Neurotoxicity of Immune Checkpoint Inhibitors

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Disclosures

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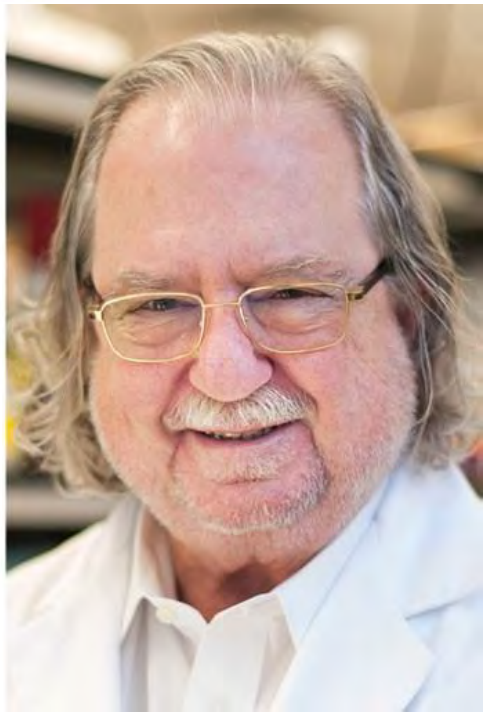
Immunotherapy

The discovery of immunotherapies for a wide range of cancers has revolutionized cancer treatment paradigms

Despite relapse/refractory disease, immunotherapy approaches can prolong the life expectancy of advanced cancer patients

Since 2011 (ipilimumab), multiple therapeutic approaches and agents are FDA approved for a over 50 types of cancers

Several other immunotherapies are being developed to manipulate various aspects of the immune system.



Tasuko Honjo *James Allison*

2018 Nobel Prize in Medicine

ICI phase 3 clinical trials:

- **Pembrolizumab (PD-1i)**
  - KEYNOTE 042 (NSCLC)
  - KEYNOTE 054 (MM)
  - KEYNOTE 062 (GI)
- **Nivolumab (PD-1i)**
  - CheckMate 067 (RCC)
  - CheckMate 026 (NSCLC)
  - CheckMate 067 (MM)
  - CheckMate 743 (mesothelioma)
- **Atezolizumab (PD-L1i)**
  - OAK (NSCLC)
  - AtTEnd (endometrial)
  - IMbassador250 (prostate)
- **Ipilimumab (CTLA-4)**
  - MDX010-20 (MM)
  - CA184-095 (prostate)
  - ECOG 1609 (MM)

ICI phase 3 clinical trials **in Neuro-oncology:**

- **Nivolumab**
  - CheckMate 548 (new GBM, MGMT+) mOS 13.4 vs. 14.9 months; mPFS 6.0 vs. 6.2 months
  - CheckMate 498 (new GBM, MGMT-) mOS 28.9 vs. 32.1 months; mPFS 10.6 vs. 10.3 months
  - CheckMate 143 (rec GBM) mOS 9.8 vs. 10.0 mo; mPFS 1.5 vs. 3.5 mo

ICI-Related Adverse Effects:

- Incidence of severe adverse effects:
  (**CTCAE grade 3-4**)
  - PD-1/PD-L1 inhibitors: 14%
  - CTLA-4 inhibitors: 34%
  - combined regimen: 55%

AE leading to discontinuation of therapy: **1-14%**

- Most common affected organs
  - skin
  - gastrointestinal tract
  - endocrine gland
  - liver

neurological involvement is rare

ICI-Related Neurologic Adverse Effects (NAE):

INCIDENCE:
1-3%

- Although infrequent, severe and potentially life-threatening neurologic symptoms may occur
- Neurologic adverse effects have the highest mortality rates (8-24%)
- Onset: within 3–4 months after therapy initiation and up to 12 months after last infusion

ICI-Related NAE incidence in <u>Breast, Lung, Melanoma ICI trials</u>

- CTLA-4i: 3.8%
- PD1, PD-L1i: 6.1%
- Combined regimen: 12%

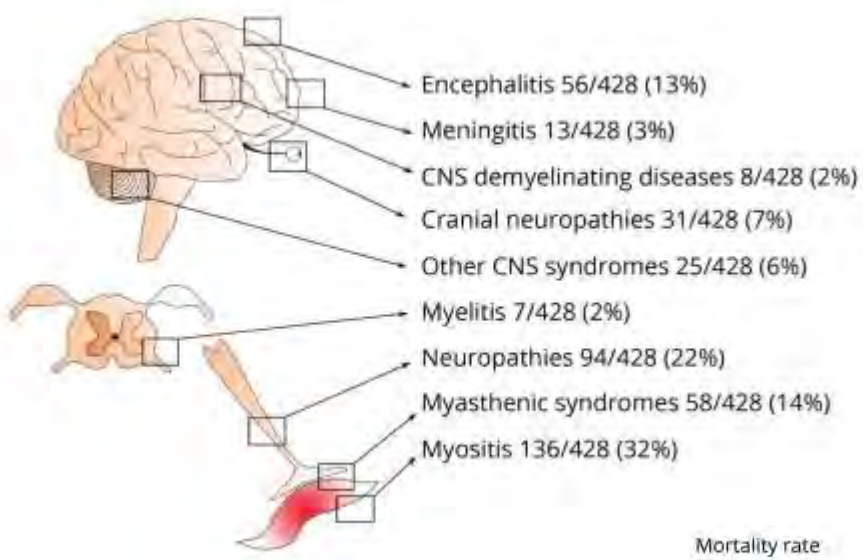
ICI-Related NAE incidence in <u>Glioblastoma ICI trials</u>

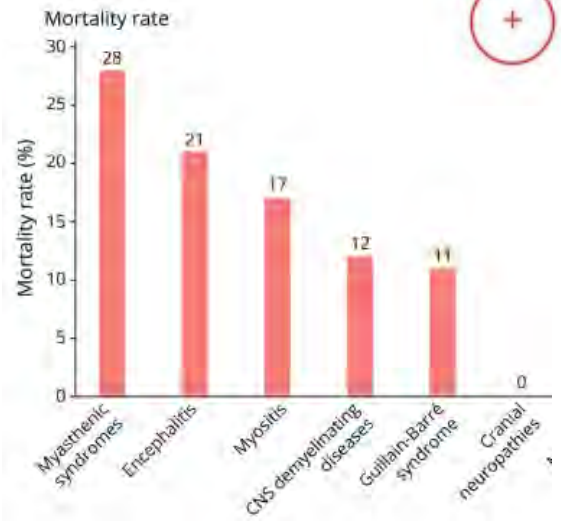
- PD-1i: 13-23% (placebo, 16%)
  - Grade 3/4 NAE: 5%
  - Most common NAE:
    - HA
    - Vasogenic edema

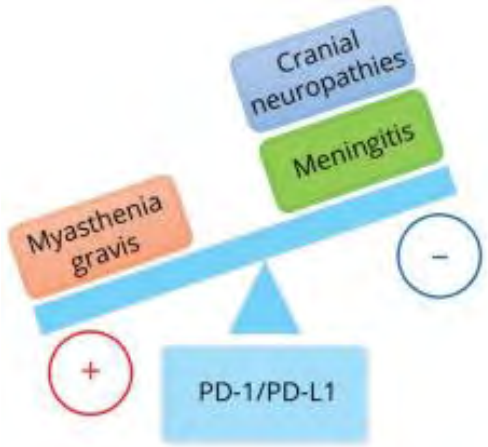
<u>3 deaths reported</u>

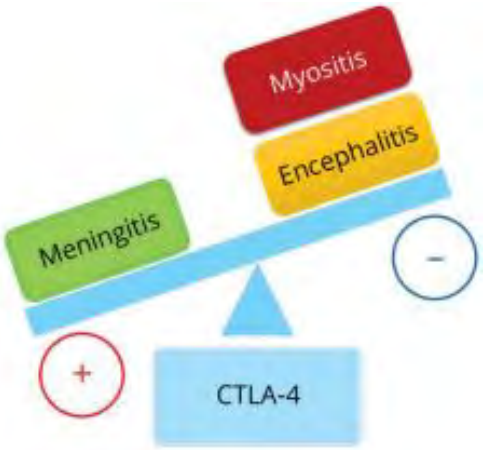
- Vasogenic edema
- Sudden death
- CV disease

ICI-Related NAE: *symptomatology*









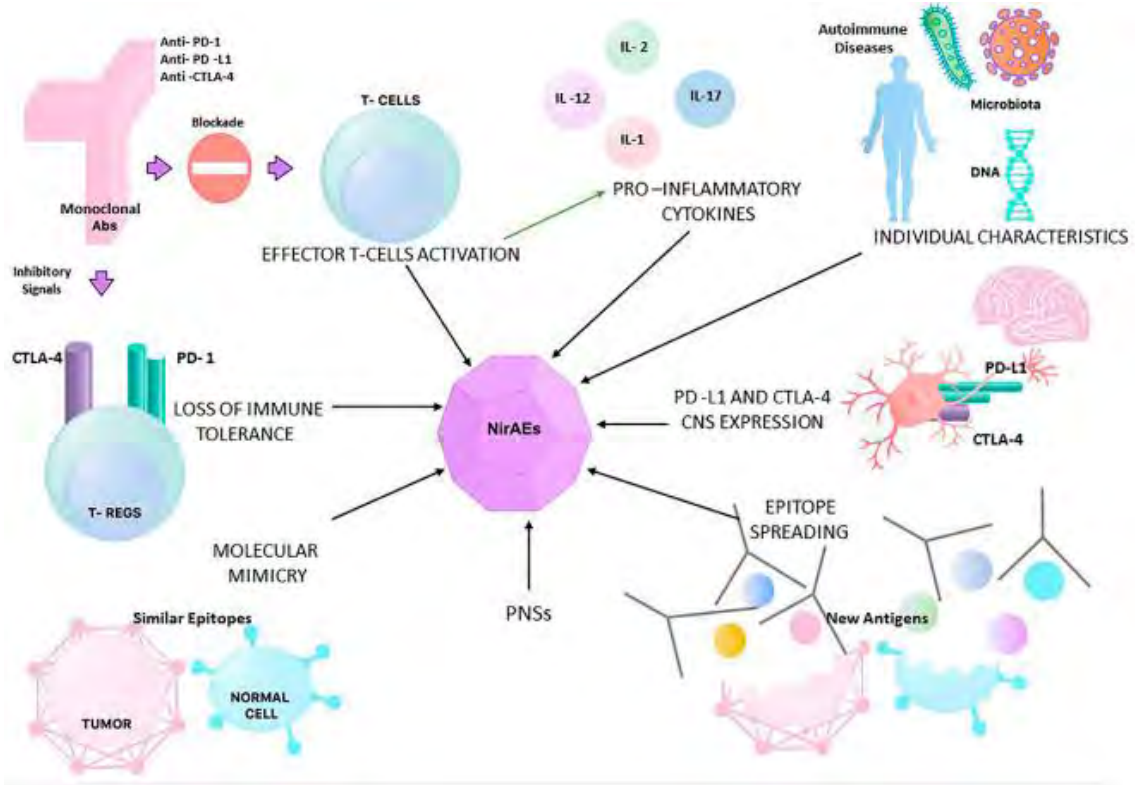
Marini, 2021. Neurology

ICI-Related NAE: *Pathophysiology*

- Heightened immunologic activation

<u>Multiple Hit Process</u>:

- Genetic background
- Autoimmune predisposition
- Tumor's mutations
- Immune system
- Environmental factors

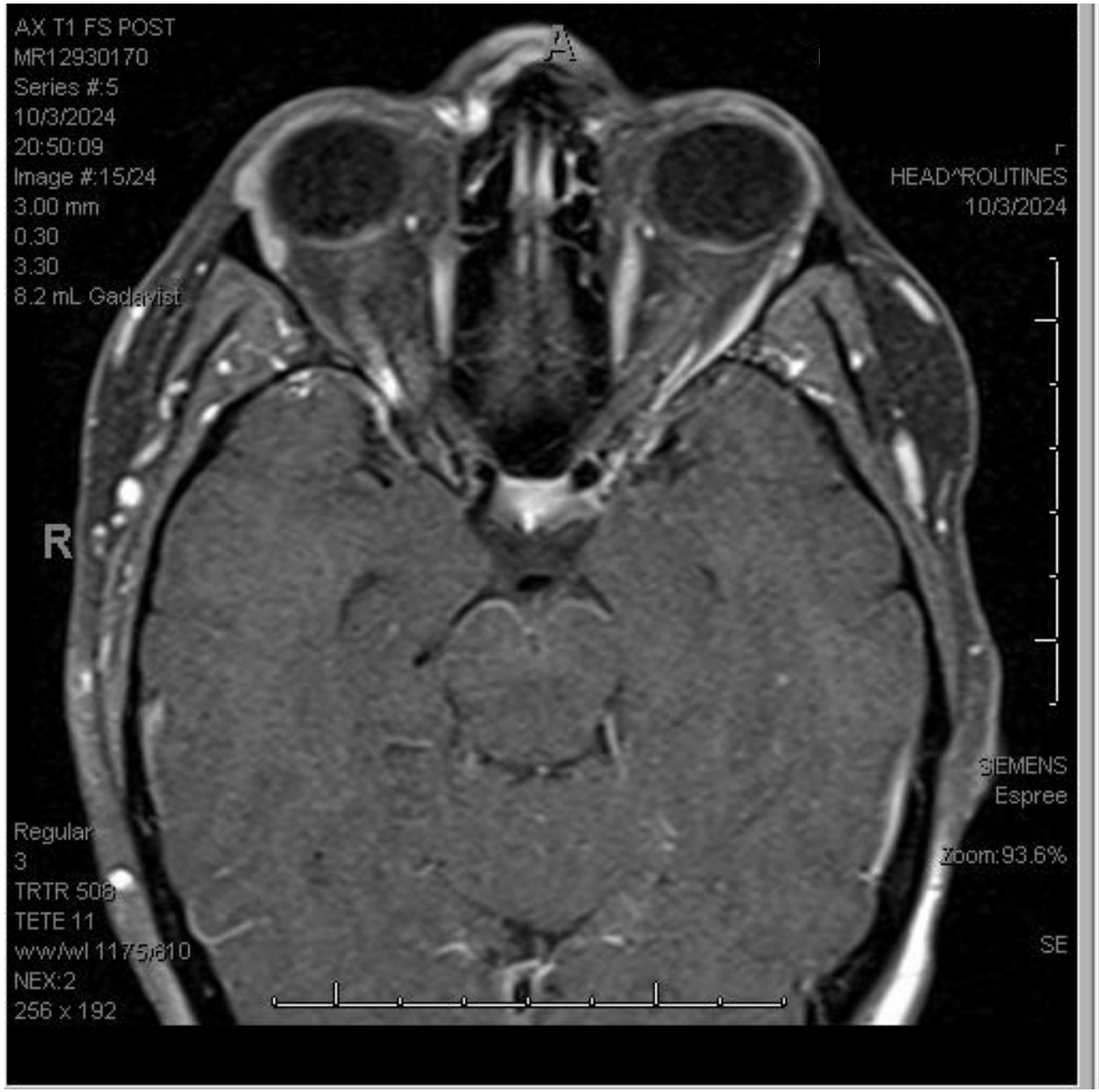


Albarran, 2022. Front Pharm

Clinical case

- 41yo female, grade 3 invasive ductal carcinoma of breast
- ER/PR/HER2neu negative, since June/2024
- No distant metastases, negative LN

- 7/15/2024: started on neoadjuvant chemotherapy (Carbo-Taxol-Pembro)
- 10/2/2024: progressive visual impairment
  - Eye institute = bilateral papilledema (post 4 doses of Pembrolizumab)


AX T1 FS POST
MR12930170
Series #:5
10/3/2024
20:50:09
Image #:15/24
3.00 mm
0.30
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8.2 mL Gadavist
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ww/wl 1175/610
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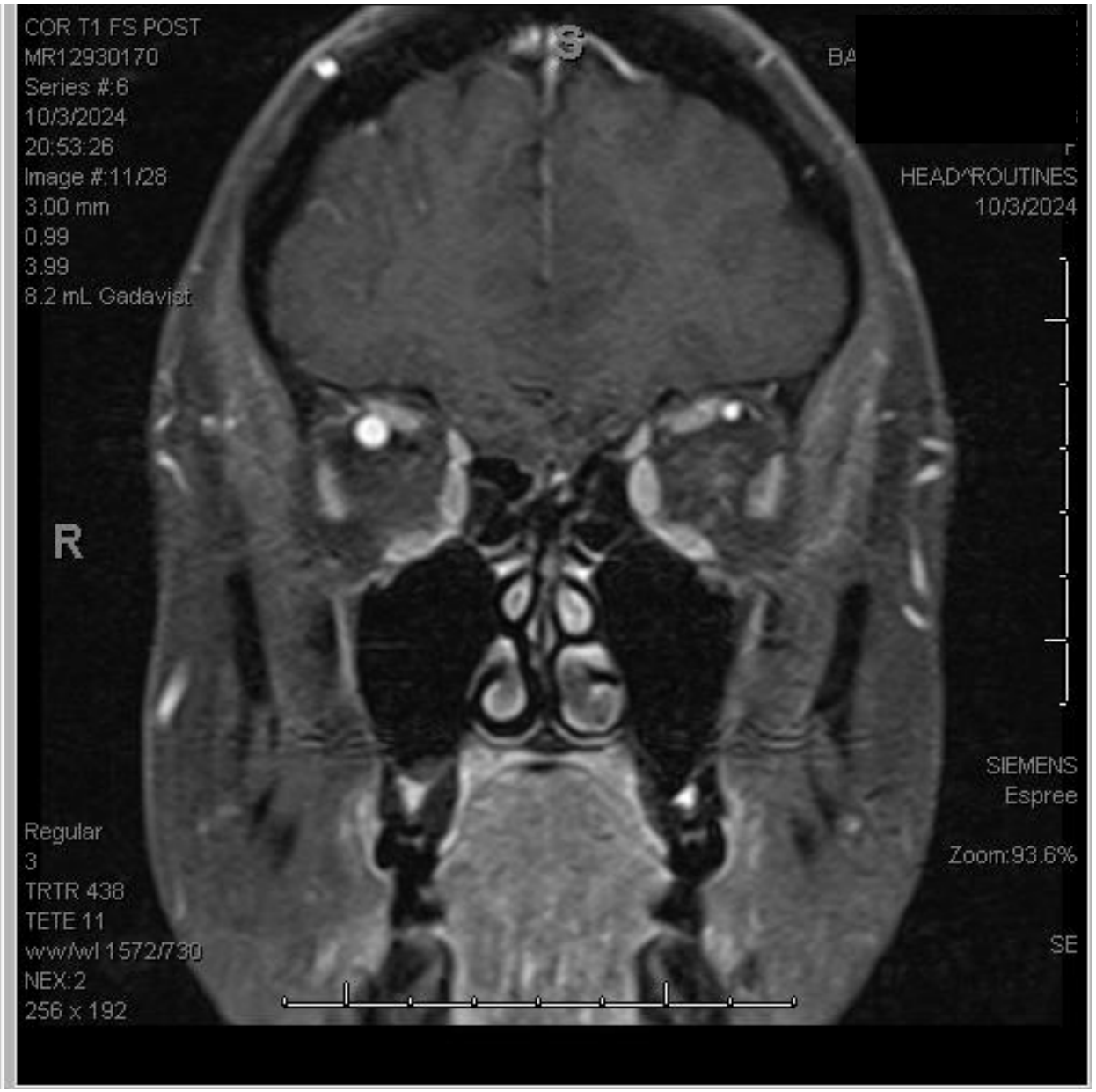
Zoom:93.6%
SE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Espree
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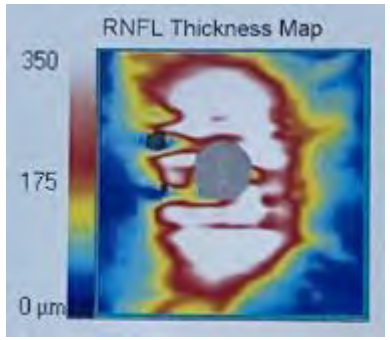
3
TRTR 438
TETE 11
ww/wl 1572/730
NEX:2
256 x 192
Zoom:93.6%
SE

Clinical Course

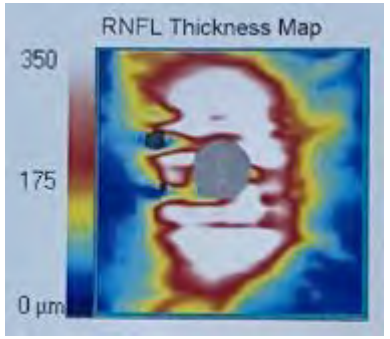
- Started steroid taper
  - Decadron duration: 2.5 months
- OCT progressively improved
- Resolution of papilledema and blurriness after 6 weeks
- Complication: adrenal insufficiency
  - improved with hydrocortisone replacement

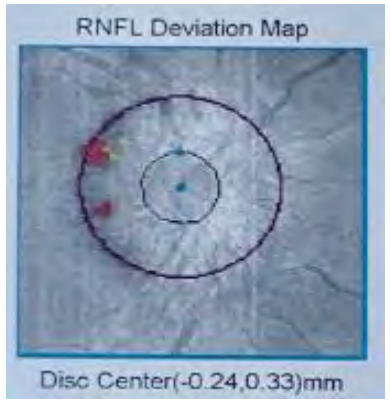
OD

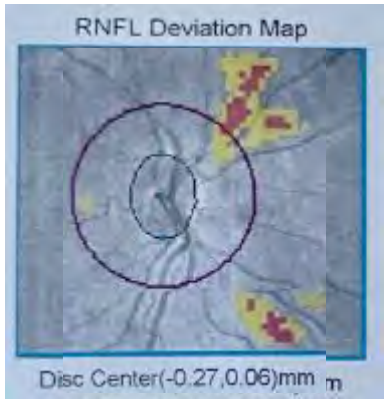
pre-steroid



post-steroid

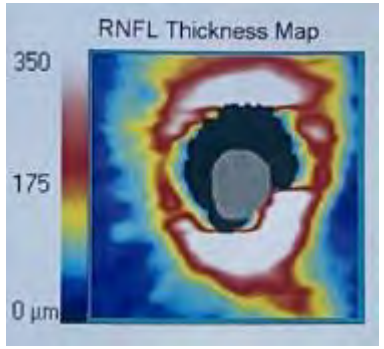




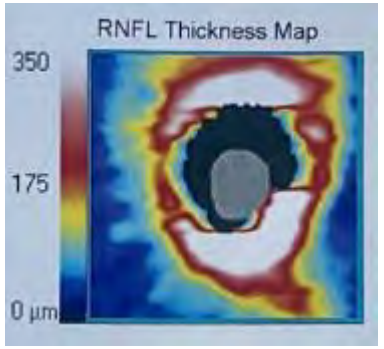


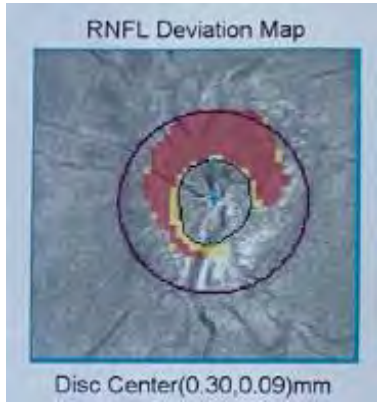
OS

pre-steroid



post-steroid





ICI-Related NeurAE: *Management*

- ICI discontinuation

- **Steroid therapy**

- Immunomodulatory strategies (for persistent or severe cases):
  - IVIG
  - PLEX
  - Immunosuppresion

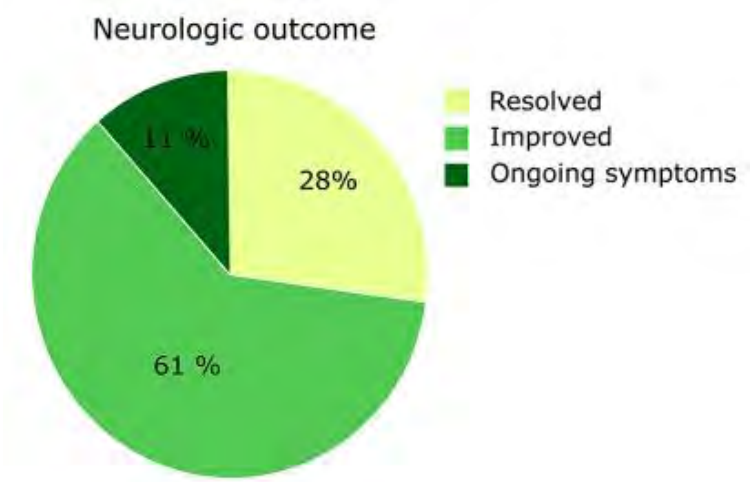
ICI-Related NeurAE: Management

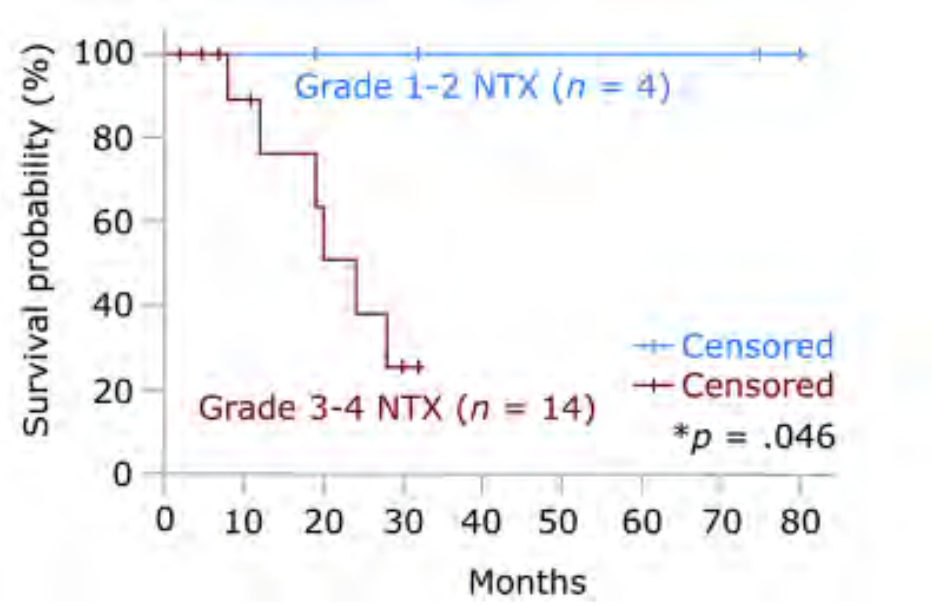
ESMO, NCCN, SITC, ASCO Guideline Compilation:

Suspected syndrome	Treatment recommendations
	Central neurological toxicity
Aseptic meningitis	Consider concurrent empiric antiviral (i.v. acyclovir) and antibacterial therapy
Encephalitis	Consider concurrent empiric antiviral (i.v. acyclovir)
Transverse myelitis	Start 2 mg kg^{-1} day^{-1} (methyl)prednisolone or 1 g/day If no improvement or worsening, consider plasmapheresis
	Peripheral neurological toxicity
Guillain–Barré syndrome (GBS)	Consider 1–2 mg kg^{-1} day^{-1} prednisolone equivalents PO or IV If no improvement or worsening, plasmapheresis or intravenous immunoglobulin indicated • Ventilatory support should be available • Steroids not recommended for idiopathic GBS
Myasthenia Gravis	Steroid indicated—dosing according with grading of symptoms Pyridostigmine, initial dose of 30 mg If no improvement or worsening, consider plasmapheresis or intravenous immunoglobulin, additional immunosuppressants azathioprine, cyclosporine, or mycophenolate *Avoid medications that may precipitate cholinergic crisis

Albarran V. Front Pharm, 2022

ICI-Related NAE: *Prognosis*





S Duong, 2021. J Neuro-oncol

ICI-Related NAE: *Summary*

- Neurologic AE (NAE) from ICI is rare yet potentially life-threatening
- Predicting NAE is challenging: multifactorial process
- Management of NAE involves:
  - withholding/discontinuing ICI in all cases
  - Steroid therapy (most cases)
  - Other immunosuppressants (Grade 3-4 NAE)
- Restarting ICI following NAE should be carefully considered