label, phase I trial of concurrent paxalisib and RT (NCT04192981) for patients with brain metastases, leptomeningeal metastases, or both with PI3K pathway mutations. Part A comprised a standard 3 + 3 dose escalation of paxalisib at 45mg, 60mg, or 75mg daily for two weeks with concomitant RT. The primary objective was to establish the maximum tolerated dose (MTD) of paxalisib when combined with cranial RT. RESULTS: Between 3/2020-1/2022, 12 patients were enrolled to Part A, of which 9 were evaluable (3 did not complete protocol therapy). Median followup was 4.5 months (0.9-14.9 months). All patients received paxalisib with whole brain RT (30Gy in 10 fractions)- 10 patients for brain metastases, and 2 for leptomeningeal metastases. The most common histology was breast cancer (4 [33%]), and the most common PI3K pathway alterations were PIK3CA mutation (7 [58%]). No patient experienced dose-limiting toxicity (DLT) at 45mg paxalisib daily with concurrent RT, and 2 experienced DLT at 60mg paxalisib: 1 with grade 3 nausea and vomiting and 1 with grade 4 enterocolitis and neutropenia. When combined with cranial RT, the paxalisib MTD was established at 45mg/day. We also observed robust response with all evaluable patients experiencing partial or complete response per RANO-BM within 3 months of protocol therapy. CONCLUSION: A MTD of 45mg/day has been established for paxalisib with concurrent cranial RT in patients with solid tumor brain metastases and leptomeningeal metastases harboring PI3K pathway mutations. Additional patients are being recruited to an expansion cohort at this dose (Part B) to confirm safety and preliminary evidence of activity.

MMAP-06

INTEGRATED TEAM-BASED BRAIN METASTASIS CARE REDUCES PATIENT VISITS AND SHORTENS TIME TO ADJUVANT IRRADIATION

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PURPOSE: Timely surgical cavity stereotactic radiosurgery (SRS) is an important adjuvant to brain metastasis resection, with earlier treatment associated with less frequent recurrence. The logistical complexity of treatment organization, however, has resulted in suboptimal start times post-surgically. We implemented a team-based process improvement approach to reduce the time from surgery to adjuvant irradiation of resected brain metastases. METHODS: A multidisciplinary working group used process-mapping to identify opportunities to reduce visits and shorten treatment times. The care delivery process was modified to streamline perioperative SRS preparation with (1) early patient identification, (2) preoperative intra-team communication, and (3) consolidation of required steps. Plan-Do-Study-Act cycles were used for process improvement. The surgery-to-SRS initiation time interval was the primary outcome. Secondary outcomes included the number of associated patient encounters. RESULTS: Following implementation, the median (IQR) interval from surgery to SRS was reduced 48% from 27 (21,34) to 14 (13,17) days (p<0.001). The rate of surgical-cavity SRS within 30 days increased from 64% (n=63/98) to 97% (n=60/62; p<0.001). The median (IQR) number of CNS-associated encounters between resection and SRS decreased from 5 (4,6) to 4 (3,5; p<0.001). The proportion of patients who had >1 MRI/CT between surgery and SRS decreased from 45% (44/98) to 13% (8/62; p<0.001). The time from surgery to systemic therapy resumption/initiation among patients treated within 90 days post-operatively decreased from 35 (24,48) to 32 days (23,40; p=0.074). There were no wound complications in either group. CONCLUSION: Adjuvant SRS latency and treatment-associated encounters were significantly reduced after care-coordination implementation. This approach reduces patient and healthcare system burden and can be applied to other scenarios where early post-operative SRS administration is critical.

MMAP-07

IMPACT OF SINGLE AND DUAL IMMUNE CHECKPOINT BLOCKADE ON RISK OF RADIATION NECROSIS AMONG PATIENTS WITH BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY

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PURPOSE: While stereotactic radiosurgery (SRS) is often an efficacious treatment for brain metastases, it carries a significant risk of radionecrosis (RN). Single and dual immune checkpoint inhibition (ICPI) have emerged as common treatment options for many patients, particularly those with melanoma and non-small cell lung cancer (NSCLC). While data suggest a cancer control benefit of combining SRS and ICPI, we hypothesized that concurrent receipt of dual ICPI with SRS increases the risk for RN. METHODS: We performed a retrospective review of serial patients with metastatic melanoma or NSCLC treated with SRS for intact brain metastases from 2014-2020 at our single institution. Patients were stratified by receipt of dual vs. single ICPI vs. SRS alone. RN was biopsy confirmed or determined radiographically, in combination with clinical assessment and steroid use. Kaplan-Meier estimates were used to compare rates of RN between cohorts. RESULTS: 673 brain lesions from 93 patients met inclusion criteria [median (Q1, Q3): 5.0 (2.0-10.0) lesions per patient]. Median follow-up of lesions was 8.1 months (95% CI: 7.3, 8.7). Most (82.8%) lesions were supratentorial and histologies included melanoma (53.5%), adenocarcinoma NSCLC (27.3%), squamous cell NSCLC (6.1%), and NSCLC NOS (6.1%). In the entire cohort, 88 lesions from 25 patients (27%) developed RN. 77 (87%) lesions were diagnosed clinico-radiographically and 11 (13%) were biopsy-proven. ICPI use was highly enriched among lesions that developed RN (85.2%) versus those that did not (19.8%). Freedom from RN at 6 months was 80% for dual ICPI, 82% for single ICPI, and 97% for SRS alone; 12 month rates were 78% in each of the ICPI cohorts and 95% with SRS alone (P=0.0002). CONCLUSIONS: In a large cohort of SRS-treated brain metastases, we observed an increased risk of RN among patients who received either dual or single ICPI concurrently with SRS.

MMAP-08

CHEMO-REIRRADIATION (NORMOFRACTIONATED VS. HYPOFRACTIONATED) WITH OR WITHOUT BEVACIZUMAB IN RECURRENT ADULT DIFFUSE HIGH-GRADE GLIOMA (COBRA): PHASE III RANDOMIZED CONTROLLED TRIAL WITH A 2 X 2 FACTORIAL DESIGN

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BACKGROUND: Adult diffuse high-grade gliomas (HGG) predominantly recur locally despite adequate treatment. At recurrence, salvage chemo-reirradiation (CTRT) provides durable local control with significant risk of symptomatic radionecrosis (RN). Reirradiation (reRT) is delivered using either conventional fractionation (CFRT) or hypofractionation based on institutional preferences. Studies have shown that the addition of bevacizumab, a monoclonal antibody inhibiting vascular endothelial growth factor to reRT reduces the risk of RN and potentially improves survival, providing strong scientific rationale for the combination. OBJECTIVE: Primary endpoint would be a composite endpoint of 1-year event-free survival (EFS) comprising recurrence, symptomatic RN or death as an event. Secondary endpoints include progression-free survival, cumulative incidence of symptomatic RN, and overall survival. Quality-of-life assessment and health-economics would be tertiary endpoints. METHODS: Target population includes adults with local recurrence (radiology and/or histology) of biopsy-proven diffuse HGG >2-years from primary RT. This is an open-label, phase III randomised control trial using a 2 x 2 factorial design comparing the addition of bevacizumab to chemo-reirradiation (test arm) versus chemo-reirradiation alone (control arm) using a superiority hypothesis. Patients in test arm will receive 6 months of bevacizumab (5mg/kg) 2 weekly, along with standard 6 cycles of temozolomide, starting 1 month following reRT completion. All patients will be further randomized to CFRT (50.4-55.8Gy/28-31/5.5-6 weeks) as control arm versus moderately HFRT (35Gy/10 fractions/2 weeks) as test arm in 1:1 ratio using a non-inferiority hypothesis. The desired sample size is 257 (two-sided alpha 0.05, power 80%, and 10% attrition rate) with a superiority hypothesis of 1-year EFS 45% (bevacizumab with CTRT) vs 30% (CTRT), and non-inferiority hypothesis of 25% (HFRT) vs 37% (CFRT),with delta of 12%. DISCUSSION: The study will answer critical questions regarding the role of bevacizumab in recurrent HGG along with reRT, along with the differences in outcomes using normofractionated or hypofractionated RT.

MMAP-09

CHARACTERISTICS CORRELATING WITH SURVIVAL IN PATIENTS TREATED FOR LARGE BRAIN METASTASES

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BACKGROUND: We aimed to identify factors predicting survival following treatment to large (>4cc) BrM. METHODS: From a prospective registry database, we identified 364 adult patients treated for brain metas-