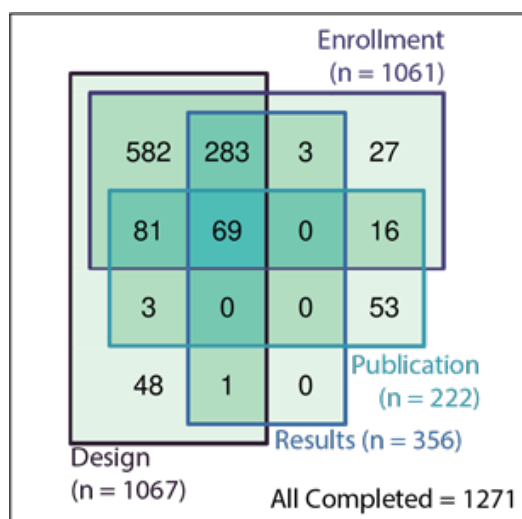
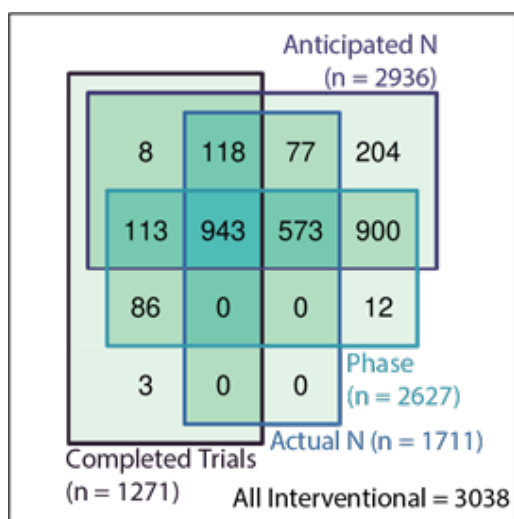


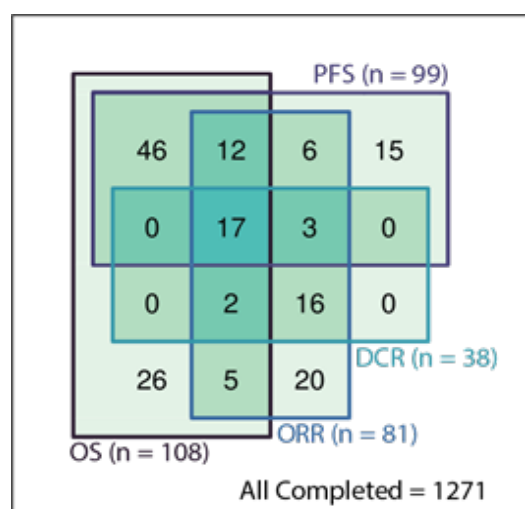
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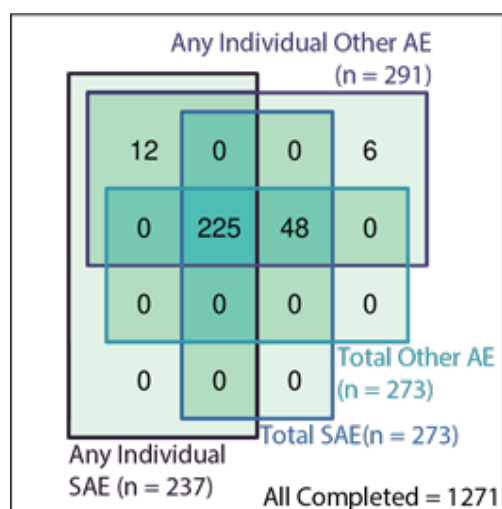
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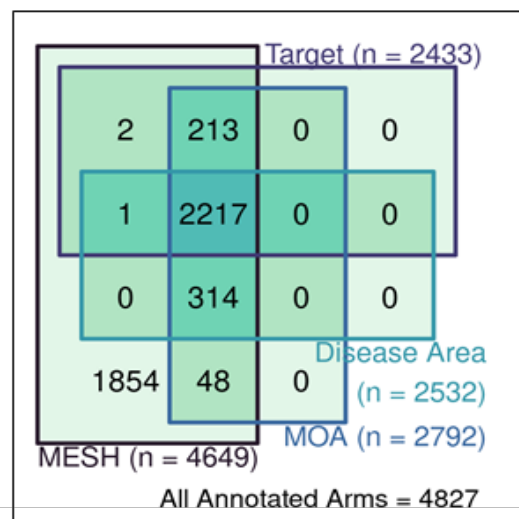
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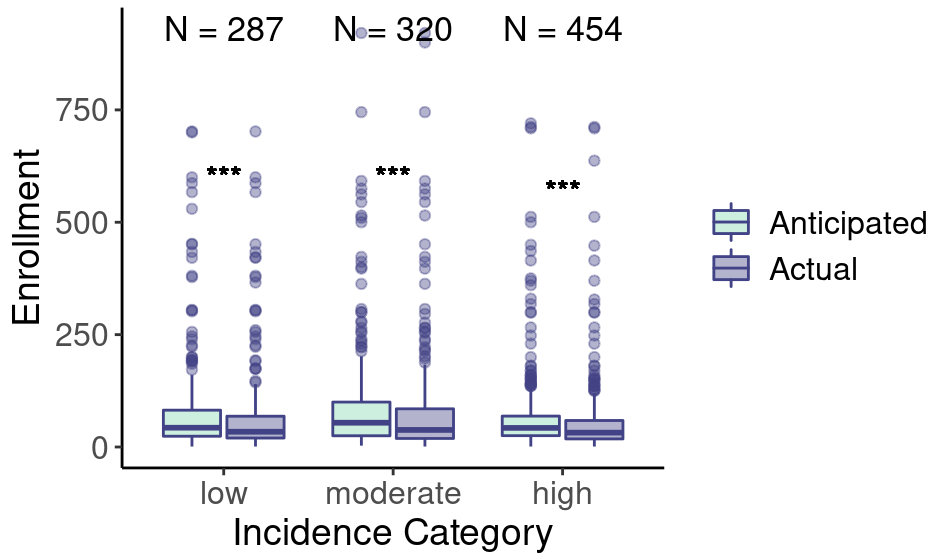
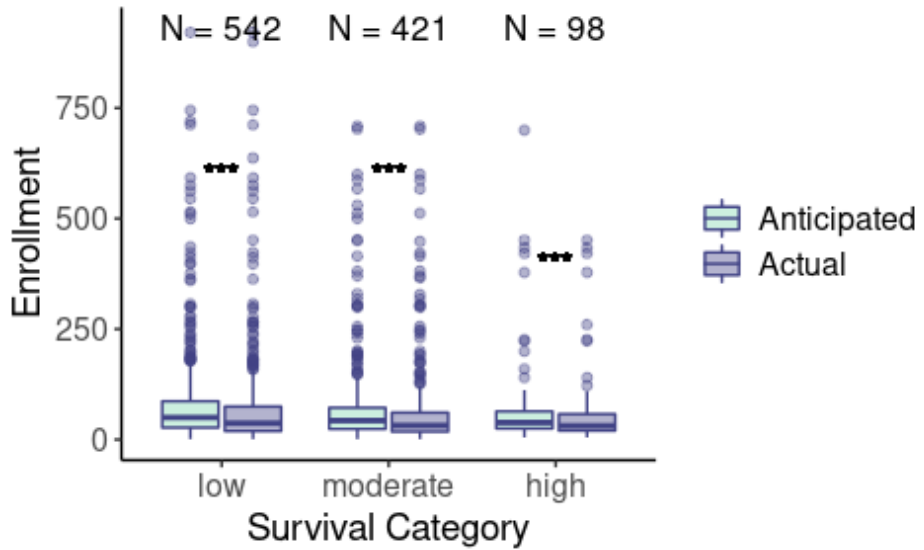
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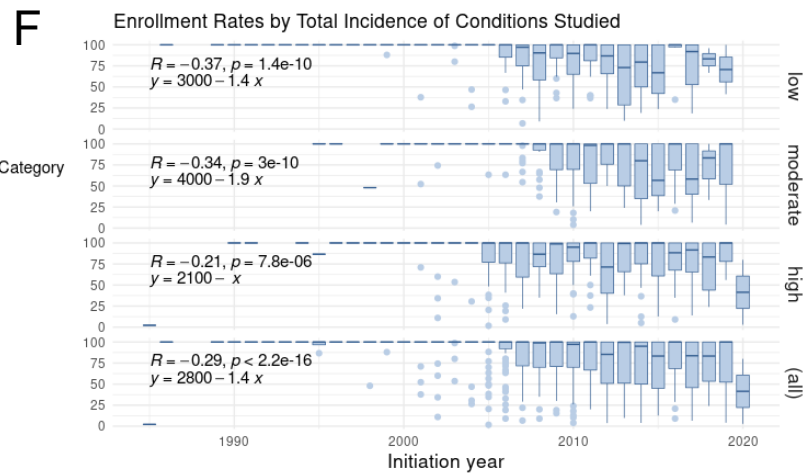
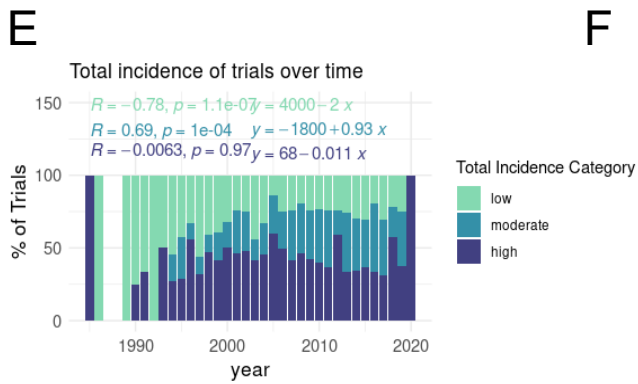
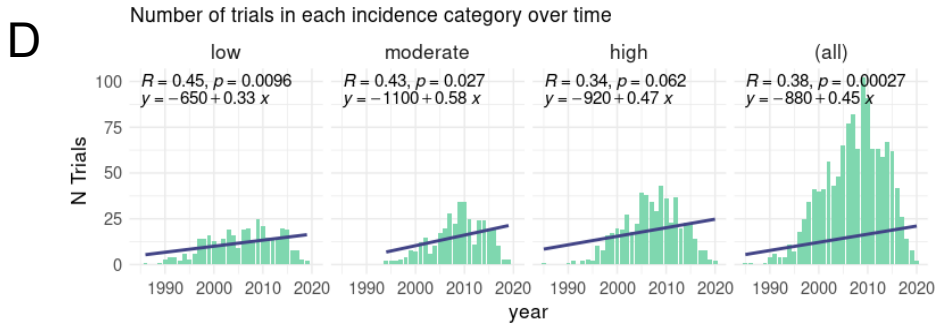
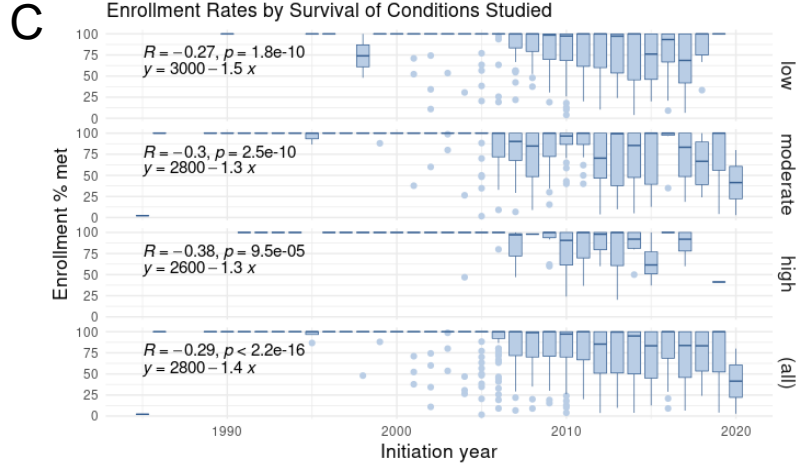
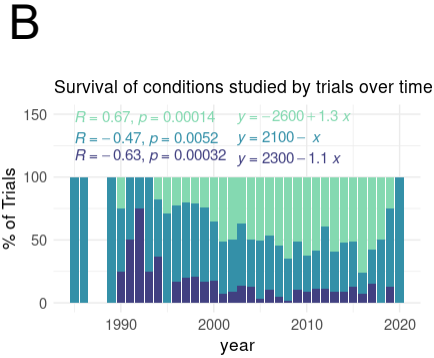
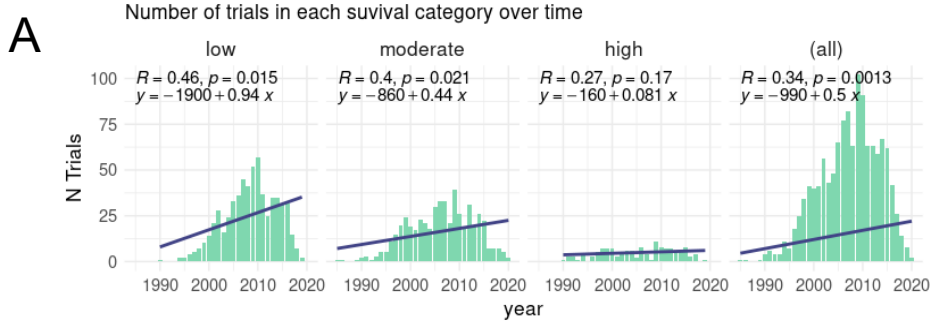
E



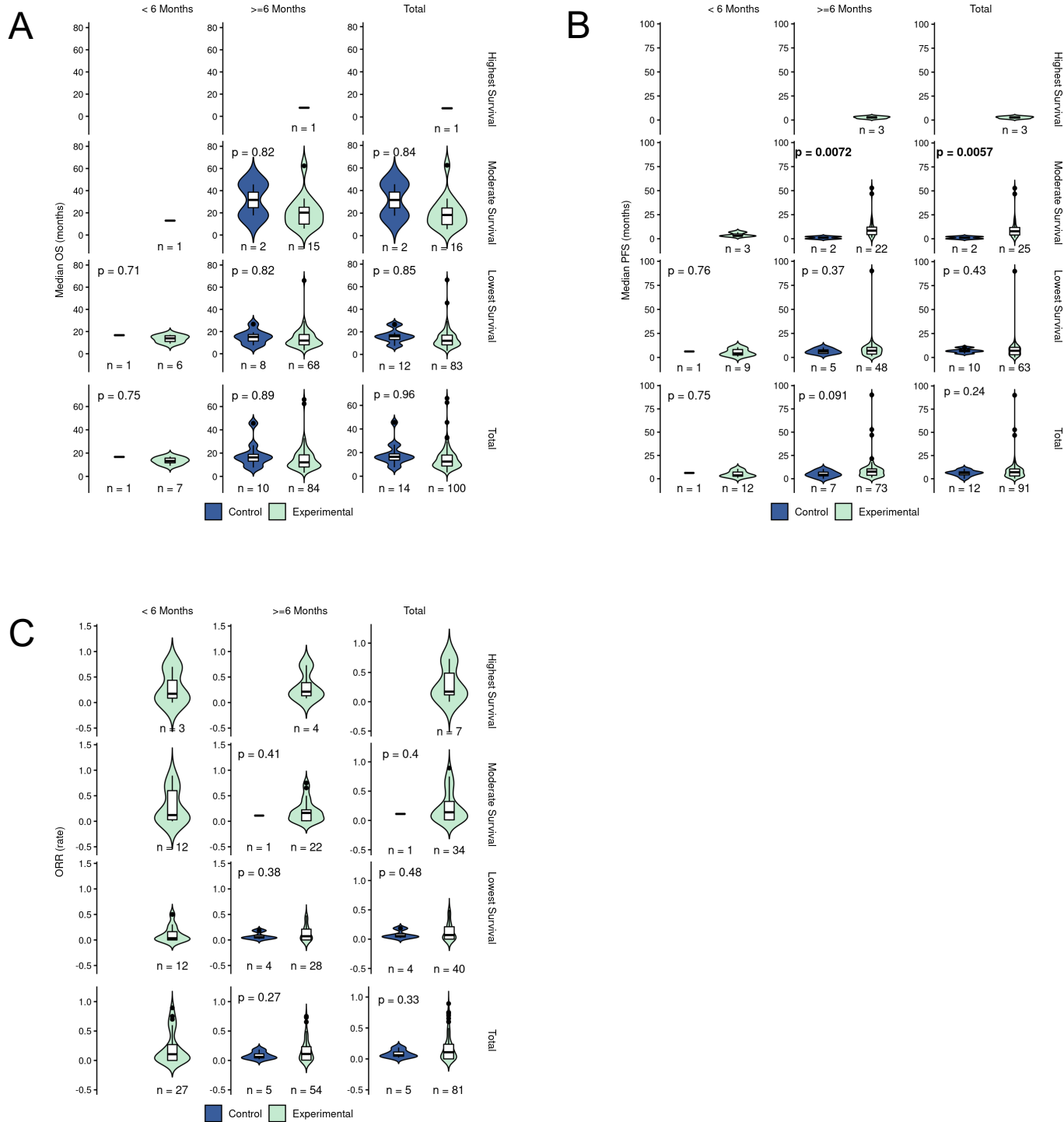
**Supplementary Figure S1.** Venn diagrams depicting data availability for (A) Main design elements, planned enrollment, publication reporting, and results reporting; (B) Detailed enrollment; (C) Reported results by planned outcome (DCR=disease control rate, defined as ORR + stable disease rate); (D) Reported adverse event results; (E) Target, mechanism of action, and disease area of interventions. The outer square indicates the set of trials or arms that are pertinent to the question. Each individual square indicates the subset of the trials/arms with indicated data element availability. The intersection among the squares indicates the number of trials/arms that have information on each of the questions represented by the overlapping squares.



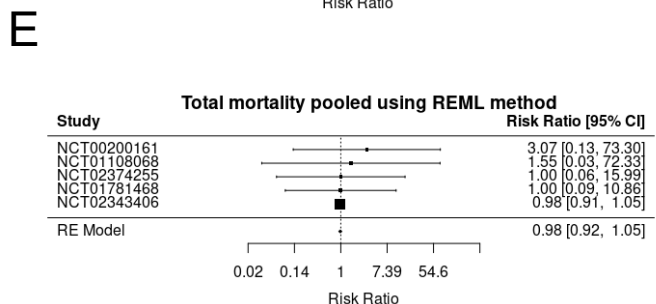
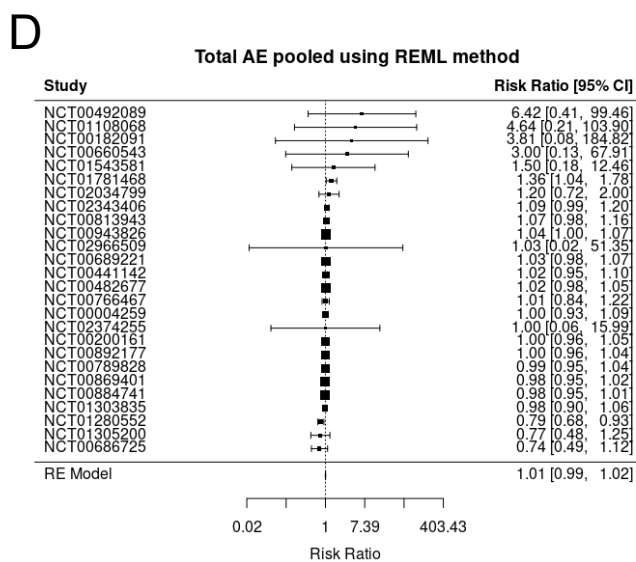
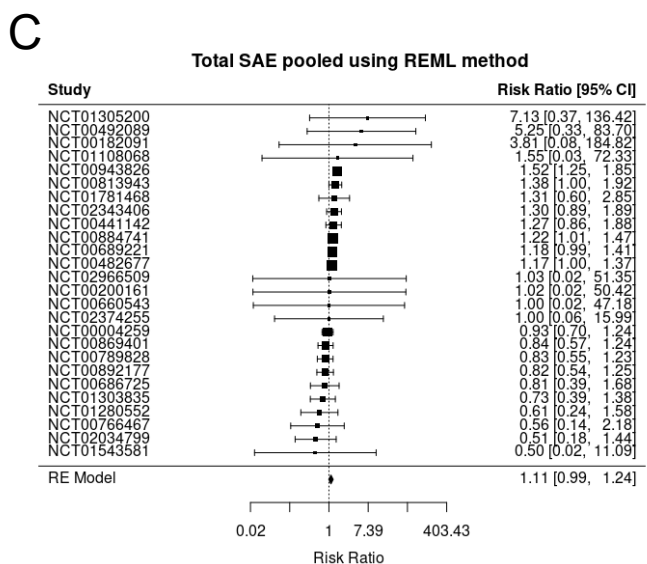
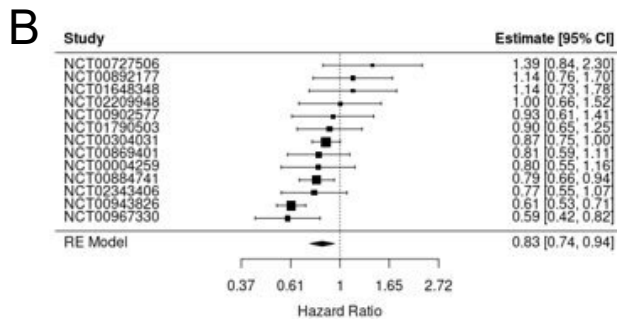
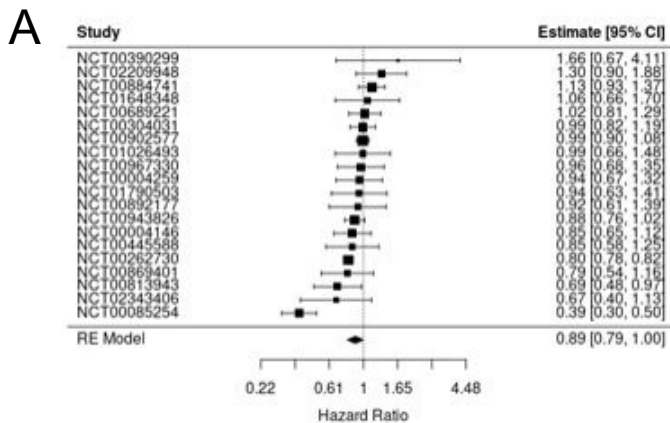
**Supplementary Figure S2.** Comparison of target enrollment with actual enrollment for completed trials by survival category and incidence categories of conditions studied using one-sided Wilcoxon tests. Significance levels for  $p\text{-adj}$ :  $0 < *** \leq 0.001 \leq ** \leq 0.01 \leq * \leq 0.05$ .



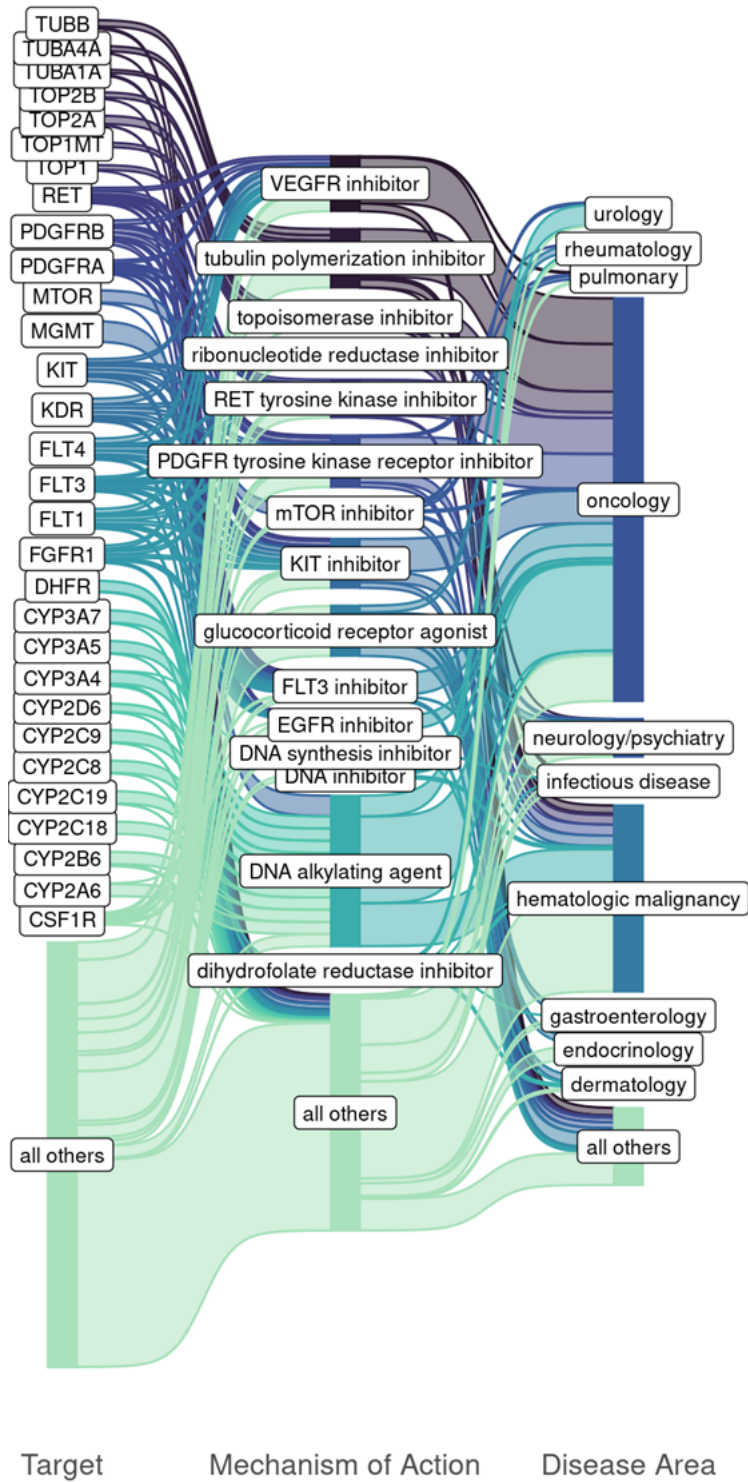
**Supplementary Figure S3. Trial Enrollment and Accrual.** Number and proportion of trials initiated each year, grouped by total incidence (**A,B**) and prognosis (**D,E**) of conditions studied. Percent of Enrollment goal met by trials each year, grouped by incidence (**C**) and prognosis (**F**) of condition studied.



**Supplementary Figure S4.** Overview of reported efficacy and toxicity, stratified by survival category of condition and timeframe of outcome collection (>=6 or <6 months). Median responses were compared for experimental and control arms using Wilcoxon one sided test for trials reporting either or both experimental and control arm responses. Raw one-sided p-values are presented. Margin totals include trials missing annotations for timeframe and survival category. **A.** OS, **B.** PFS, **C.** ORR



**Supplementary Figure S5.** Pooled Hazard Ratios and Intervention Toxicity Risk Ratios. **A.** OS and **B.** PFS outcomes from data reported by trials. **C.** Total Serious Adverse Events, **D.** Total Other Adverse Events, and **E.** Total All-Cause Mortality. Risk Ratios derived from studies reporting data for matched control and experimental arms.



**Supplementary Figure S6.** Most frequently studied interventions and their mechanisms of actions and disease areas obtained through annotations using the Drug Repurposing Hub database.

**Supplementary Table S1.** Search term derived from WHO classification of malignant CNS tumors to query neuro-oncology trials, by excluding non-malignant conditions as indicated by ICDO-O codes).

\*To exclude pediatric-targeted trials, we used the following parameter in our RPostgreSQL query: `calculated_values.maximum_age_num <= 18`.

**Term\***

Astrocytoma  
Astrocytic Tumor  
Glioblastoma  
GBM  
Gliosarcoma  
Glioma  
Oligodendroglioma  
Oligodendroglial Tumor  
Oligoastrocytoma  
Oligoastrocytic Tumor  
Astrocytoma  
Xanthoastrocytoma  
Ependymoma  
Ependymal Tumor  
Astroblastoma  
Choroid Plexus Papilloma  
Choroid Plexus Carcinoma  
Choroid Plexus Tumor  
Neuronal Tumor  
Neuronal-Glial Tumor  
Ganglioglioma  
Glioneuronal Tumor  
Neurocytoma  
Liponeurocytoma  
Paranglioma  
Tumor of the Pineal Region  
Pineal Region Tumor  
Pineal Tumor  
Pineocytoma  
Pineal Parenchymal Tumor  
Pineoblastoma  
Medulloblastoma  
Melanotic Schwannoma  
Nerve Sheath Tumor  
Meningioma  
Meningeal Tumor  
Tumor of Meninges  
Meningeal Melanocytoma

Meningeal Melanoma  
Meningeal Melanomatosis  
Lymphoma of the Central Nervous System  
Lymphoma of the CNS  
CNS Lymphoma  
Central Nervous System Lymphoma  
Lymphoma of the Dura  
Tumor of the Sellar Region  
Craniopharyngioma  
Tumor of Cranial and Spinal Nerves  
Tumor of Cranial Nerve  
Tumor of Spinal Nerve  
Cranial and Spinal Nerve Tumor  
Cranial Nerve Tumor  
Spinal Nerve Tumor  
Pituicytoma  
Pituitary Tumor  
Tumor of Neuroepithelial Tissue  
Tumor of the Neuroepithelial Tissue  
Neuroepithelial Tumor  
Chordoma  
Germ Cell Tumor  
Germinoma  
Embryonal Carcinoma  
Yolk Sac Tumor  
Choriocarcinoma  
Teratoma  
Primary Central Nervous System Sarcoma  
Primary CNS Sarcoma  
Sarcoma of the Central Nervous System  
Sarcoma of the CNS  
PNET  
Neuro-ectodermal Tumor  
Neuroectodermal Tumor  
Gliomatosis  
Hemangiopericytoma  
DIPG  
Diffuse Intrinsic Pontine Glioma  
Primary CNS Tumor  
Primary Central Nervous System Tumor  
Astrocytic Neoplasm  
Oligodendroglial Neoplasm  
Oligoastrocytic Neoplasm



Ependymal Neoplasm  
Neuronal Neoplasm  
Neuronal-Glial Neoplasm  
Glioneuronal Neoplasm  
Neoplasm of the Pineal Region  
Pineal Neoplasm  
Pineal Region Neoplasm  
Pineal Parenchymal Neoplasm  
Nerve Sheath Neoplasm  
Meningeal Neoplasm  
Neoplasm of Meninges  
Neoplasm of the Sellar Region  
Neoplasm of Cranial and Spinal Nerves  
Neoplasm of Cranial Nerve  
Neoplasm of Spinal Nerve  
Cranial and Spinal Nerve Neoplasm  
Cranial Nerve Neoplasm  
Spinal Nerve Neoplasm  
Pituitary Neoplasm  
Neoplasm of Neuroepithelial Tissue  
Neoplasm of the Neuroepithelial Tissue  
Neuroepithelial Neoplasm  
Germ Cell Neoplasm  
Yolk Sac Neoplasm  
Primitive Neuro-Ectodermal Neoplasms  
Primitive Neuroectodermal Neoplasms  
Primary CNS Neoplasm  
Primary Central Nervous System Neoplasm  
Astrocytic Cancer  
Oligodendroglial Cancer  
Oligoastrocytic Cancer  
Ependymal Cancer  
Neuronal Cancer  
Neuronal-Glial Cancer  
Glioneuronal Cancer  
Cancer of the Pineal Region  
Pineal Cancer  
Pineal Region Cancer  
Pineal Parenchymal Cancer  
Nerve Sheath Cancer  
Meningeal Cancer  
Cancer of Meninges  
Cancer of the Sellar Region

Cancer of Cranial and Spinal Nerves  
Cancer of Cranial Nerve  
Cancer of Spinal Nerve  
Cranial and Spinal Nerve Cancer  
Cranial Nerve Cancer  
Spinal Nerve Cancer  
Pituitary Cancer  
Cancer of Neuroepithelial Tissue  
Cancer of the Neuroepithelial Tissue  
Neuroepithelial Cancer  
Germ Cell Cancer  
Yolk Sac Cancer  
Primitive Neuro-Ectodermal Cancers  
Primitive Neuroectodermal Cancers  
Primary CNS Cancer  
Primary Central Nervous System Cancer

**Supplementary Table S2.** MeSH terms under “Neoplasm by Site”. These terms were used to search for general oncology trials in the clinicaltrials.gov registry.

### Neoplasms by Site [C04.588]

- Abdominal Neoplasms [C04.588.033]
  - Peritoneal Neoplasms [C04.588.033.513]
  - Retroperitoneal Neoplasms [C04.588.033.731]
  - Sister Mary Joseph's Nodule [C04.588.033.740]
- Anal Gland Neoplasms [C04.588.083]
- Bone Neoplasms [C04.588.149]
  - Adamantinoma [C04.588.149.030]
  - Femoral Neoplasms [C04.588.149.276]
  - Skull Neoplasms [C04.588.149.721]
    - Jaw Neoplasms [C04.588.149.721.450]
      - Mandibular Neoplasms [C04.588.149.721.450.583]
      - Maxillary Neoplasms [C04.588.149.721.450.601]
      - Palatal Neoplasms [C04.588.149.721.450.692]
    - Nose Neoplasms [C04.588.149.721.600]
    - Orbital Neoplasms [C04.588.149.721.656]
    - Skull Base Neoplasms [C04.588.149.721.828]
  - Spinal Neoplasms [C04.588.149.828]
- Breast Neoplasms [C04.588.180]
  - Breast Carcinoma In Situ [C04.588.180.130]
  - Breast Neoplasms, Male [C04.588.180.260]
  - Carcinoma, Ductal, Breast [C04.588.180.390]
  - Carcinoma, Lobular [C04.588.180.437]
  - Hereditary Breast and Ovarian Cancer Syndrome [C04.588.180.483]
  - Inflammatory Breast Neoplasms [C04.588.180.576]
  - Triple Negative Breast Neoplasms [C04.588.180.788]
  - Unilateral Breast Neoplasms [C04.588.180.800]
- Digestive System Neoplasms [C04.588.274]
  - Biliary Tract Neoplasms [C04.588.274.120]
    - Bile Duct Neoplasms [C04.588.274.120.250]
      - Common Bile Duct Neoplasms [C04.588.274.120.250.250]
    - Gallbladder Neoplasms [C04.588.274.120.401]
  - Gastrointestinal Neoplasms [C04.588.274.476]
    - Esophageal Neoplasms [C04.588.274.476.205]
      - Esophageal Squamous Cell Carcinoma [C04.588.274.476.205.500]
    - Intestinal Neoplasms [C04.588.274.476.411]
      - Cecal Neoplasms [C04.588.274.476.411.184]
        - Appendiceal Neoplasms [C04.588.274.476.411.184.290]
      - Colorectal Neoplasms [C04.588.274.476.411.307]
        - Adenomatous Polyposis Coli [C04.588.274.476.411.307.089]
          - Gardner Syndrome [C04.588.274.476.411.307.089.393]
        - Colonic Neoplasms [C04.588.274.476.411.307.180]
          - Colitis-Associated Neoplasms [C04.588.274.476.411.307.180.400]

- [Sigmoid Neoplasms \[C04.588.274.476.411.307.180.800\]](#)
    - [Colorectal Neoplasms, Hereditary Nonpolyposis \[C04.588.274.476.411.307.190\]](#)
    - [Rectal Neoplasms \[C04.588.274.476.411.307.790\]](#)
      - [Anus Neoplasms \[C04.588.274.476.411.307.790.040\]](#)
        - [Anal Gland Neoplasms \[C04.588.274.476.411.307.790.040.040\]](#)
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  - [Liver Neoplasms \[C04.588.274.623\]](#)
    - [Adenoma, Liver Cell \[C04.588.274.623.040\]](#)
    - [Carcinoma, Hepatocellular \[C04.588.274.623.160\]](#)
    - [Liver Neoplasms, Experimental \[C04.588.274.623.460\]](#)
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    - [Carcinoma, Islet Cell \[C04.588.274.761.500\]](#)
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      - [Vipoma \[C04.588.274.761.500.750\]](#)
    - [Carcinoma, Pancreatic Ductal \[C04.588.274.761.750\]](#)
    - [Pancreatic Intraductal Neoplasms \[C04.588.274.761.875\]](#)
  - [Peritoneal Neoplasms \[C04.588.274.780\]](#)
- [Endocrine Gland Neoplasms \[C04.588.322\]](#)
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    - [Adrenal Cortex Neoplasms \[C04.588.322.078.265\]](#)
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    - [Multiple Endocrine Neoplasia Type 2b \[C04.588.322.400.510\]](#)
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    - [Carcinoma, Ovarian Epithelial \[C04.588.322.455.199\]](#)
    - [Granulosa Cell Tumor \[C04.588.322.455.398\]](#)
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    - [Meigs Syndrome \[C04.588.322.455.531\]](#)
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    - [Thecoma \[C04.588.322.455.765\]](#)
  - [Pancreatic Neoplasms \[C04.588.322.475\]](#)
    - [Adenoma, Islet Cell \[C04.588.322.475.249\]](#)
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    - [Carcinoma, Islet Cell \[C04.588.322.475.500\]](#)
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- [Glucagonoma \[C04.588.322.475.500.249\]](#)
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    - [Vipoma \[C04.588.322.475.500.750\]](#)
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    - [Esophageal Neoplasms \[C04.588.443.353\]](#)
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      - [Gingival Neoplasms \[C04.588.443.591.402\]](#)
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        - [Leukoplakia, Hairy \[C04.588.443.591.545.500\]](#)
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      - [Palatal Neoplasms \[C04.588.443.591.692\]](#)
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        - [Sublingual Gland Neoplasms \[C04.588.443.591.824.882\]](#)
        - [Submandibular Gland Neoplasms \[C04.588.443.591.824.885\]](#)
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    - [Otorhinolaryngologic Neoplasms \[C04.588.443.665\]](#)
      - [Ear Neoplasms \[C04.588.443.665.312\]](#)

- [Laryngeal Neoplasms \[C04.588.443.665.481\]](#)
- [Nose Neoplasms \[C04.588.443.665.650\]](#)
  - [Paranasal Sinus Neoplasms \[C04.588.443.665.650.693\]](#)
- [Pharyngeal Neoplasms \[C04.588.443.665.710\]](#)
  - [Hypopharyngeal Neoplasms \[C04.588.443.665.710.485\]](#)
  - [Nasopharyngeal Neoplasms \[C04.588.443.665.710.650\]](#)
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  - [Oropharyngeal Neoplasms \[C04.588.443.665.710.684\]](#)
    - [Tonsillar Neoplasms \[C04.588.443.665.710.684.800\]](#)
- [Parathyroid Neoplasms \[C04.588.443.680\]](#)
- [Thyroid Neoplasms \[C04.588.443.915\]](#)
  - [Thyroid Cancer, Papillary \[C04.588.443.915.400\]](#)
  - [Thyroid Nodule \[C04.588.443.915.800\]](#)
- [Tracheal Neoplasms \[C04.588.443.925\]](#)
- [Hematologic Neoplasms \[C04.588.448\]](#)
  - [Bone Marrow Neoplasms \[C04.588.448.200\]](#)
    - [Polycythemia Vera \[C04.588.448.200.500\]](#)
- [Mammary Neoplasms, Animal \[C04.588.531\]](#)
  - [Mammary Neoplasms, Experimental \[C04.588.531.500\]](#)
- [Nervous System Neoplasms \[C04.588.614\]](#)
  - [Central Nervous System Neoplasms \[C04.588.614.250\]](#)
    - [Brain Neoplasms \[C04.588.614.250.195\]](#)
      - [Cerebral Ventricle Neoplasms \[C04.588.614.250.195.205\]](#)
        - [Choroid Plexus Neoplasms \[C04.588.614.250.195.205.200\]](#)
          - [Papilloma, Choroid Plexus \[C04.588.614.250.195.205.200.500\]](#)
      - [Infratentorial Neoplasms \[C04.588.614.250.195.411\]](#)
        - [Brain Stem Neoplasms \[C04.588.614.250.195.411.100\]](#)
          - [Diffuse Intrinsic Pontine Glioma \[C04.588.614.250.195.411.100.500\]](#)
        - [Cerebellar Neoplasms \[C04.588.614.250.195.411.211\]](#)
      - [Neurocytoma \[C04.588.614.250.195.648\]](#)
      - [Pinealoma \[C04.588.614.250.195.766\]](#)
      - [Supratentorial Neoplasms \[C04.588.614.250.195.885\]](#)
        - [Hypothalamic Neoplasms \[C04.588.614.250.195.885.500\]](#)
          - [Pallister-Hall Syndrome \[C04.588.614.250.195.885.500.299\]](#)
          - [Pituitary Neoplasms \[C04.588.614.250.195.885.500.600\]](#)
    - [Central Nervous System Cysts \[C04.588.614.250.387\]](#)
      - [Arachnoid Cysts \[C04.588.614.250.387.100\]](#)
      - [Colloid Cysts \[C04.588.614.250.387.200\]](#)
    - [Meningeal Neoplasms \[C04.588.614.250.580\]](#)
      - [Meningeal Carcinomatosis \[C04.588.614.250.580.150\]](#)
      - [Meningioma \[C04.588.614.250.580.500\]](#)
    - [Spinal Cord Neoplasms \[C04.588.614.250.803\]](#)
      - [Epidural Neoplasms \[C04.588.614.250.803.342\]](#)
  - [Cranial Nerve Neoplasms \[C04.588.614.300\]](#)

- [Neuroma, Acoustic \[C04.588.614.300.015\]](#)
    - [Optic Nerve Neoplasms \[C04.588.614.300.600\]](#)
      - [Optic Nerve Glioma \[C04.588.614.300.600.600\]](#)
  - [Paraneoplastic Syndromes, Nervous System \[C04.588.614.550\]](#)
    - [Anti-N-Methyl-D-Aspartate Receptor Encephalitis \[C04.588.614.550.112\]](#)
    - [Limbic Encephalitis \[C04.588.614.550.450\]](#)
    - [Myasthenia Gravis \[C04.588.614.550.500\]](#)
      - [Lambert-Eaton Myasthenic Syndrome \[C04.588.614.550.500.225\]](#)
    - [Myelitis, Transverse \[C04.588.614.550.550\]](#)
    - [Opsoclonus-Myoclonus Syndrome \[C04.588.614.550.600\]](#)
    - [Paraneoplastic Cerebellar Degeneration \[C04.588.614.550.650\]](#)
    - [Paraneoplastic Polyneuropathy \[C04.588.614.550.700\]](#)
  - [Peripheral Nervous System Neoplasms \[C04.588.614.596\]](#)
    - [Cranial Nerve Neoplasms \[C04.588.614.596.240\]](#)
      - [Neuroma, Acoustic \[C04.588.614.596.240.015\]](#)
      - [Optic Nerve Neoplasms \[C04.588.614.596.240.240\]](#)
        - [Optic Nerve Glioma \[C04.588.614.596.240.240.500\]](#)
- [Pelvic Neoplasms \[C04.588.699\]](#)
- [Skin Neoplasms \[C04.588.805\]](#)
  - [Acanthoma \[C04.588.805.040\]](#)
  - [Mastocytosis, Cutaneous \[C04.588.805.309\]](#)
    - [Mastocytoma, Skin \[C04.588.805.309.500\]](#)
    - [Urticaria Pigmentosa \[C04.588.805.309.850\]](#)
  - [Sebaceous Gland Neoplasms \[C04.588.805.578\]](#)
    - [Muir-Torre Syndrome \[C04.588.805.578.500\]](#)
  - [Sweat Gland Neoplasms \[C04.588.805.776\]](#)
- [Soft Tissue Neoplasms \[C04.588.839\]](#)
  - [Muscle Neoplasms \[C04.588.839.500\]](#)
  - [Vascular Neoplasms \[C04.588.839.750\]](#)
- [Splenic Neoplasms \[C04.588.842\]](#)
- [Thoracic Neoplasms \[C04.588.894\]](#)
  - [Heart Neoplasms \[C04.588.894.309\]](#)
    - [Cardiac Papillary Fibroelastoma \[C04.588.894.309.250\]](#)
    - [Carney Complex \[C04.588.894.309.500\]](#)
  - [Mediastinal Neoplasms \[C04.588.894.479\]](#)
  - [Respiratory Tract Neoplasms \[C04.588.894.797\]](#)
    - [Lung Neoplasms \[C04.588.894.797.520\]](#)
      - [Adenocarcinoma of Lung \[C04.588.894.797.520.055\]](#)
        - [Adenocarcinoma, Bronchiolo-Alveolar \[C04.588.894.797.520.055.500\]](#)
      - [Bronchial Neoplasms \[C04.588.894.797.520.109\]](#)
        - [Carcinoma, Bronchogenic \[C04.588.894.797.520.109.220\]](#)
          - [Carcinoma, Non-Small-Cell Lung \[C04.588.894.797.520.109.220.249\]](#)
          - [Small Cell Lung Carcinoma \[C04.588.894.797.520.109.220.624\]](#)
        - [Mesothelioma, Malignant \[C04.588.894.797.520.173\]](#)
        - [Multiple Pulmonary Nodules \[C04.588.894.797.520.237\]](#)

- [Pancoast Syndrome \[C04.588.894.797.520.734\]](#)
  - [Pulmonary Blastoma \[C04.588.894.797.520.867\]](#)
  - [Pulmonary Sclerosing Hemangioma \[C04.588.894.797.520.933\]](#)
  - [Pleural Neoplasms \[C04.588.894.797.640\]](#)
    - [Mesothelioma, Malignant \[C04.588.894.797.640.350\]](#)
    - [Pleural Effusion, Malignant \[C04.588.894.797.640.700\]](#)
    - [Solitary Fibrous Tumor, Pleural \[C04.588.894.797.640.800\]](#)
  - [Tracheal Neoplasms \[C04.588.894.797.760\]](#)
- [Thymus Neoplasms \[C04.588.894.949\]](#)
  - [Thymoma \[C04.588.894.949.500\]](#)
- [Urogenital Neoplasms \[C04.588.945\]](#)
  - [Genital Neoplasms, Female \[C04.588.945.418\]](#)
    - [Fallopian Tube Neoplasms \[C04.588.945.418.365\]](#)
    - [Uterine Neoplasms \[C04.588.945.418.948\]](#)
      - [Endometrial Neoplasms \[C04.588.945.418.948.585\]](#)
        - [Carcinoma, Endometrioid \[C04.588.945.418.948.585.124\]](#)
      - [Uterine Cervical Neoplasms \[C04.588.945.418.948.850\]](#)
    - [Vaginal Neoplasms \[C04.588.945.418.955\]](#)
    - [Vulvar Neoplasms \[C04.588.945.418.968\]](#)
  - [Genital Neoplasms, Male \[C04.588.945.440\]](#)
    - [Penile Neoplasms \[C04.588.945.440.715\]](#)
    - [Prostatic Neoplasms \[C04.588.945.440.770\]](#)
      - [Prostatic Neoplasms, Castration-Resistant \[C04.588.945.440.770.500\]](#)
    - [Testicular Neoplasms \[C04.588.945.440.915\]](#)
      - [Sertoli-Leydig Cell Tumor \[C04.588.945.440.915.500\]](#)
        - [Leydig Cell Tumor \[C04.588.945.440.915.500.249\]](#)
        - [Sertoli Cell Tumor \[C04.588.945.440.915.500.500\]](#)
  - [Urologic Neoplasms \[C04.588.945.947\]](#)
    - [Kidney Neoplasms \[C04.588.945.947.535\]](#)
      - [Carcinoma, Renal Cell \[C04.588.945.947.535.160\]](#)
      - [Wilms Tumor \[C04.588.945.947.535.585\]](#)
        - [Denys-Drash Syndrome \[C04.588.945.947.535.585.220\]](#)
        - [WAGR Syndrome \[C04.588.945.947.535.585.950\]](#)
      - [Nephroma, Mesoblastic \[C04.588.945.947.535.790\]](#)
    - [Ureteral Neoplasms \[C04.588.945.947.940\]](#)
    - [Urethral Neoplasms \[C04.588.945.947.945\]](#)
    - [Urinary Bladder Neoplasms \[C04.588.945.947.960\]](#)
  - [Venereal Tumors, Veterinary \[C04.588.945.956\]](#)



**Supplementary Table S3.** Malignant primary CNS tumors categorized by 5-year survival rates of CBTRUS Report

<b>Category</b> (5-Year Overall Survival Rates)	<b>CBTRUS CNS Tumor Diagnoses</b>
<b>Lowest Survival</b> (7.2% - 32%)	Glioblastoma Anaplastic Astrocytoma Primary Melanocytic Lesions - malignant Neoplasm Unspecified – malignant
<b>Moderate Survival</b> (37.6% - 70.7%)	Lymphoma Diffuse Astrocytoma Glioma Malignant, NOS* Unique Astrocytoma Variants – malignant Embryonal Tumors – malignant Anaplastic Oligodendroglioma Mesenchymal Tumors – malignant Meningioma – malignant Other Hemopoietic Neoplasms Oligoastrocytic Tumors Choroid Plexus Tumors – malignant Tumors of the Pineal Region – malignant Choroid Plexus Tumors – malignant Nerve Sheath Tumors – malignant Other Neuroepithelial Tumors – malignant All Other – malignant
<b>Highest Survival</b> (76.9% - 94.5%)	Neuronal and Mixed Neuronal Glial Tumors – malignant Other Neoplasms Related to the Meninges – malignant Tumors of the Pituitary – malignant Oligodendroglioma Craniopharyngioma Ependymal Tumors – malignant Germ Cell Tumors, Cysts and Heterotopias – malignant Other Tumors of Cranial and Spinal Nerves Hemangioma Pilocytic Astrocytoma
<b>All</b> (36%)	Average for All Malignant CNS Tumors

\*NOS=not otherwise specified

**Supplementary Table S4.** CBTRUS malignant CNS tumor diagnoses (linked to incidence) mapped to CNS tumor search terms (linked to trial conditions).

<b>CBTRUS CNS Tumor Diagnoses for Incidence Data</b>	<b>CNS Tumor Search Terms derived from WHO Classification</b>	<b>Method</b>
“pilocytic astrocytoma”, “diffuse astrocytoma”, “anaplastic astrocytoma”	“astrocytoma”	Grouped among trial terms
“anaplastic oligodendroglioma” and “oligodendroglioma”	“oligodendroglioma”	
“glioblastoma”	“GBM”	Synonym
“other neoplasms related to the meninges”	Any terms containing “meninge” *	Synonym
“tumors of the pituitary”	Any terms containing “pituitary”	Synonym
“ependymal tumors”	Any terms containing “ependym”	Synonym
“oligoastrocytic tumors”	Any terms containing “oligoastro”	Synonym
“nerve sheath tumors”	Any terms containing “nerve sheath”	Synonym
“germ cell tumors, cysts and heterotopias”	Any terms containing “germ cell”	Synonym
“choroid plexus tumors”	Any terms containing “choroid plexus”	Synonym
“oligodendroglioma”	“oligodendroglial tumor”	Synonym
“embryonal tumors”	“Medulloblastoma”; any terms containing “embryonal”, “neuroectodermal tumor”, “neuroectodermal tumor”	Grouping indicated by CBTRUS report
“germ cell tumors, cysts and heterotopias”	“teratoma”, “yolk sac tumor”, “choriocarcinoma”, “germinoma”,	Mapped term to ICD-O-3 code that are grouped by CBTRUS report
“mesenchymal tumors”	“hemangiopericytoma”	Mapped term to ICD-O-3 code that are grouped by CBTRUS report
“tumors of the pineal region”	Any terms containing “pineal” or “pineo”	Mapped term to ICD-O-3 code that are grouped by CBTRUS report
“other neoplasms related to the meninges”	“chordoma”	Mapped term to ICD-O-3 code that are grouped by CBTRUS report

“glioblastoma”	“gliosarcoma”	Mapped term to ICD-O-3 code that are grouped by CBTRUS report
“astrocytoma”	“xanthoastrocytoma”, “gliomatosis”	Mapped term to ICD-O-3 code that are grouped by CBTRUS report
“neuronal and mixed neuronal glial tumors”	“paraganglioma”, “neurocytoma”, “neuroepithelial tumor”, “ganglioglioma”, “neuronal tumor”; any terms containing “glioneuronal”	Mapped term to ICD-O-3 code that are grouped by CBTRUS report
“astrocytoma”	“diffuse intrinsic pontine glioma”	Using WHO 2016 definition <a href="https://pubmed.ncbi.nlm.nih.gov/27157931/">https://pubmed.ncbi.nlm.nih.gov/27157931/</a>

\*This excludes meningiomas, which has a separate incidence

**Supplementary Table S5.** Top 15 most frequently studied combinations of conditions among trials.

<b>Combination of Conditions Studied</b>	<b>Number of Trials</b>
Glioblastoma	532
Glioma	264
Central Nervous System Neoplasms, Glioma, Nervous System Neoplasms	261
Central Nervous System Neoplasms, Glioblastoma, Nervous System Neoplasms	243
Glioblastoma, Gliosarcoma	174
Glioblastoma, Glioma	158
Central Nervous System Neoplasms, Nervous System Neoplasms	110
Astrocytoma, Glioblastoma, Glioma	93
Central Nervous System Neoplasms, Ependymoma, Glioma, Hepatoblastoma, Histiocytosis, Histiocytosis, Langerhans-Cell, Lymphoma, Lymphoma, Non-Hodgkin, Medulloblastoma, Neoplasms, Neoplasms, Germ Cell and Embryonal, Nervous System Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Osteosarcoma, Rhabdoid Tumor, Rhabdomyosarcoma, Sarcoma, Sarcoma, Ewing, Wilms Tumor	88
Adenoma, Pituitary Diseases, Pituitary Neoplasms	72
Brain Neoplasms, Glioma	72
Lymphoma	71
Astrocytoma, Glioblastoma	70
Brain Neoplasms, Glioblastoma	70
Astrocytoma, Glioblastoma, Glioma, Oligodendroglioma	64

**Supplementary Table S6.** Primary outcomes of trials by phase and number of trial arm by design. Single arm trials were defined as studies reporting “number of arms” as one. Trials without number of arms, phase, or outcome type information were excluded.

Phase n (%), N = 1238)	Single Arm		Outcome	
	Design	n (%)		n (%)
Early Phase 1 15 (1.38%)	Single Arm	12 (80%)	OS	6 (50%)
			PFS	7 (58.33%)
			OS or PFS	10 (83.33%)
			RESPONSE	2 (16.67%)
	Multi Arm	3 (20%)	OS	1 (33.33%)
			PFS	0 (0%)
			OS or PFS	1 (33.33%)
			RESPONSE	2 (66.67%)
Phase 1 58 (5.34%)	Single Arm	35 (60.34%)	OS	10 (28.57%)
			PFS	19 (54.29%)
			OS or PFS	24 (68.57%)
			RESPONSE	15 (42.86%)
	Multi Arm	23 (39.66%)	OS	3 (13.04%)
			PFS	14 (60.87%)
			OS or PFS	14 (60.87%)
			RESPONSE	12 (52.17%)
Phase 1/Phase 2 182 (16.76%)	Single Arm	92 (50.55%)	OS	33 (35.87%)
			PFS	37 (40.22%)
			OS or PFS	59 (64.13%)
			RESPONSE	39 (42.39%)
	Multi Arm	90 (49.45%)	OS	26 (28.89%)
			PFS	44 (48.89%)
			OS or PFS	61 (67.78%)
			RESPONSE	39 (43.33%)
Phase 2 714 (65.75%)	Single Arm	463 (64.85%)	OS	93 (20.09%)
			PFS	184 (39.74%)
			OS or PFS	257 (55.51%)
			RESPONSE	237 (51.19%)
	Multi Arm	251 (35.15%)	OS	67 (26.69%)
			PFS	139 (55.38%)
			OS or PFS	189 (75.3%)
			RESPONSE	80 (31.87%)
Phase 2/Phase 3 23 (2.12%)	Single Arm	5 (21.74%)	OS	3 (60%)
			PFS	1 (20%)
			OS or PFS	4 (80%)
			RESPONSE	1 (20%)
	Multi Arm	18 (78.26%)	OS	12 (66.67%)
			PFS	9 (50%)
			OS or PFS	17 (94.44%)
			RESPONSE	2 (11.11%)
Phase 3 86 (7.92%)	Single Arm	1 (1.16%)	OS	0 (0%)
			PFS	0 (0%)
			OS or PFS	0 (0%)
			RESPONSE	1 (100%)
	Multi Arm	85 (98.84%)	OS	51 (60%)
			PFS	36 (42.35%)
			OS or PFS	81 (95.29%)
			RESPONSE	4 (4.71%)
	Single Arm	1 (12.5%)	OS	0 (0%)

Phase 4 8 (0.74%)		PFS	1 (100%)	
		OS or PFS	1 (100%)	
		RESPONSE	1 (100%)	
	Multi Arm	7 (87.5%)	OS	5 (71.43%)
			PFS	2 (28.57%)
			OS or PFS	7 (100%)
			RESPONSE	0 (0%)

**Supplementary Table S7.** All outcomes of trials by phase and number of trial arm by design. All outcomes include primary, secondary, or other. Single arm trials were defined as studies reporting “number of arms” as one. Trials without number of arms, phase, or outcome type information were excluded.

Phase n (% , N = 1238)	Single Arm		Outcome	n (%)
	Design	n (%)		
Early Phase 1 39 (2.38%)	Single Arm	24 (61.54%)	OS	15 (62.5%)
			PFS	19 (79.17%)
			OS or PFS	22 (91.67%)
			RESPONSE	8 (33.33%)
	Multi Arm	15 (38.46%)	OS	11 (73.33%)
			PFS	13 (86.67%)
			OS or PFS	14 (93.33%)
			RESPONSE	6 (40%)
Phase 1 360 (21.98%)	Single Arm	235 (65.28%)	OS	147 (62.55%)
			PFS	164 (69.79%)
			OS or PFS	199 (84.68%)
			RESPONSE	125 (53.19%)
	Multi Arm	125 (34.72%)	OS	81 (64.8%)
			PFS	105 (84%)
			OS or PFS	112 (89.6%)
			RESPONSE	70 (56%)
Phase 1/Phase 2 269 (16.42%)	Single Arm	143 (53.16%)	OS	104 (72.73%)
			PFS	107 (74.83%)
			OS or PFS	123 (86.01%)
			RESPONSE	80 (55.94%)
	Multi Arm	126 (46.84%)	OS	86 (68.25%)
			PFS	96 (76.19%)
			OS or PFS	111 (88.1%)
			RESPONSE	85 (67.46%)
Phase 2 820 (50.06%)	Single Arm	534 (65.12%)	OS	339 (63.48%)
			PFS	395 (73.97%)
			OS or PFS	458 (85.77%)
			RESPONSE	362 (67.79%)
	Multi Arm	286 (34.88%)	OS	216 (75.52%)
			PFS	241 (84.27%)
			OS or PFS	261 (91.26%)
			RESPONSE	168 (58.74%)
Phase 2/Phase 3 27 (1.65%)	Single Arm	6 (22.22%)	OS	6 (100%)
			PFS	1 (16.67%)
			OS or PFS	6 (100%)
			RESPONSE	1 (16.67%)
	Multi Arm	21 (77.78%)	OS	20 (95.24%)
			PFS	19 (90.48%)
			OS or PFS	21 (100%)
			RESPONSE	11 (52.38%)
Phase 3 111 (6.78%)	Single Arm	2 (1.8%)	OS	1 (50%)
			PFS	1 (50%)
			OS or PFS	1 (50%)
			RESPONSE	1 (50%)
	Multi Arm	109 (98.2%)	OS	92 (84.4%)
			PFS	84 (77.06%)
			OS or PFS	104 (95.41%)
			RESPONSE	40 (36.7%)

Phase 4  12 (0.73%)	Single Arm    3 (25%)	OS	2 (66.67%)
		PFS	3 (100%)
		OS or PFS	3 (100%)
		RESPONSE	2 (66.67%)
	Multi Arm    9 (75%)	OS	9 (100%)
		PFS	5 (55.56%)
		OS or PFS	9 (100%)
		RESPONSE	2 (22.22%)



**Supplementary Table S8.** Reporting of baseline patient counts by subgroup stratification. The registry provides space to report baseline patient counts by trial arm, stratification, or subgroups. To demonstrate availability of data that may of interest for downstream analyses, we assessed the proportion of trials reporting baseline counts by various patient subgroups among all interventional studies and among completed studies with sufficient information to curate trial arms (as described in methods) and any data on an efficacy outcome.

	% of trials reporting baseline counts by subgroup	
	Completed studies (N=1271)	Completed studies with curated arms and efficacy data (N=168)
Any baseline counts	28.0% (n=356)	100% (n=168)
<b>Subgroups</b>		
Sex/gender	28.0% (n=356)	100% (n=168)
Age groups	28.0% (n=356)	100% (n=168)
Enrollment location	16.5% (n=210)	53.6% (n=90)
Race/ethnicity	13.6% (n=173)	44.6% (n=75)
Performance status or comorbidity index	3.9% (n=50)	17.9% (n=30)
Diagnostic, histologic, or molecular subgroups	3.6% (n=46)	14.9% (n=25)
Prior treatment	2.0% (n=26)	7.1% (n=12)
Steroid use	0.4% (n=6)	2.4% (n=4)
Anticonvulsant use	0.3% (n=4)	1.8% (n=3)
All other	17.8% (n=226)	57.8% (n=97)

**Supplementary Table S9.** Logistic regression analysis of reporting of designs, enrollment, results, and publications by trial characteristics.

Trial Characteristic (n trials reporting)		Number of Trials (%)**	Logistic Regression – OR (FDR adjusted p-value)			
			Reported Design	Reported Enrollment*	Reported Results	Reported Publication
<b>Primary Sponsor</b> (n = 1270)	Industry	228 (18%)	-	-	-	-
	Other	861 (68%)	0.72 (0.999)	1.18 (0.999)	1.70 (0.861)	0.90 (0.999)
	NIH	181 (14%)	INF (0.999)	INF (0.999)	INF (0.999)	0.68 (0.999)
<b>Phase</b> (n = 1142)	Phase 3	77 (7%)	-	-	-	-
	Early Phase 1	28 (2%)	-	1.40 (0.999)	-INF (0.999)	-INF (0.999)
	Phase 1	353 (31%)	-	1.72 (0.999)	<b>0.07 (0.020)</b>	0.56 (0.999)
	Phase 1/Phase 2	148 (13%)	-	INF (0.999)	0.83 (0.999)	0.75 (0.999)
	Phase 2	517 (45%)	-	3.66 (0.019)	1.34 (0.999)	0.54 (0.999)
	Phase 2/Phase 3	8 (1%)	-	INF (0.999)	0.60 (0.999)	0.24 (0.999)
	Phase 4	11 (1%)	-	INF (0.999)	2.63 (0.999)	1.35 (0.999)
<b>Primary Purpose</b> (n = 1259)	Treatment	1110 (88%)	-	-	-	-
	Diagnostic	65 (5%)	INF (0.999)	0.12 (0.856)	0.53 (0.999)	1.63 (0.999)
	Supportive Care	36 (3%)	INF (0.999)	INF (0.999)	0.31 (0.999)	2.20 (0.999)
	Other	16 (1%)	INF (0.999)	INF (0.999)	INF (0.999)	-INF (0.999)
	Basic Science	12 (1%)	INF (0.999)	0.28 (0.999)	-INF (0.999)	18.92 (0.746)
	Prevention	11 (1%)	INF (0.999)	INF (0.999)	-INF (0.999)	-INF (0.999)
<b>Intervention Model</b> (n = 1073)	Parallel	258 (24%)	-	-	-	-
	Single Group	778 (73%)	-	0.34 (0.861)	0.51 (0.821)	0.66 (0.999)
	Sequential	20 (2%)	-	INF (0.999)	5.04 (0.701)	4.20 (0.701)
	Crossover	13 (1%)	-	INF (0.999)	1.01 (0.999)	1.43 (0.999)
	Factorial	4 (0.4%)	-	2.51 (0.999)	-INF (0.999)	INF (0.999)
<b>Has DMC</b> (n = 871)	TRUE	545 (63%)	-	-	-	-
	FALSE	326 (37%)	0.71 (0.999)	0.44 (0.861)	0.95 (0.999)	0.35 (0.269)
<b>Randomization</b> (n = 500)	TRUE	220 (44%)	-	-	-	-
	FALSE	280 (56%)	-	1.46 (0.999)	2.97 (0.296)	1.35 (0.999)
<b>Blinding</b> (n = 1108)	Double	27 (2%)	-	-	-	-
	Open Label	1029 (93%)	-	-INF (0.999)	0.09 (0.179)	2.58 (0.999)
	Single	30 (3%)	-	1.32 (0.999)	0.08 (0.701)	-INF (0.999)
	Triple	11 (1%)	-	2.28 (0.999)	0.11 (0.701)	8.84 (0.821)
	Quadruple	11 (1%)	-	-INF (0.999)	-INF (0.999)	-INF (0.999)
<b>Year</b>	Median	2008		1.01 (0.999)	1.03 (0.999)	<b>0.87 (0.020)</b>

(n = 1271)	(range, IQR)	(1985-2020, 2003-2012)	<b>1.24</b> <b>(&lt;0.00001)</b>			
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\*Trials reporting both anticipated and actual enrollment

**Supplementary Table S10.** Accrual analyses stratified by conditions studied by each trial

Condition Term	Survival Category	Enrollment Type	median N	Q1	Q3	median % enrolled	Q1 (%)	Q3 (%)	p val*	N Trials
glioblastoma	Low	Actual	37	19.3	74.8	100	71.0	100	<b>0.00000</b>	542
		Anticipated	50	27	86.8					
astrocytoma	Moderate	Actual	29	18.8	55.8	100	66.3	100	<b>0.00024</b>	48
		Anticipated	39.5	26.5	60					
chordoma	Moderate	Actual	45.5	35	157	100	77.2	100	0.05017	10
		Anticipated	52.5	41	163.8					
choriocarcinoma	Moderate	Actual	28	20	51.8	100	100	100	0.50000	10
		Anticipated	38.5	20.3	52					
choroid plexus tumor	Moderate	Actual	20	15.5	100.5	100	84.4	100	0.50000	3
		Anticipated	20	18	100.5					
cns lymphoma	Moderate	Actual	29.5	13.5	53.3	100	73.9	100	<b>0.00024</b>	36
		Anticipated	37	20	60					
dipg	Moderate	Actual	29	25	36	96.67	85.	100	<b>0.01776</b>	9
		Anticipated	32	28	42					
embryonal carcinoma	Moderate	Actual	20	15	21	100	37.5	100	0.18555	5
		Anticipated	24	21	43					
ganglioglioma	Moderate	Actual	23	23	23	100	100	100	1.00000	1
		Anticipated	23	23	23					
germinoma	Moderate	Actual	38	22	77.5	100	100	100	0.09072	19
		Anticipated	41	22	77.5					
glioma	Moderate	Actual	30	17	58	100	71.43	100	<b>0.00000</b>	225
		Anticipated	40	24	64					
gliosarcoma	Moderate	Actual	25	14.5	35.5	27.1	15.6	38.5	0.25000	2
		Anticipated	94	93	95					
hemangiopericytoma	Moderate	Actual	45	24.8	50.8	90.5	67.8	100	<b>0.02953</b>	10
		Anticipated	50	42.5	57.8					
meningeal melanocytoma	Moderate	Actual	11	11	11	68.8	68.8	68.8	0.50000	1
		Anticipated	16	16	16					
meningeal tumor	Moderate	Actual	88.5	65	125.5	100	100	100	0.50000	8
		Anticipated	88.5	65	130.5					
meningioma	Moderate	Actual	29	14	70	100	76	100	<b>0.00082</b>	33
		Anticipated	44	20	70					
nerve sheath tumor	Moderate	Actual	41.5	26.3	68.5	81.9	56.2	100	<b>0.00296</b>	18
		Anticipated	54	31.5	113					
neuroectodermal tumor	Moderate	Actual	60	28.8	113.8	100	69.4	100	<b>0.00016</b>	48
		Anticipated	79	38.8	129.3					
neuronal tumor	Moderate	Actual	8	8	8	6.7	6.7	6.7	0.50000	1
		Anticipated	120	120	120					

oligoastrocytoma	Moderate	Actual	33	15	61.5	100	79.5	100	0.05017	15
		Anticipated	42	25.5	61.5					
paraganglioma	Moderate	Actual	23	19	36.8	97.3	49.2	100	<b>0.00713</b>	14
		Anticipated	38.5	25.5	50					
pineal tumor	Moderate	Actual	5	5	5	100	100	100	1.00000	1
		Anticipated	5	5	5					
pineoblastoma	Moderate	Actual	81.5	46.3	111	100	100	100	1.00000	4
		Anticipated	81.5	46.4	111					
pineocytoma	Moderate	Actual	17	14	20	57.4	51.7	63.1	0.25000	2
		Anticipated	33	24.5	41.5					
pituitary tumor	Moderate	Actual	9	9	9	42.9	42.9	42.9	0.50000	1
		Anticipated	21	21	21					
pnet	Moderate	Actual	54	19.5	122.3	85.7	39.5	100	<b>0.00001</b>	40
		Anticipated	78.5	29.8	182					
primary cns sarcoma	Moderate	Actual	4	4	4	4.2	4.2	4.2	0.50000	1
		Anticipated	96	96	96					
primary cns tumor	Moderate	Actual	32	30.5	35	100	95.0	100	0.18555	6
		Anticipated	34	32	36					
teratoma	Moderate	Actual	30.5	16.3	50	100	59.8	100	<b>0.02953</b>	18
		Anticipated	43	30.5	53.8					
xanthoastrocytoma	Moderate	Actual	23	23	23	100	100	100	1.00000	1
		Anticipated	23	23	23					
yolk sac tumor	Moderate	Actual	28	20	45.3	100	100	100	0.50000	8
		Anticipated	38.5	20.75	46					
craniopharyngioma	High	Actual	19	12	23.5	100	92	100	0.18555	7
		Anticipated	19	12	37.5					
ependymoma	High	Actual	26	18	52.5	60	55	100	0.05017	7
		Anticipated	40	25	79					
germ cell tumor	High	Actual	28.5	19	46.75	100	96.1675	100	<b>0.00036</b>	50
		Anticipated	30.5	24	49.5					
medulloblastoma	High	Actual	43	27.5	62.5	100	60.855	100	<b>0.00458</b>	19
		Anticipated	53	33.5	106					
oligodendroglial tumor	High	Actual	39	39	39	100	100	100	1.00000	1
		Anticipated	39	39	39					
pituitary tumor	High	Actual	42	30	80.25	100	80.5525	100	<b>0.02953</b>	18
		Anticipated	42	30	103					

\*from One-Sided Paired Wilcoxon Test

**Supplementary Table S11.** Association between the odds of trial meeting enrollment goal (logistic regression) and percent of enrollment goal met by trials (linear regression) with year, existence of US trial sites, and anticipated enrollment target.

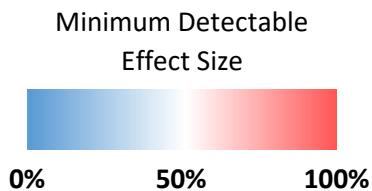
	<b>Logistic Regression</b>
	Odds of Trial Meeting Enrollment Goal (p)
Trial Year	<b>0.85 (p&lt;0.00001)*</b>
Has a US Trial Site	<b>0.50 (p&lt;0.00001)</b>
Anticipated Enrollment	1.00 (p=0.357)

\*Bolded values indicate significance at  $\alpha = 0.05$

**Supplementary Table S12. Size Effect Assumption Analysis.** For completed trials reporting actual enrollment and primary endpoints of OS/PFS/ORR, the minimum effect size that the trial is sufficiently powered to assess was computed. For OS/PFS calculations as described in the methods, survival information was based on data for Glioblastoma (100%) for the low survival category; on Glioma (56.2%), Neuroectodermal Neoplasm (9.0%), Astrocytoma (7.7%), Meningioma (7.7%), CNS Lymphoma (7.2%), and others (<7%) for the moderate survival category, and on Germ Cell Neoplasm (46.6%), Pituitary Neoplasm (24.6%), Medulloblastoma (16.7%), Ependymoma (8.5%), Craniopharyngioma (5.6%) and others (<1%) for the high survival category.

Survival Category	Phase	OS		PFS		Response Rate	
		N Trials	Minimum Detectable ES	N Trials	Minimum Detectable ES	N Trials	Minimum Detectable ES
			Median (IQR)		Median (IQR)		Median (IQR)
Low	All	90	44% (36%-51%)	153	52% (42%-61%)	59	15% (12%-19%)
	Early Phase 1	0	-	1	63% (63%-63%)	0	-
	Phase 1	2	53% (49%-57%)	7	65% (63%-75%)	4	22% (20%-24%)
	Phase 1/Phase 2	20	43% (38%-48%)	33	52% (42%-66%)	15	15% (10%-19%)
	Phase 2	50	44% (39%-54%)	107	51% (43%-58%)	40	15% (12%-18%)
	Phase 2/Phase 3	0	-	0	-	0	-
	Phase 3	13	22% (20%-32%)	5	24% (20%-31%)	0	-
	Phase 4	1	47% (47%-47%)	0	-	0	-
Moderate	All	15	55% (33%-60%)	58	49% (42%-62%)	95	16% (12%-20%)
	Early Phase 1	1	100% (100%-100%)	0	-	1	37% (37%-37%)
	Phase 1	0	-	6	52% (49%-76%)	3	20% (17%-21%)
	Phase 1/Phase 2	3	56% (55%-60%)	6	47% (44%-51%)	7	17% (16%-20%)
	Phase 2	7	55% (50%-61%)	39	52% (42%-76%)	80	16% (12%-20%)
	Phase 2/Phase 3	1	27% (27%-27%)	0	-	1	13% (13%-13%)
	Phase 3	3	29% (29%-31%)	3	24% (21%-42%)	3	8% (8%-9%)
	Phase 4	0	-	1	44% (44%-44%)	0	-
High	All	2	64% (48%-80%)	7	60% (51%-81%)	19	19% (15%-25%)
	Early Phase 1	1	96% (96%-96%)	1	92% (92%-92%)	0	-
	Phase 1	0	-	0	-	0	-
	Phase 1/Phase 2	0	-	0	-	1	8% (8%-8%)
	Phase 2	1	33% (33%-33%)	4	57% (52%-63%)	16	20% (16%-26%)
	Phase 2/Phase 3	0	-	0	-	0	-
	Phase 3	0	-	1	28% (28%-28%)	1	15% (15%-15%)
	Phase 4	0	-	0	-	0	-

Legend



**Supplementary Table S13.** Association between experimental rates of total adverse events and summary measures of efficacy outcomes via linear regression.

Adverse Event, (Experimental Arm Rate)	Median OS (months), Experimental Arm		Median PFS (months), Experimental Arm		ORR, Experimental Arm	
	$\beta^*$	P value	$\beta$	P value	$\beta$	P value
(intercept)	16.801	<0.001	24.928	<0.001	0.318	0.116
Total SAE	10.941	0.477	-2.040	0.949	-0.347	0.621
Total Other AE	-0.652	0.906	<b>-18.920</b>	<b>0.001</b>	-0.079	0.742
Total Other AE : Total SAE	-14.717	0.405	5.843	0.864	0.112	0.888
N	91		81		72	
Post Hoc Power** ( $R^2$ )	18% ( $R^2 = 0.02$ )		74% ( $R^2 = 0.11$ )		32% ( $R^2 = 0.05$ )	

\*  $\beta$  = linear regression coefficient. \*\* Power to assess the model's predicted  $R^2$  given number of observations and number of covariates; \*\*\*- = covariate not included due to low data availability; ":" indicates interaction between covariates.



**Supplementary Table S14.** Association between experimental rates of top 3 serious and other adverse events and summary measures of efficacy outcomes via linear regression.

Adverse Event**** (Experimental Arm Rate)	Median OS (months), Experimental Arm		Median PFS (months), Experimental Arm		ORR, Experimental Arm	
	$\beta^*$	P value	$\beta$	P value	$\beta$	P value
(Intercept)	14.384	0.090	1.152	0.65	-0.006	0.986
Serious Seizure	34.631	0.782	24.603	0.303	1.663	0.747
Serious Vomiting	-26.444	0.947	-80.974	0.401	-8.417	0.566
Serious Nausea	27.983	0.925	<b>436.495</b>	<b>0.013</b>	6.66	0.749
Serious Seizure : Serious Vomiting	-6056	0.414	1654.72	0.294	124.864	0.505
Serious Seizure : Serious Nausea	2891.105	0.336	-1370.46	0.362	-83.151	0.709
Serious Nausea : Serious Vomiting	-488.137	0.940	-5863.97	0.063	-16.031	0.958
N	17		16		10	
Post Hoc Power** (R <sup>2</sup> )	60% (R <sup>2</sup> = 0.49)		94% (R <sup>2</sup> = 0.71)		12% (R <sup>2</sup> = 0.38)	
(Intercept)	32.995	<0.001	25.848	<0.001	0.068	0.462
fatigue	<b>-44.856</b>	<b>&lt;0.001</b>	<b>-40.529</b>	<b>&lt;0.001</b>	0.096	0.693
nausea	3.159	0.889	-0.091	0.997	-0.529	0.277
vomiting	-69.291	0.194	-77.126	0.115	1.693	0.149
fatigue : nausea	-0.917	0.987	6.754	0.893	1.233	0.266
fatigue : vomiting	130.416	0.160	110.913	0.175	-2.39	0.199
vomiting : nausea	51.552	0.213	64.117	0.090	-1.103	0.251
N	55		51		48	
Post Hoc Power** (R <sup>2</sup> )	98% (R <sup>2</sup> = 0.35)		97% (R <sup>2</sup> = 0.34)		25% (R <sup>2</sup> = 0.08)	

\*  $\beta$  = linear regression coefficient. \*\* Power to assess the model's predicted R2 given number of observations and number of covariates; \*\*\*- = covariate not included due to low data availability.

\*\*\*\*Top adverse events reporting sufficient data were selected, among trials reporting data for each efficacy outcome; ":" indicates interaction between covariates.