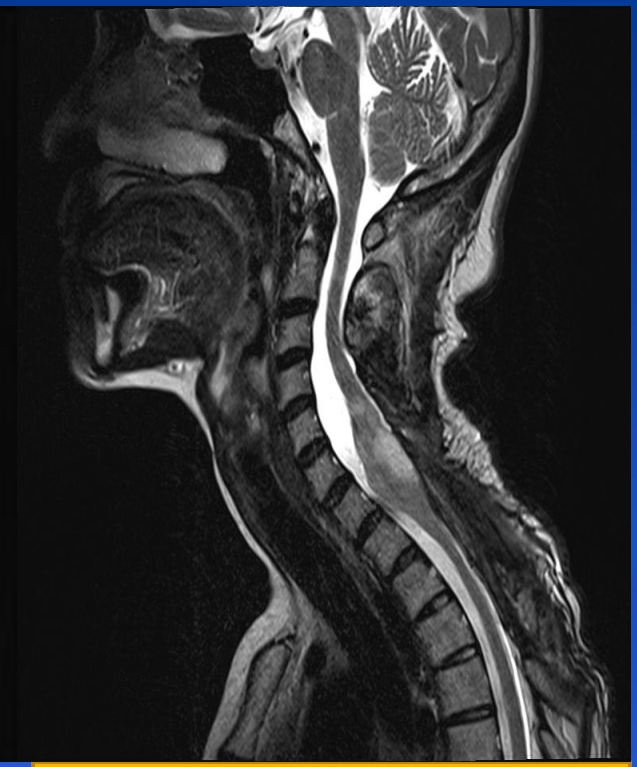
Fast forward 6-10 months: progressive symptoms of left hand stiffness with contractures. She still has residual right upper and lower extremity weakness.



SAG T2 on 1st presentation



Post-operative



2nd presentation

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Management

- Revised pathology based on new criteria and molecular testing: Diffuse midline glioma H3 K27M-mutant WHO grade IV.
- Surgery was not recommended.
- Treatment: concurrent chemotherapy (Temozolomide), Valproic acid and radiation therapy.
- Physical therapy.

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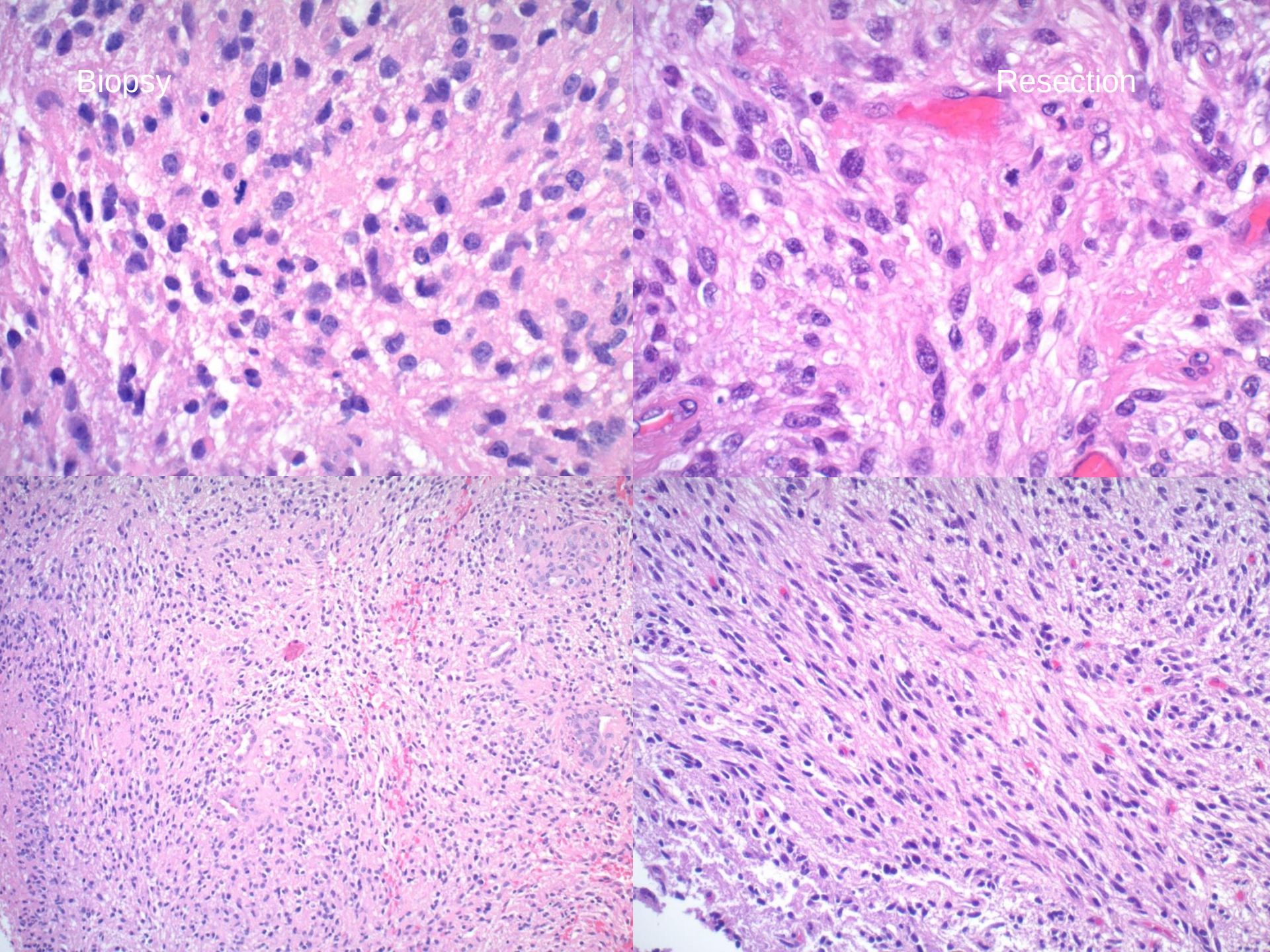
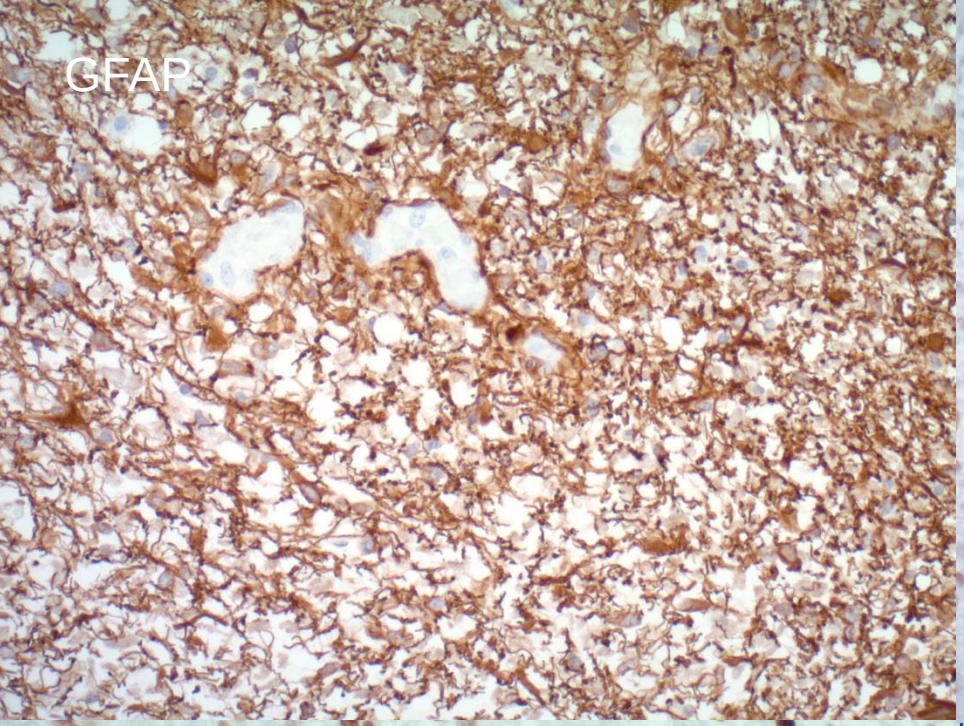
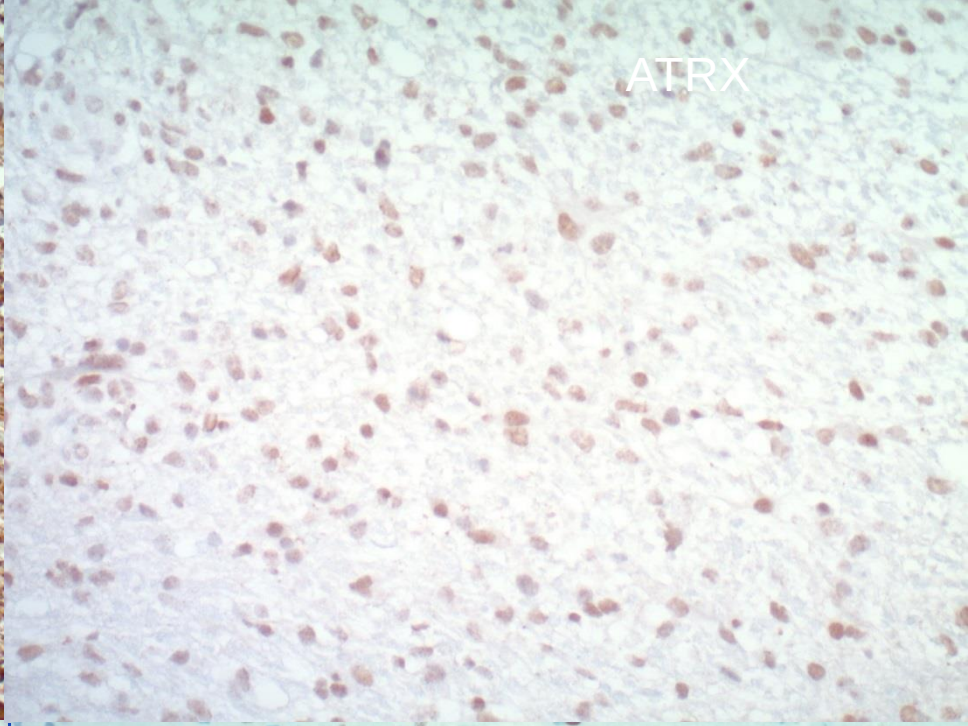
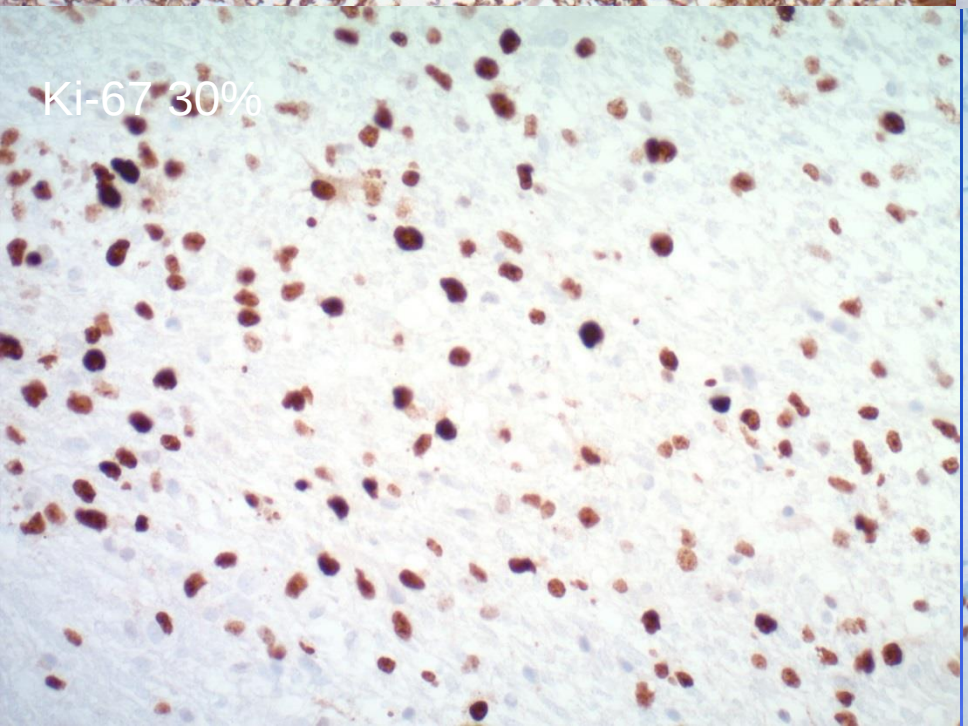
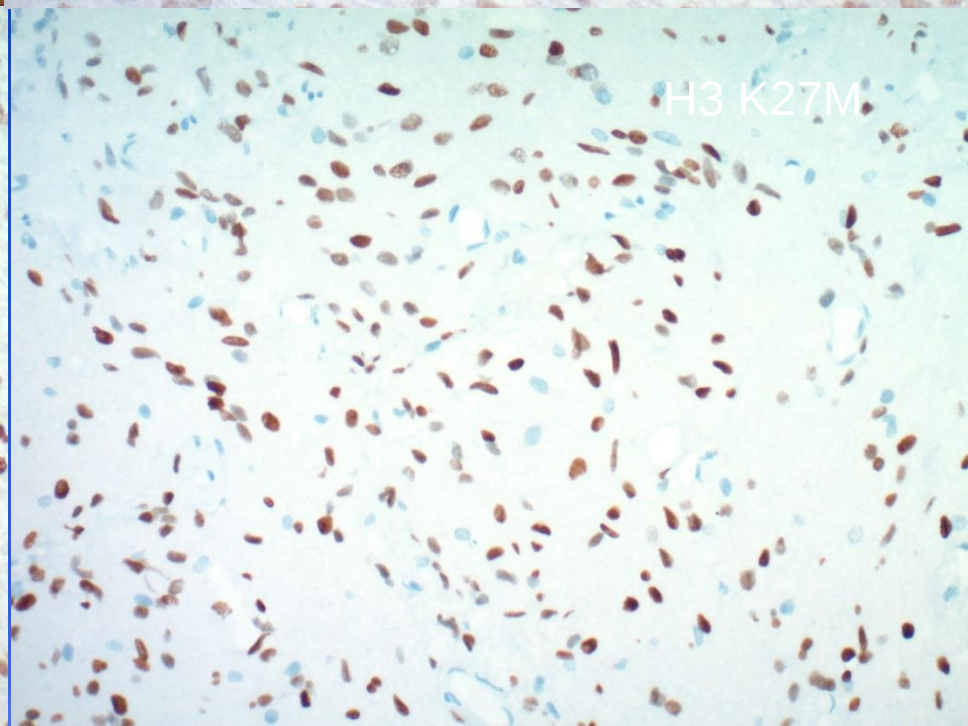
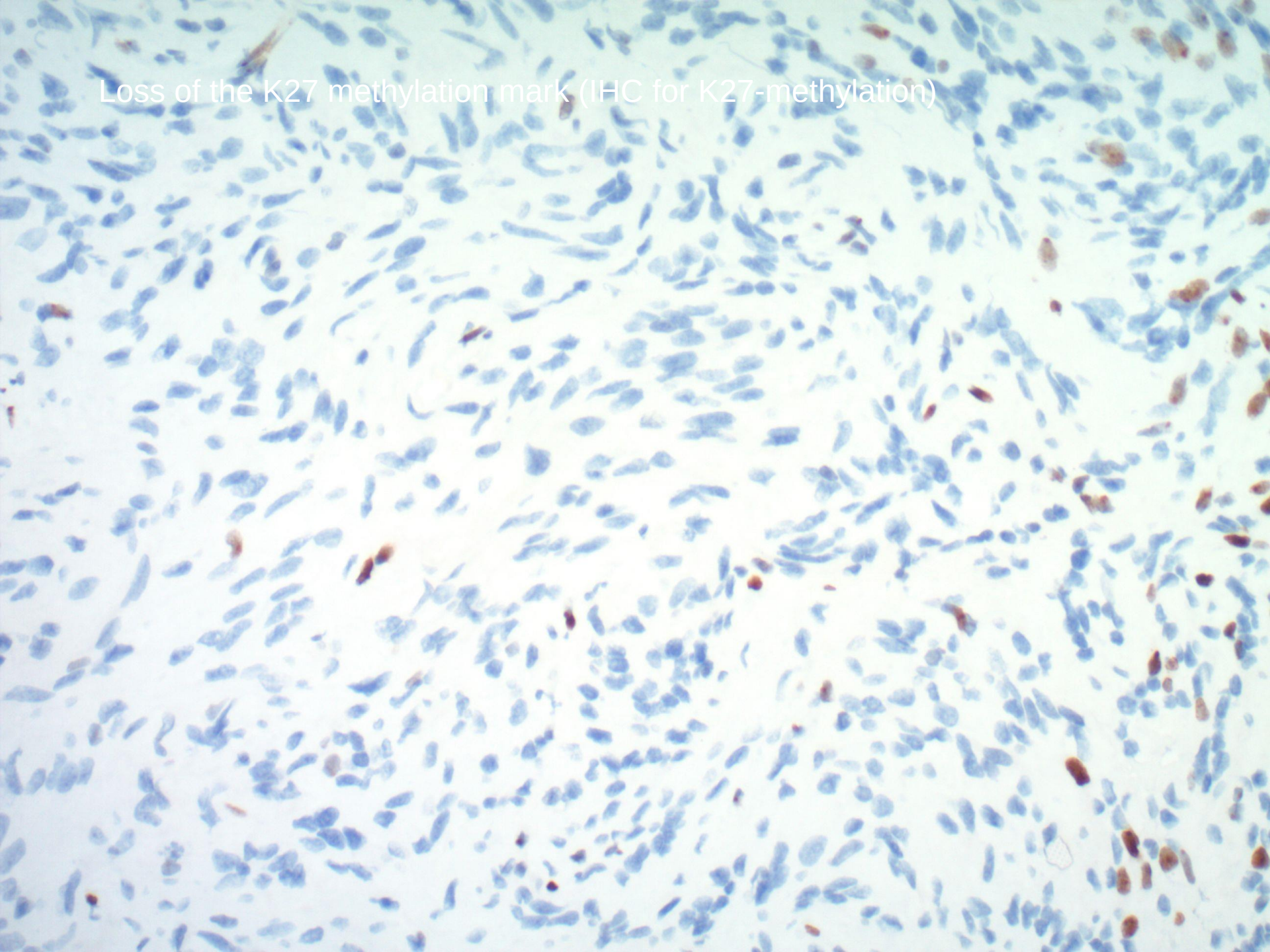

Biopsy
Resection

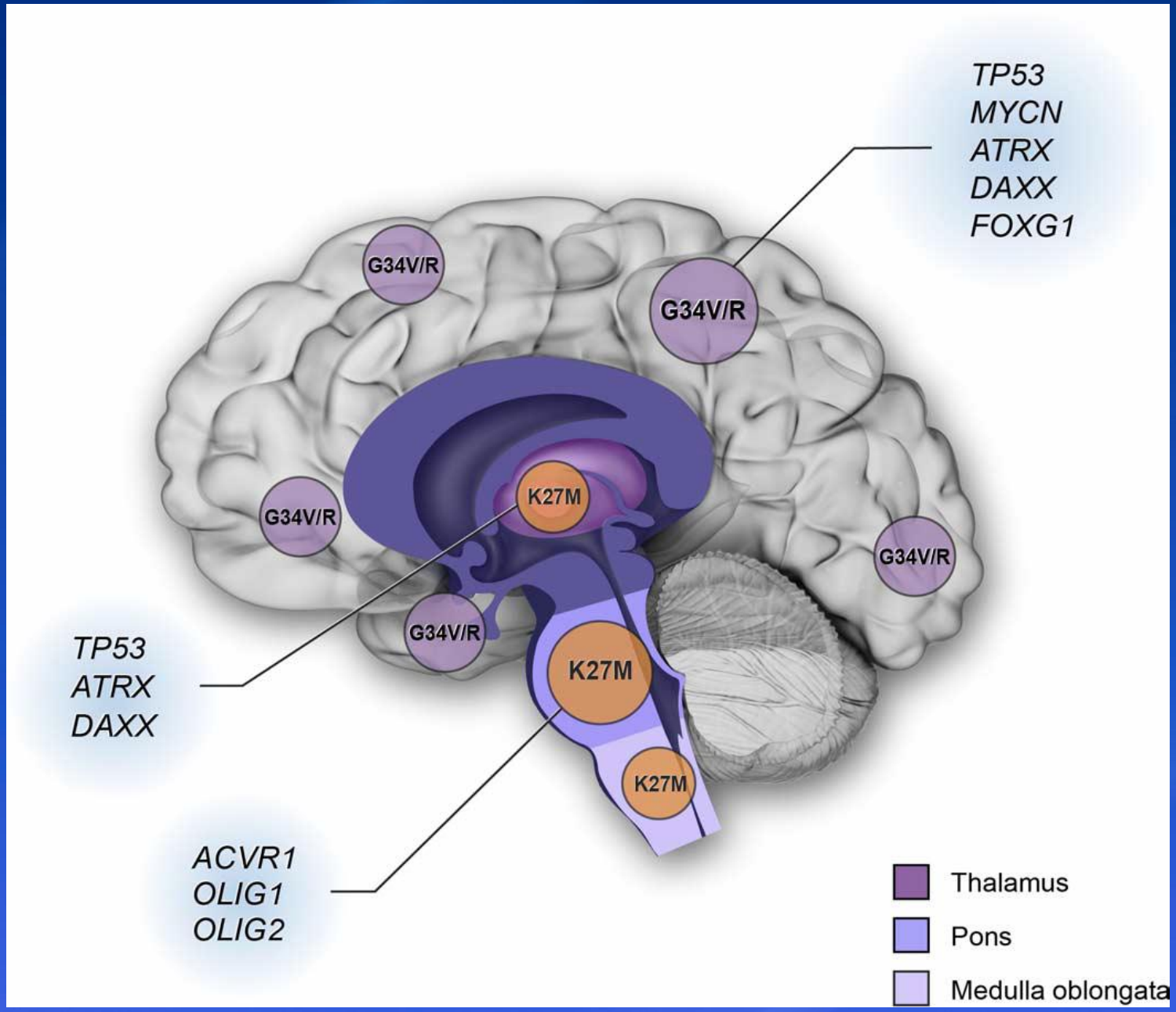

GFAP


ATRX


Ki-67 30%


H3 K27M


Loss of the K27 methylation mark (IHC for K27-methylation)



Lulla, Saratsis, Hashizume Sci. Adv. 2016; 2 : e1501354

Diffuse mid-line gliomas H3K27M

- 2016 WHO classification of CNS tumors - Diffuse midline glioma, H3 K27M-mutant Grade IV (new entity).
- Mutation in histone H3 at position amino acid 27 resulting in the replacement of Lysine by methionine (K27M).
- Can occur in mid-brain, pons, and spinal cord.
- Mostly occur in children and rare in adults.

Orillac et al. Acta Neuropathologica Communications (2016) 4:84; *Nature 2012;484:130; Cell 2012;22:425–37; Neuropathol. 2015;129:669–78; Acta Neuropathol 2016;131:803–20.*

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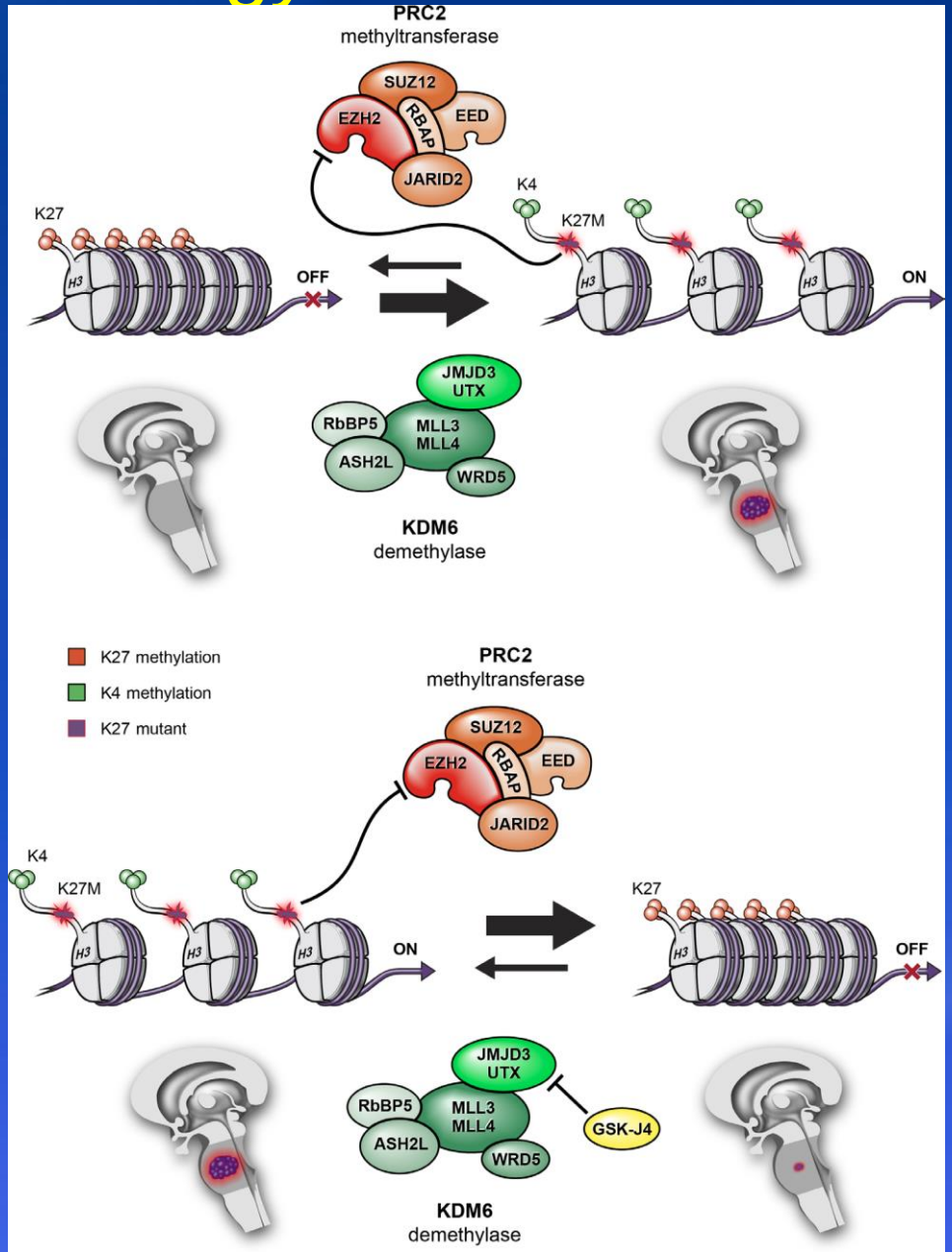
Molecular biology



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Targeted therapy

- GSKJ4 has *in-vitro* and *in-vivo* anti-tumor activity against K27M mutant tumors.
- Vorinostat: pan-HDACi showed benefit in pre-clinical data.
- Panobinostat: better activity than Vorinostat *in-vitro.*
- Trial of Panobinostat in Children With Diffuse Intrinsic Pontine Glioma (PBTC-047) is currently open.
- In-vitro: combination of Panobinostat and GSKJ4 has shown synergestic effect.
- Valproic acid: can be a potential therapeutic agent

*Journal of Clinical Oncology Vol 34, No 25 (September 1), 2016: pp 3104-3105; Hennika T, Hu G, Olaciregui NG, Barton KL, Ehteda A, Chitranjan A, et al. (2017) PLoS ONE 12(1): e0169485.*Nature 488, 404–408 (2012).

Summary

- Diffuse mid-line glioma with H3K27M Grade IV tumors are defined as separate clinical entity in WHO classification in 2016 with aggressive course and poor prognosis.
- We have better understanding of the epigenetic pathways.
- Currently, pre-clinical data has shown some benefit with histone deacetylase inhibitors.
- Further clinical trials are required to assess their efficacy and effect on PFS/OS.

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Thank you.

Acknowledgment

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