Motexafin gadolinium (MGd) combined with prompt whole brain radiation therapy (RT) prolongs time to neurologic progression in non-small cell lung cancer (NSCLC) patients with brain metastases: Results of a phase III trial.

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Background
- Motexafin gadolinium (MGd) is a radiosensitizer that is MRI-detectable and selectively localizes in tumors. It can induce redox stress and is an inhibitor of thioredoxin reductase, an enzyme whose overexpression is correlated with poor prognosis in NSCLC.
- A subgroup analysis of a randomized trial showed that there was a time to neurologic progression (TNP) benefit from the addition of MGd to whole brain radiation (WBI) for metastatic NSCLC only (p=0.048).
- That subgroup analysis prompted this randomized phase III trial of MGd in patients with intracranial NSCLC metastasis.

Materials and Methods
- Phase III study design:
  - International (34% USA, 29% Canada, Europe, Australia, etc.)
  - 550 patients with NSCLC diagnosed with brain metastasis randomized to:
    - WBI (30 Gy in 10 fractions) vs. WBI + MGd, 5 mg/kg daily for 10 days
    - Criteria: KPS >=70. No liver metastasis or greater than 2 extracranial sites of metastasis
- Endpoints:
  - Primary: Time to neurologic progression (TNP) as assessed centrally
  - Secondary: TNP as assessed by physician, Time to neurocognitive progression

Results
- MGd was well-tolerated with >92% of intended doses given
- Most common adverse events were skin and urine discoloration
- Analysis of TNP by intent to treat as measured from time from randomization showed a benefit from MGd that did not reach statistical significance
  - 15.4 months (95% CI 10.7-24.2) for WBI + MGd vs. 10 months (95% CI 7.4-13.5) for WBI (p=0.12, HR 0.78)
- Analysis of TNP as measured from time from diagnosis of brain metastasis showed a significant benefit from MGd (p=0.05)
  - It turned out that more patients in North America were randomized promptly after diagnosis of brain metastasis for planned WBI, however in the other geographic sites, there was a delay that was attributed to the practice of treating brain metastasis with chemotherapy before WBI (3% in North America vs. 32% in the rest of the world)
  - In the subset of North American patients (n=348), TNP was significantly delayed by MGd (8.8 months vs. 24.2 months, HR 0.53, p=0.004)
  - In the subset of patients where WBI was initiated within 3 wks of diagnosis (n=378), TNP was significantly prolonged by MGd (HR 0.59, p=0.006)
- In patients with a delay, the benefit from MGd disappeared
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**Author's Conclusions**
- MGd significantly prolonged TNP in NSCLC patients with brain metastasis when combined with prompt WBI.

**Clinical/Scientific Implications**
- Once again, the study of MGd combined with WBI is plagued by a non-significant primary endpoint result, but a very intriguing subset analysis
- There was a clear benefit of MGd in the subset of North American patients and promptly treated patients
- The unanticipated, routine use of chemotherapy that delayed WBI initiation in non-North American sites hampered this study. This could have been prevented by mandating an interval between diagnosis and initiation of treatment, but it is difficult to predict all possible scenarios during study design.
- This agent is being tested as a radiosensitizer in other CNS malignancies such as glioblastoma multiforme and pediatric tumors

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