A Phase I/II Study of Ribociclib, a CDK4/6 Inhibitor, following radiation therapy in Children with Newly Diagnosed non-biopsied Diffuse Pontine Gliomas (DIPG) and RB+ biopsied DIPG and High Grade Gliomas (HGG)

NCT02607124

Protocol version date October 27, 2016

Protocol #: *CLEE011XUS17T*

TITLE: A Phase I/II Study of Ribociclib, a CDK4/6 Inhibitor, following radiation therapy in Children with Newly Diagnosed non-biopsied Diffuse Pontine Gliomas (DIPG) and RB+ biopsied DIPG and High Grade Gliomas (HGG)

Coordinating Center: Cincinnati Children's Hospital Medical Center

Sponsor Investigator/ Study Chair
Mariko DeWire, M.D.
Cincinnati Children's Hospital Medical Center
Cancer and Blood Diseases Institute
MLC 7018
3333 Burnet Ave,
Cincinnati, OH 45229
TEL: (513) 636-1849
FAX: (513) 636-3549
EMAIL: mariko.dewire@cchmc.org

Co-Chair
Maryam Fouladi, M.D., M.S.
Cincinnati Children's Hospital Medical Center
Cancer and Blood Diseases Institute
MLC 7018
3333 Burnet Ave,
Cincinnati, OH 45229
TEL: (513) 803 0721
FAX: (513) 636-3549
EMAIL: maryam.fouladi@cchmc.org

Co-Investigators
Lionel Chow, M.D., PhD
Trent Hummel, M.D.
Ralph Salloum, M.D.
Charles Stevenson, M.D
Christine Fuller, MD
David Witte, M.D.
Rachid Drissi, PhD
Richard Lu, PhD

Neuroradiology Co-Investigators
Jim Leach, M.D.
Division of Neuroradiology
Department of Radiology

Radiation Oncology Coordinator
John Breneman, M.D.
Luke Pater, M.D.
University of Cincinnati

Biostatistician
Adam Lane, PhD
Department of Biostatistics

Biology Correlative Study Laboratories
Lionel Chow, MD, PhD
Cancer and Blood Diseases Institute
Cincinnati Children's Hospital Medical Center
240 Albert Sabin Way
Cincinnati, OH 45229-3039
Telephone: (513) 803-1369
Email: lionel.chow@cchmc.org

Rachid Drissi, PhD
Cancer and Blood Diseases Institute
Cincinnati Children's Hospital Medical Center
240 Albert Sabin Way
Cincinnati, OH 45229-3039
Telephone: (513) 803-0674
Email: rachid.drissi@cchmc.org

Qing Lu, PhD
Cancer and Blood Diseases Institute
Cincinnati Children's Hospital Medical Center
240 Albert Sabin Way
Cincinnati, OH 45229-3039
Telephone: (513) 636-7684
Email: Richard.Lu@cchmc.org

Coordinating Center
Cincinnati Children's Hospital Medical Center
Clinical Management & Research Support Core (CMRSC)
Contact: Lori Backus
Sr. Specialist Project Manager
Telephone: (513) 636-2047
Email: Lori.backus@cchmc.org

Novartis Supplied Agent: [redacted]

Protocol Abstract and Schema

Rationale for Study

The prognosis for patients diagnosed with diffuse intrinsic pontine gliomas (DIPG) remains dismal. Although radiotherapy can extend survival by 2-3 months, no adjuvant therapy has proven effective. Similarly, high-grade gliomas (HGG), particularly those which are not resectable and/or are Grade IV, have a poor outcome, with standard of care remaining upfront radiotherapy. Despite clinical trials testing a multitude of chemotherapeutic agents, no major advances have been made in the treatment of children with DIPG and HGG for several decades and DIPG/HGG remain the leading cause of brain cancer death in children and young adults.[1,2]

[redacted]

[redacted] Tissue for the RB screening may be obtained from an outside institution or from a diagnostic biopsy/surgery performed at CCHMC to determine if RB is present prior to initiation of therapy with Ribociclib. However, patients diagnosed with DIPG will have the option to have a diagnostic biopsy but is not required for eligibility as over 70% of patients with DIPG have been reported to have an intact RB (RB+). [6,10,11]

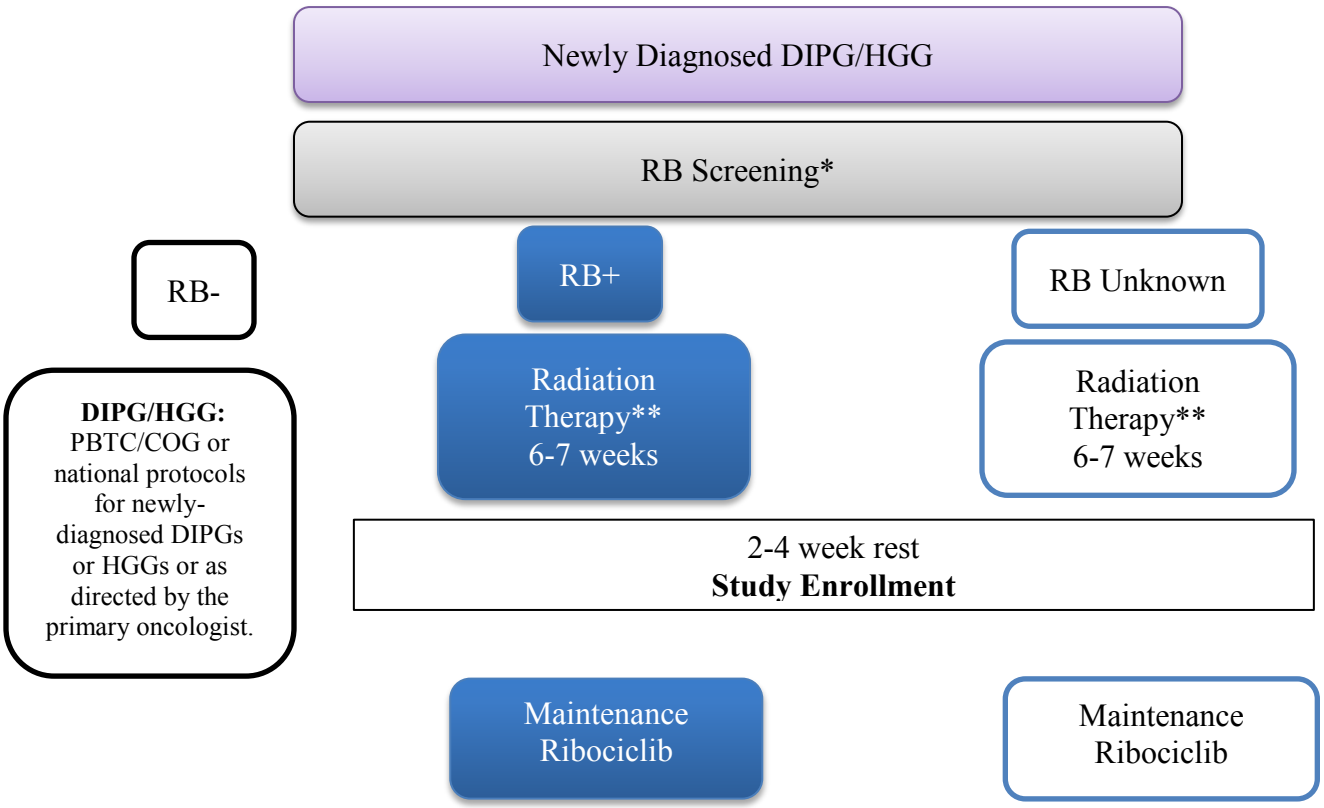
[redacted]

Description

This is an early phase II study to determine: 1) feasibility of Ribociclib administered once daily at the recommended phase II dose (RP2D) (350 mg/m^2/day) for 21 days followed by a 7-day break every 28 days following completion of radiation therapy for at least 6 courses and up to 12 courses in patients with newly-diagnosed non-biopsied DIPG and RB+ biopsied DIPG and HGG, 2) early efficacy of Ribociclib defined by the 1-year overall survival (OS) separately in two strata for newly-diagnosed patients with DIPG and HGG treated with the proposed therapy.

DIPG patients who choose to have a diagnostic biopsy for clinical purposes, a portion of the tissue may be used to evaluate RB status. Patients without RB (negative RB) DIPG and HGG tumors will have the opportunity to enroll on other DIPG or HGG protocols as directed by the family and their treating physician. Patients with RB+ tumors and non-biopsied DIPG will receive radiation therapy followed by Ribociclib as maintenance therapy. Upon completion of radiation therapy, a 2 - 4 week break will occur and then Ribociclib will be given orally daily for 21 days followed by a 7 day break every 28 days at the RP2D (350 mg/m^2/day) for at least 6 courses and up to 12 courses. One course is equivalent to 28 days. One intra-patient dose-de-escalation (280 mg/m^2/day) will be allowed if dose mode-modifying toxicities arise and may continue study treatment for up to 12 courses in the absence of disease progression or unacceptable toxicity.

Study Schema



* RB screening is required for all participants with available tissue. For patients with DIPG or bi-thalamic HGG may elect to have diagnostic biopsy for RB evaluation prior to starting radiation therapy.
**All patients that have biopsy/surgery at CCHMC, will have radiation therapy at CCHMC per institutional guidelines without radio-sensitizers.
** All other patients may receive radiation therapy (photons or proton) at local institution according to recommended guidelines without radio-sensitizers.

The Long-term Feasibility/Safety Treatment Plan

Maintenance Phase of Therapy (Patients ≤ 21 years of age)		
Each Course	**May receive a maximum of 12 courses**	
Day	**1-21**	**22-28**
Ribociclib starting dose level*	350 mg/m^2/day	Rest/ Evaluation
Ribociclib dose reduction	280 mg/m^2/day	

*starting dose

Maintenance Phase of Therapy (DIPG Patients > 21 years of age)		
Each Course	**May receive a maximum of 12 courses**	
Day	**1-21**	**22-28**
Ribociclib starting dose level*	600 mg daily	Rest/ Evaluation
Ribociclib dose reduction	400 mg daily	

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To identify safety and long-term feasibility of Ribociclib at the proposed dosing schedule of 350 mg/m^2/day once daily for 21 days/off 7 days every 28 days for at least 6 courses and up to 12 courses following completion of radiation therapy with newly diagnosed non-biopsied DIPG and Rb+ biopsied DIPG and HGG.

1.1.2 To estimate the 1-year overall survival (OS) of DIPG and HGG separately and compare to historical controls.

1.2 Secondary Objectives

Biopsy

1.2.1 To estimate the consent rate to biopsy in patients diagnosed with DIPG when therapy is based on biopsy results.

1.2.2 To estimate the morbidity associated with biopsy in patients diagnosed with DIPG.

Imaging

1.2.3 To estimate the proportion of newly diagnosed DIPG/HGG patients treated on protocol that are determined to have experienced pseudoprogression.

1.2.4 To explore volumetric measurements and correlate with 2-dimensional measurements and compare response criteria.

1.2.5 To explore the quantitative MR measures of relative cerebral blood volume (rCBV), vascular permeability (Ktrans, vp, and ve values), and apparent diffusion coefficient (ADC) within the first six months of initiating protocol treatment to correlate with disease outcome and determine whether such metrics differentiate patients with pseudoprogression from those with true early progressive disease.

Exploratory

Biomarkers/ Biology/Genomics

1.2.6 To explore whether RB status correlates with response to proposed therapy.

1.2.7 To assess pharmacodynamics on paraffin sections of skin biopsy for analysis of the cell cycle G1/S checkpoint and the PI3K/AKT/mTOR pathway.

1.2.8 To explore the relationships between the activation status of the cell cycle and PI3-kinase/AKT/mTOR pathways in patient tumor samples.

1.2.9 To examine hTERT promoter mutations and methylation, H3F3A, HIST1H3B (H3.3 and H3.1 genes), ATRX, and DAXX mutations and examine the effects of these modifications using targeted gene, exome, RNA sequencing and methylation arrays of targeted genomic regions.

1.2.10 To evaluate the telomere length in match samples (diagnosis/recurrence) in DIPG and HGG specimens.

1.2.11 To evaluate whole genome sequencing to identify the genetic alterations in DIPG and HGG tissue at biopsy, and recurrence and/or autopsy if available.

Late effects

1.2.12 To evaluate pubertal development by evaluating the gonadotropin response to and degree of recovery from irradiation and treated with maintenance therapy Ribociclib as evidenced by Tanner staging, FSH, LH and Estradiol (female) and Testosterone (male) prior to therapy with Ribociclib, 6 months post-completion of radiation therapy and yearly thereafter among pre-pubertal and pubertal female and male patients diagnosed with DIPG and HGG.

1.2.13 To evaluate the effect of proposed therapy (radiation therapy followed by maintenance therapy with Ribociclib) on ovarian reserve in female patients as evidenced by anti-mullerian hormone levels (AMH) prior to therapy with Ribociclib, 6 months post-completion of radiation therapy and yearly thereafter among pre-pubertal and pubertal female patients diagnosed with DIPG and HGG.

Quality of life

1.2.14 To assess the health-related quality-of-life of patients by parent report, and when possible, patient report at key points in therapy using the patient reported outcomes measurement information system (PROMIS) survey.

2. BACKGROUND

2.1 Study Disease(s)

Pediatric Diffuse Intrinsic Pontine Gliomas

Diffuse intrinsic pontine glioma (DIPG) accounts for 10-15% of all new pediatric brain tumor diagnoses and is the leading cause of brain tumor-related death in children. [11] DIPG can affect patients of any age, adults [12] as well as infants/ toddlers; [13] however the median age at diagnosis is 6 to 7 years [1,2], and patients commonly present with cranial nerve deficits, upper motor neuron signs, and ataxia. [1] DIPG is generally diagnosed on the basis of clinical and radiographic findings. Typical MRI appearance is a T1-hypointense, T2-hyperintense, variably contrast enhancing, expansile mass involving ≥ 50% of the pons. Though often not apparent at diagnosis, several recent studies have demonstrated leptomeningeal dissemination and spread to proximal areas of brain at autopsy. [14,15] Prognosis for patients diagnosed with DIPG is dismal, with a median overall survival of less than one year. [1,2] Standard treatment at diagnosis consists of local radiation therapy, but this intervention is only useful to improve symptoms and prolong survival by 2 to 3 months in some.[16] Over 50 clinical trials have been investigated in the last three decades with various interventions including radiation therapy, high dose chemotherapy, and addition of radiation sensitizers; none have demonstrated benefit.[2] Assuming that these aggressive tumors are generally irradiation resistant, and intensification of traditional chemotherapy agents failed to improve outcome, it is reasonable to hypothesize that novel agents that target a critical tumor-specific pathway mediating irradiation and/or chemotherapy resistance may be worthy of clinical investigation.

Historically, histopathological diagnosis has not been routinely performed due to perceived risks of brainstem biopsy[17] but was instead reserved for patients with atypical imaging characteristics. The consequence of this paradigm is scarcity of tissue and thus grave limitation of our understanding of the molecular biology of DIPG. In recent years, tissue has become more available through collaborative determination to overcome barriers to tissue procurement. This has been accomplished in the following ways: 1) efforts to study and implement safe surgical techniques for brainstem biopsy, which were pioneered in Europe [18-20] and have become more recently accepted in the United States [21],and 2) initiation of programs for tissue collection at autopsy, which have been instigated by family advocacy groups and physicians.[22-24]

High Grade Gliomas

High Grade Gliomas (HGG) are tumors of glial origin with an aggressive infiltrative nature that account for 3-7% of primary brain tumors in children with a peak in incidence during adolescence. [25] Anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) are the more common histological variants and the less frequently occurring histologies include grade III anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, anaplastic pilocytic astrocytoma, and grade IV giant cell glioblastoma, gliomatosis cerebri and gliosarcoma.

[redacted]

[27]

Figure 1

[redacted]

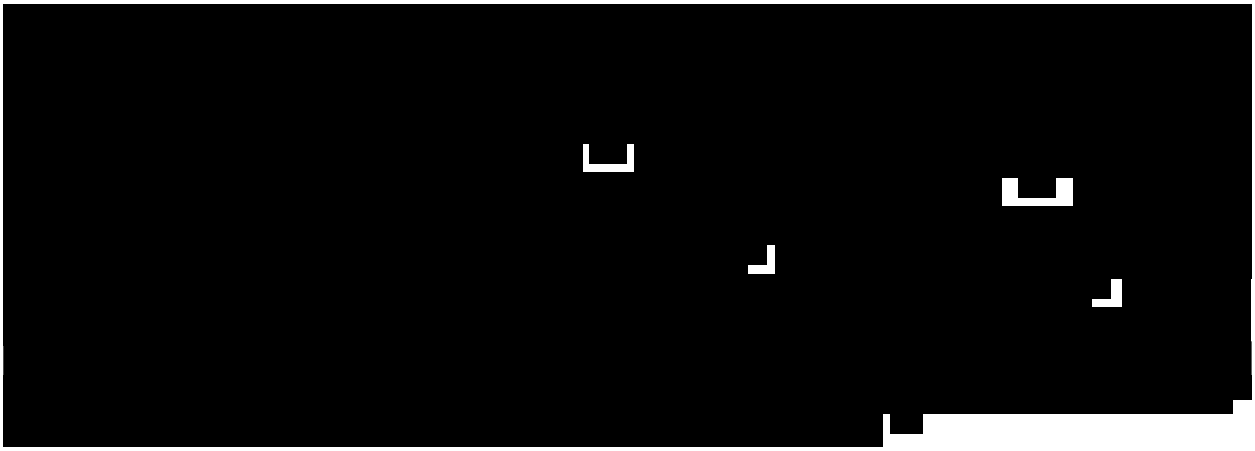
2.1.1 *Role of cell cycle in Cancer*

The cell cycle is a tightly regulated process through which cells undergo division. DNA is doubled in S phase and cells undergo mitosis and division in M phase with checkpoints at G1 and G2 that say STOP or GO. The mammalian cell cycle is dependent on multiple checkpoints regulated by cyclins and their associated cyclin-dependent kinase activation (CDK). Checkpoints are transitions between various phases of the cell cycle when the integrity of replication and division are carefully monitored before allowing the cell to move to the next phase.[30] In mammalian cells, cyclins and the CDKs can be divided into G_1 Cyclins

(cyclin D1-3, and E) and CDK 4, 6, and 2; S phase cyclins (cyclins A and E) and CDK2, and mitotic cyclins (Cyclin A and E).[3] CDK 1 and 2 are the positive regulators.[30] The two main classes of inhibitors include inhibitor of CDK4 (INK4) family of inhibitors and the CDK inhibitor protein (CIP)/kinase inhibitor protein family of inhibitors. [30,31] The INK4 family of inhibitors ($p16^{INK4A}$ and $p14^{ARF}$, $p15^{INK4B}$, $p18^{INK4C}$, and $p19^{INK4D}$) specifically inhibits only CDK4/6 during G_1; whereas, CIP/KIP ($p21^{CIP1}$, $p27^{KIP1}$, $p57^{KIP2}$) are capable of inhibiting kinases and cyclins during all phases of the cell cycle (Figure 2). [30,31]

G_1-S transition in the mammalian cell cycle is divided into the early G_1 (pre-restriction point (RP) which is mediated by the CDK-4/cyclin D complex following release of INK4 (an inhibitor of cell cycle progression) from CDK4/6.[30] CDK4/6 binds cyclin D1, which then phosphorylates and inactivates the Rb protein and releases the E2F-DPI transcriptional complex, which is then free to bind to promotor regions of E2F target genes required for transition into the S-phase and progression (Figure 3).[30,32] Deregulation of cyclin expression or CDKs activation are hallmarks of tumorgenesis by causing proliferation, genomic instability, and invasiveness. [3]

2.1.2 *Alterations in Cell Cycle regulating genes in pediatric/young adult CNS tumors*



[redacted]

2.1.3.2 *In vivo activity of CDK 4/6 inhibition leads to survival benefit in brainstem glioma xenograft with radiation therapy*

[redacted]

2.1.3.3 *Animal Toxicity*

[redacted]

2.1.4 Adult Clinical Trials

2.1.4.1 *Phase I Trial of Ribociclib in Adults*

[redacted]

[redacted]

[redacted]

[redacted].

2.1.4.2 *Phase Ib/II/III Trials/Combination of LEE001 in Adults*

[redacted]

[redacted]

[redacted]

2.1.5 Pediatric Studies

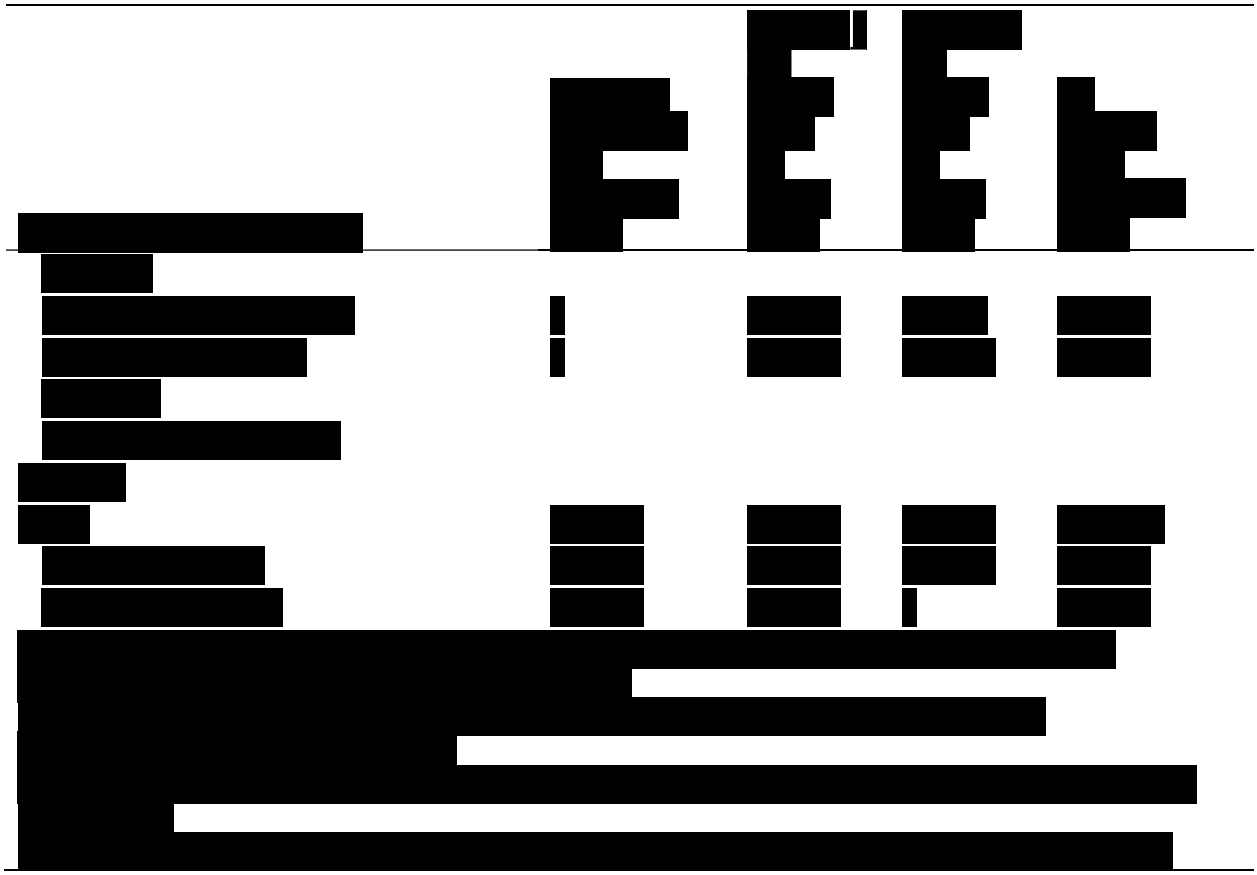
2.1.5.1 *Phase l Trial of Ribociclib*

[redacted]

[redacted]	[redacted]
[redacted]	

[redacted]

[redacted]



2.2 Overview and Study Rationale

Survival for children with DIPG and HGG is dismal and novel therapeutic options need to be developed in order to improve outcome. Tumor initiation and progression is dependent on deregulation of the components and phases of the cell cycle. [30]

[redacted]

[redacted]

All patients will receive radiation therapy. Upon completion of radiation therapy, a 2-4 week break will occur and then Ribociclib will be given orally daily for 3 weeks on/1 week off every 28 days post completion of radiation therapy at the RP2D (350 mg/m^2/day) for at least 6 months and up to 12 months. One course is equivalent to 28 days.

The long- term feasibility component of the study will assess Ribociclib at the defined RP2D 350 mg/m^2/day once daily for 3 weeks on/one week off every 28 days following radiation therapy for at least 6 courses and up to 12 courses. Safety monitoring and stopping rules will be instituted to ensure that serious treatment-related toxicities are reported and study continuation re-evaluated. Follow-up will be for 2 years following the last dose of Ribociclib. Any Ribociclib related adverse event as outlined in section 6.1 during the maintenance therapy will lead to one intra-patient dose reduction. Therapy will be discontinued if a dose modifying toxicity occur after one dose modification and will be considered infeasible.

2.3 Correlative Studies Background

2.3.1 *Rationale for diagnostic biopsy in DIPG*

[redacted]

[redacted]

[redacted]

[redacted]

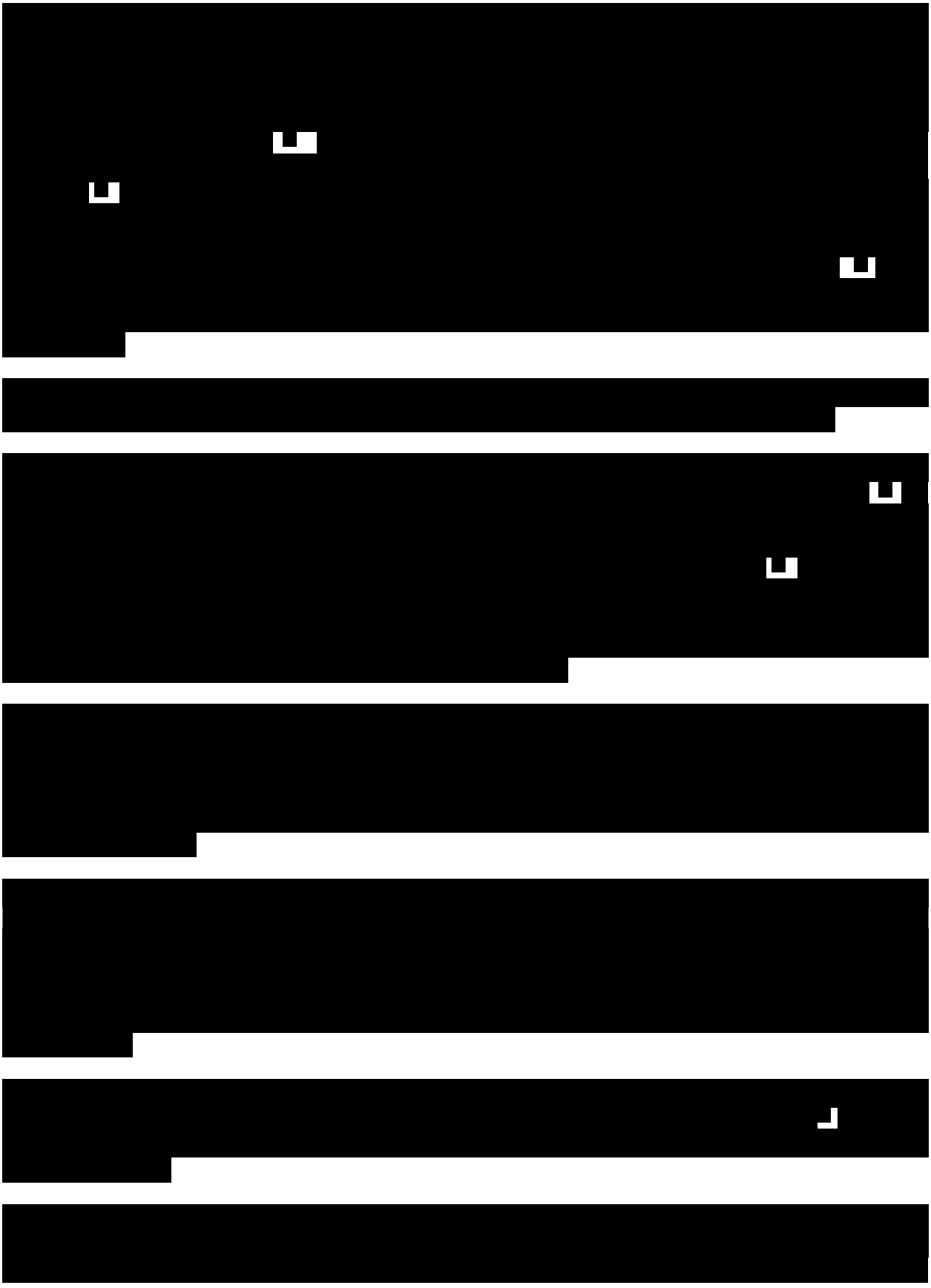
[redacted]

[redacted] Rationale for Imaging Studies

[redacted]

[redacted]

[redacted]



[redacted]

2.3.3 *Rationale for Exploratory Correlatives*

[redacted]

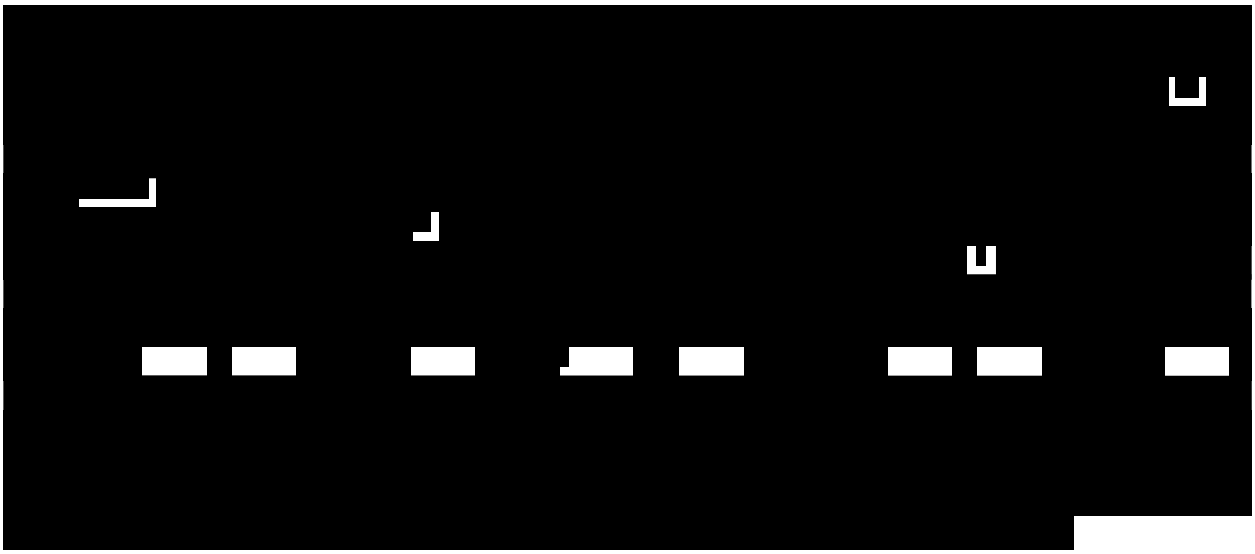
2.3.3.1 *Molecular markers may predict sensitivity to CDK4/6 inhibitors such as Ribociclib*

[redacted]

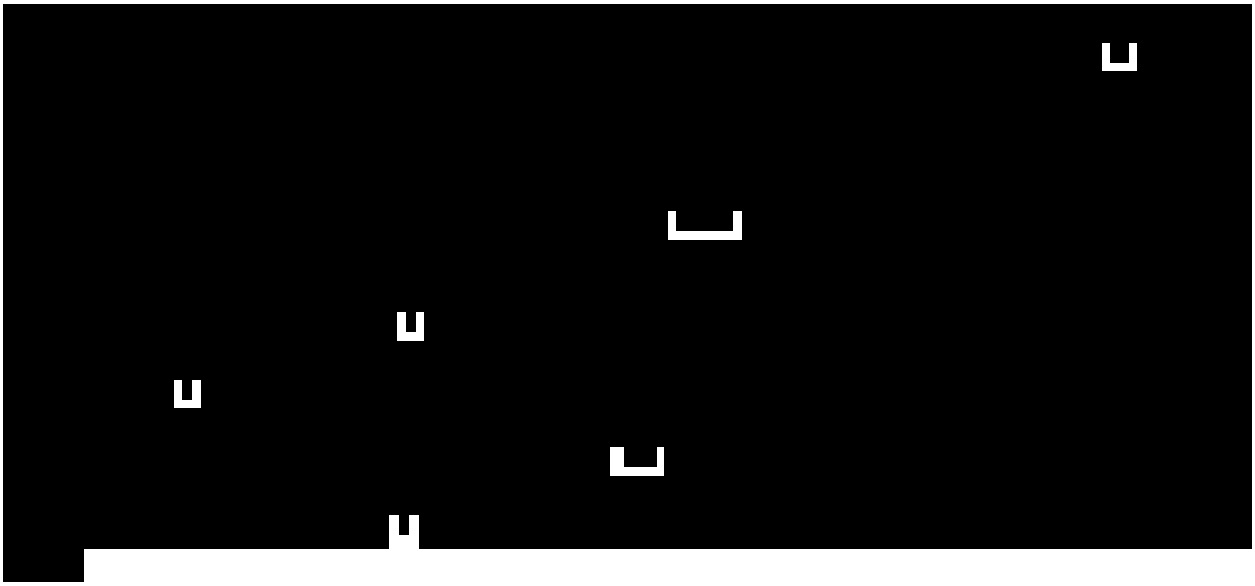
2.3.3.2 *Surrogate pharmacodynamics studies confirm inhibition of the molecular target*

[redacted]

2.3.3.3 *Molecular correlates of telomerase activity: H3F3A (H3.3 gene), ATRX, and DAXX mutations/DNA methylation sequencing*



2.3.3.4 *The genomic landscape of pediatric HGG and DIPG differs from adult HGG*



[redacted]

[redacted]

[redacted]

2.3.4.1 *Rationale for correlative gonadal function in patients*

[redacted]

[redacted]

[redacted]

2.3.5 Quality of Life Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. PATIENT SELECTION

Patients may be recruited at the participating institutions. The investigational nature and objectives of this trial, the procedures, and treatments involved and their attendant risks and discomforts and benefits, as well as potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if he/she is a child, and a signed informed consent document will be obtained. Consent will be obtained by the site PI or a delegated sub- investigator on the trial. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial. Requirement for documentation of assent will be determined by the local IRB.

3.1 Eligibility Criteria

The eligibility criteria listed below are to be interpreted literally and cannot be waived. All clinical and laboratory data required to determine eligibility of a patient enrolled on this trial must be available in the patient's medical or research record.

3.1.1 Age

Patients must be ≥ 12 months of age and ≤ 30 years of age at the time of study entry for patients diagnosed with DIPG.

Patients must be ≥ 12 months of age and ≤ 21 years of age at the time of study entry for patients diagnosed with HGG.

3.1.2 RB status

Diagnostic stereotactic biopsy: Patients diagnosed with DIPG may choose to have a stereotactic biopsy prior to starting radiation therapy.

Screening for RB applies to all patients with available tissue except for patients diagnosed with DIPG and bi-thalamic tumors.

If resection occurred at an outside institution, eligibility and treatment MRI evaluations in

addition to RB testing must be formally evaluated at CCHMC.

3.1.3 Tumor

Diffuse Intrinsic Pontine Glioma (DIPG)

Patients with newly diagnosed diffuse intrinsic pontine gliomas (DIPGs), defined on neuroimaging as tumors with a pontine epicenter and diffuse intrinsic involvement of the pons, are eligible without histologic confirmation.

Patients with brainstem tumors that do not meet these criteria or not considered to be typical intrinsic pontine gliomas will only be eligible if the tumors are biopsied and proven to have + RB and be the following according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System [97]:
Anaplastic astrocytoma (IDH mutant, IDH wildtype, or NOS)
Glioblastoma (IDH mutant, IDH wildtype or NOS)
Diffuse midline glioma, H3 K27M mutant or H3 K27M negative
Diffuse astrocytoma (IDH mutant, IDH wildtype, or NOS)

Note: Patients with juvenile pilocytic astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma with or without anaplasia, gangliogliomas, or other mixed gliomas without anaplasia are not eligible.

Patients with diffuse intrinsic brain stem glioma (DIPG) can be enrolled without the need for available tumor tissue for RB protein status confirmation. If DIPG or bi-thalamic patients have been biopsied and if available tissue, RB status will be tested. These must be RB+ to be eligible for enrollment.

Bi-thalamic tumors, biopsied and noted to have intact RB. Bi-thalamic tumors that are not biopsied will be eligible to enroll on the DIPG non-biopsied arm. [42]

High-grade Glioma (HGG)

Patients must have had histologically verified the following according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System [97]:
Anaplastic astrocytoma (IDH mutant, IDH wildtype, or NOS)
Glioblastoma (IDH mutant, IDH wildtype or NOS)
Diffuse astrocytoma (IDH mutant, IDH wildtype, or NOS)
AND RB+ noted on immunohistochemistry.

Patients with primary spinal cord tumors are eligible. Patients with multi-focal disease within the cerebrum are eligible.

Patients with a diagnosis of oligodendroglioma or oligoastrocytoma are not eligible.

3.1.4 Performance Status

Karnofsky ≥ 50% for patients >16 years of age or Lansky ≥ 50 for patients ≤ 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. See APPENDIX A.

3.1.5 Prior Therapy

Patients must have not received any prior therapy other than surgery, radiation and/or steroids.

3.1.6 Radiation therapy requirements

- Patients diagnosed with DIPG: any variances in the radiotherapy dose within 10% of the current standard dose (54 Gy) will be discussed with the Sponsor-Investigator to confirm eligibility prior to study enrollment.
- Patients diagnosed with HGG: any variances in the radiotherapy dose within 10% of the current standard dose (59.4 Gy) will be discussed with the Sponsor-Investigator to confirm eligibility prior to study enrollment.
- Patients diagnosed with primary spinal tumors any variances in the radiotherapy dose within 10% of the current standard dose (54 Gy) will be discussed with the Sponsor-Investigator to confirm eligibility prior to study enrollment.

- Timing of Radiation

  Radiation therapy must begin no later than 30 days after the date of radiographic diagnosis or definitive surgery, whichever is the later date.

3.1.7 Organ Function

Patients must have normal organ and marrow function documented within 7 days of study enrollment as defined below:

- Absolute neutrophil count $\geq$ 1,000 mm^3
- Platelets $\geq$ 100,000/mm^3 (unsupported for 7 days)
- Hemoglobin $\geq$ 9g/dL (unsupported) for 7 days
- Total bilirubin $\leq$ 3 times upper limit of normal (ULN) for age
- ALT (SGPT) $\leq$ 2.5 x ULN institutional upper limit of normal for age
- AST (SGOT) $\leq$ 2.5 x ULN institutional upper limit of normal for age
- Albumin $\geq$ 2g/dL
- Creatinine clearance or radioisotope GFR $\geq$ 70 mL/min/1.73 m^2 or
  Serum creatinine based on age/gender as follows:

Table 1

Serum Creatinine for age/gender		
Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
$\geq$ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

3.1.8 All patients must have recovered from all acute RT-related toxicities to ≤ grade 2 prior to initiating the use of Ribociclib.

3.1.9 Pregnancy Status

Female patients of childbearing potential, as defined in section 3.1.10, must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum or urine pregnancy test.

3.1.10 Pregnancy Prevention

Women of child-bearing potential are defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception throughout the study and for 21 days after study drug discontinuation. Highly effective contraception have less than 1% chance of unwanted pregnancy during one year, if used appropriately according to the instructions of the manufacturer. Examples of highly effective birth control methods are:

- Total abstinence (no sexual relations) when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Tubal ligation at least 6 weeks before taking study drug.
- Male partner has had vasectomy with the appropriate documentation. Sterilized male partner should be the sole partner of the female.
- Use of a Combination of any of the two following (a+b or a+c or b+c)
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

Patients of child fathering potential (defined as > Tanner stage 2) must use a condom during intercourse while taking the drug during treatment, for 21 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men during intercourse with a male or female partner in order to prevent delivery of the study drug via semen.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

3.1.11 Female patients with infants must agree not to breastfeed their infants while on this study.

3.1.12 Informed Consent

Signed informed consent according to institutional guidelines must be obtained. Assent, when appropriate, will be obtained according to institutional guidelines.

3.2 Exclusion Criteria

3.2.1 Concurrent Illness

Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) that would compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results.

3.2.2 Inability to Participate

Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.

3.2.3

Received a radiosensitizer, investigational agent or any additional adjuvant therapy during radiation therapy.

3.2.4

Patients with disseminated disease to the spine are not eligible, and MRI of spine must be performed prior to enrollment if the treating physician suspects disseminated disease.

3.2.5 Seizures

Patients who are currently receiving enzyme inducing anti-epileptic drugs that are known strong inducers or inhibitors of CYP3A4/5 (EIAEDs) (Appendix D). Patients with a history of seizures and maintained on an anti-epileptic drug that is not a strong inducers or inhibitor of CYP3A4/5 are eligible.

3.2.6

Patient has a known hypersensitivity to Ribociclib or any of its excipients.

3.2.7

Clinically significant active cardiac disease, uncontrolled heart disease and/or history of cardiac dysfunction including any of the following;

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 12 months prior to screening
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Documented cardiomyopathy
- Patient has a Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening
- History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months of screening
- Long QT syndrome or known family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:

  Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.

  Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication.

- Hypertension defined below:

Patients1-17 years of age with blood pressure that is ≥ 95th percentile for age, height and gender at the time of enrollment (Appendix B)

Patients who are ≥ 18 years of age with a systolic blood pressure that is >160 or diastolic > 90 mm of Hg at the time of enrollment.

* Note: If a BP reading prior to enrollment does not meet parameters, blood pressure should be rechecked and documented to be within eligibility range prior to patient enrollment.

3.2.8 Inability to determine the QTc interval on the ECG (i.e.: unreadable or not interpretable) or QTc >480 msec as determined by screening ECG.

3.2.9 Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug Ribociclib (see Appendix D for details):

- Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
- Medications that have a known risk to prolong the QT interval or induce Torsades de Pointes
- Herbal preparations/medications, dietary supplements.

3.2.10 Patient is currently receiving warfarin or other coumadin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed

3.2.11 Patient has a history of non-compliance to medical regimen.

3.2.12 Known need for major surgery within 14 days of the first dose of Ribociclib. Gastrostomy, insertion of a G tube, Ventriculo-peritoneal shunt, endoscopic ventriculostomy and central venous access are NOT considered major surgery.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. GENERAL GUIDELINES

4.1 Screening Informed Consent

[redacted]

4.2 Treatment informed consent

[redacted]

4.3 **Patient /Enrollment**

[redacted]

4.4 [redacted]

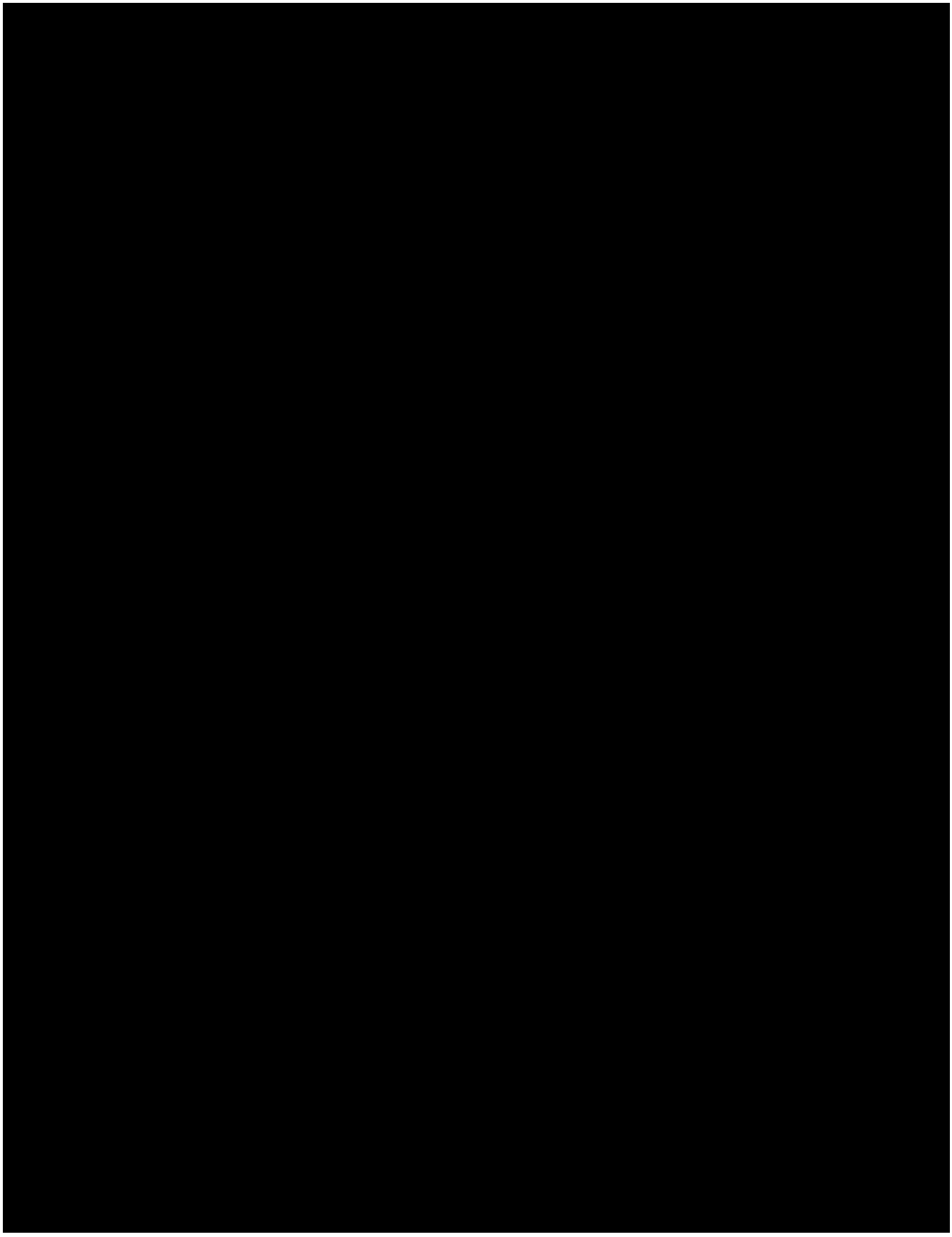
[redacted]

4.4.1.1 Surgical Technique for stereo-tactic biopsy in patients diagnosed with DIPG:

[redacted]

4.5 [redacted]

[redacted]



[redacted]

5.2 General Concomitant Medication and Supportive Care Guidelines

[redacted]

[redacted]

5.3 [redacted]

[redacted]

5.4 [redacted]

[redacted]

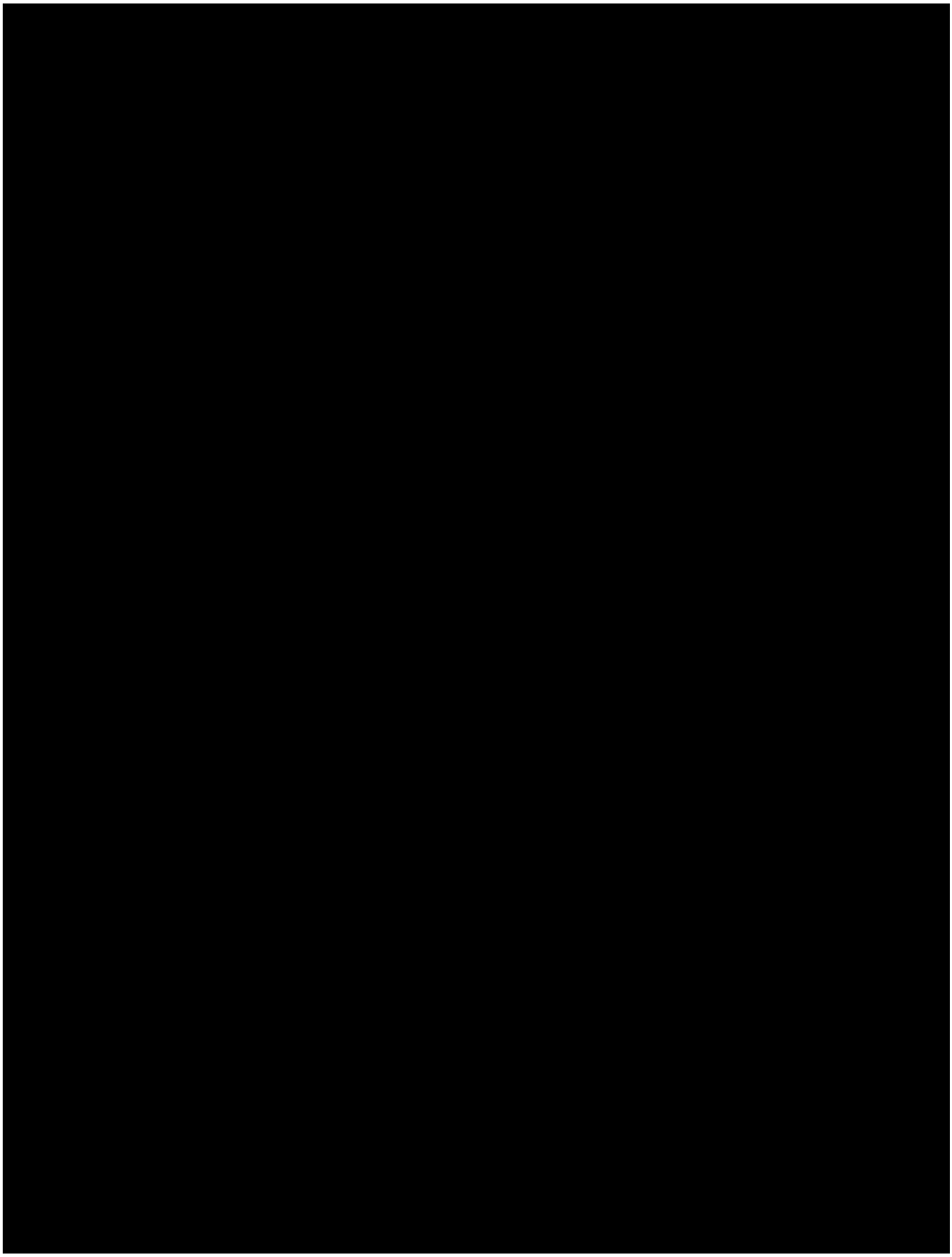
[redacted]

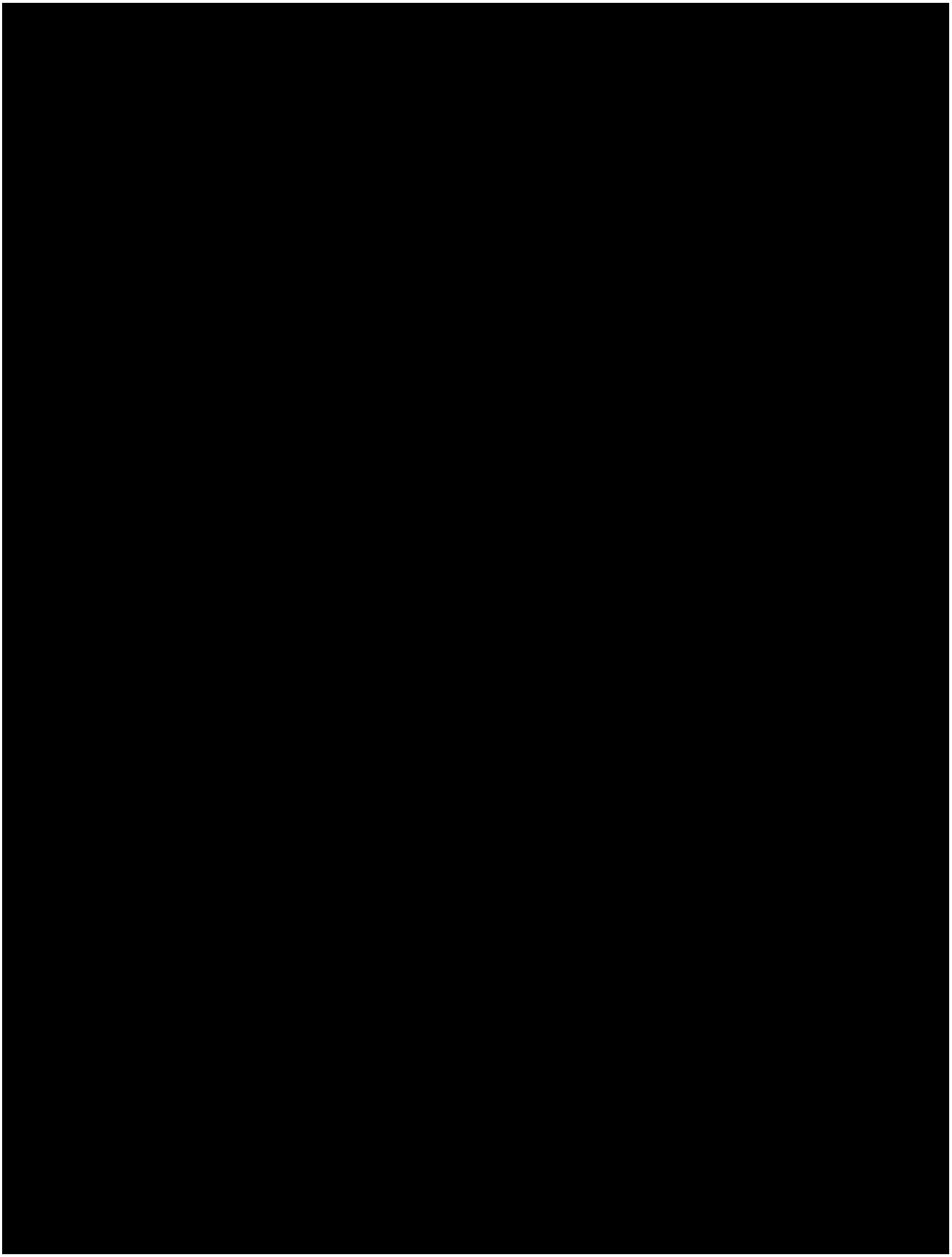
5.5 [redacted]

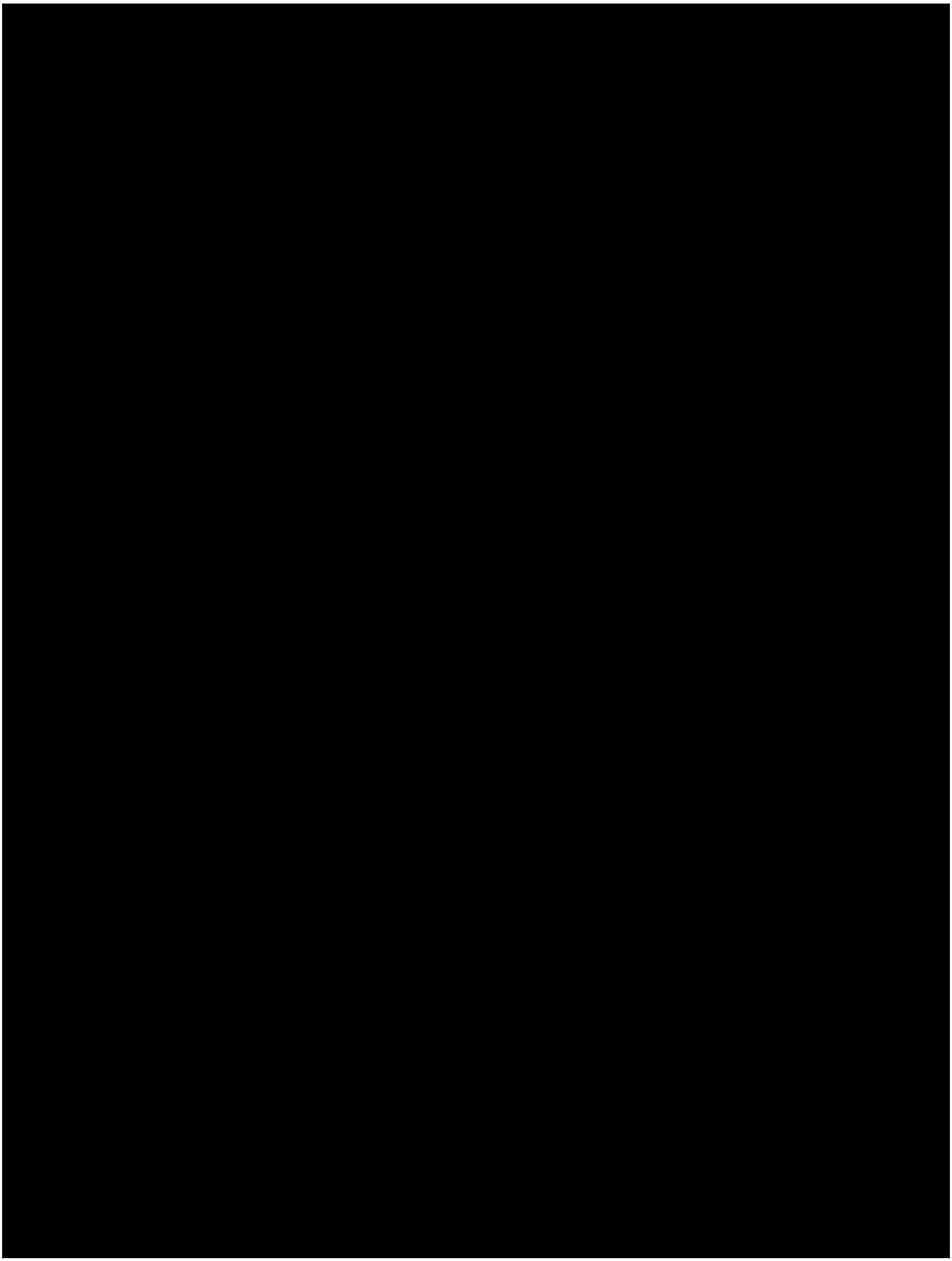
[redacted]

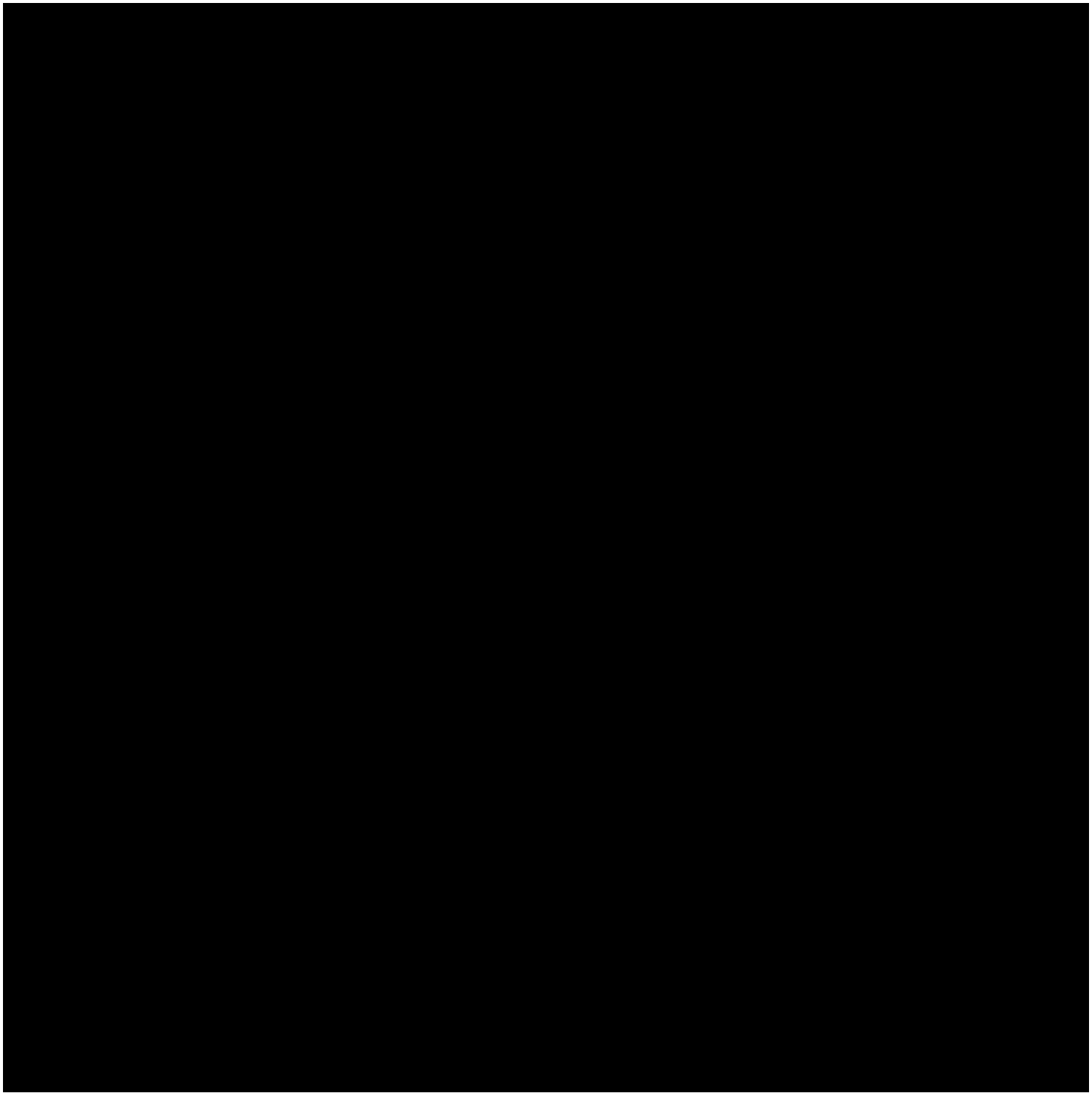
6.1 [redacted]

[redacted]



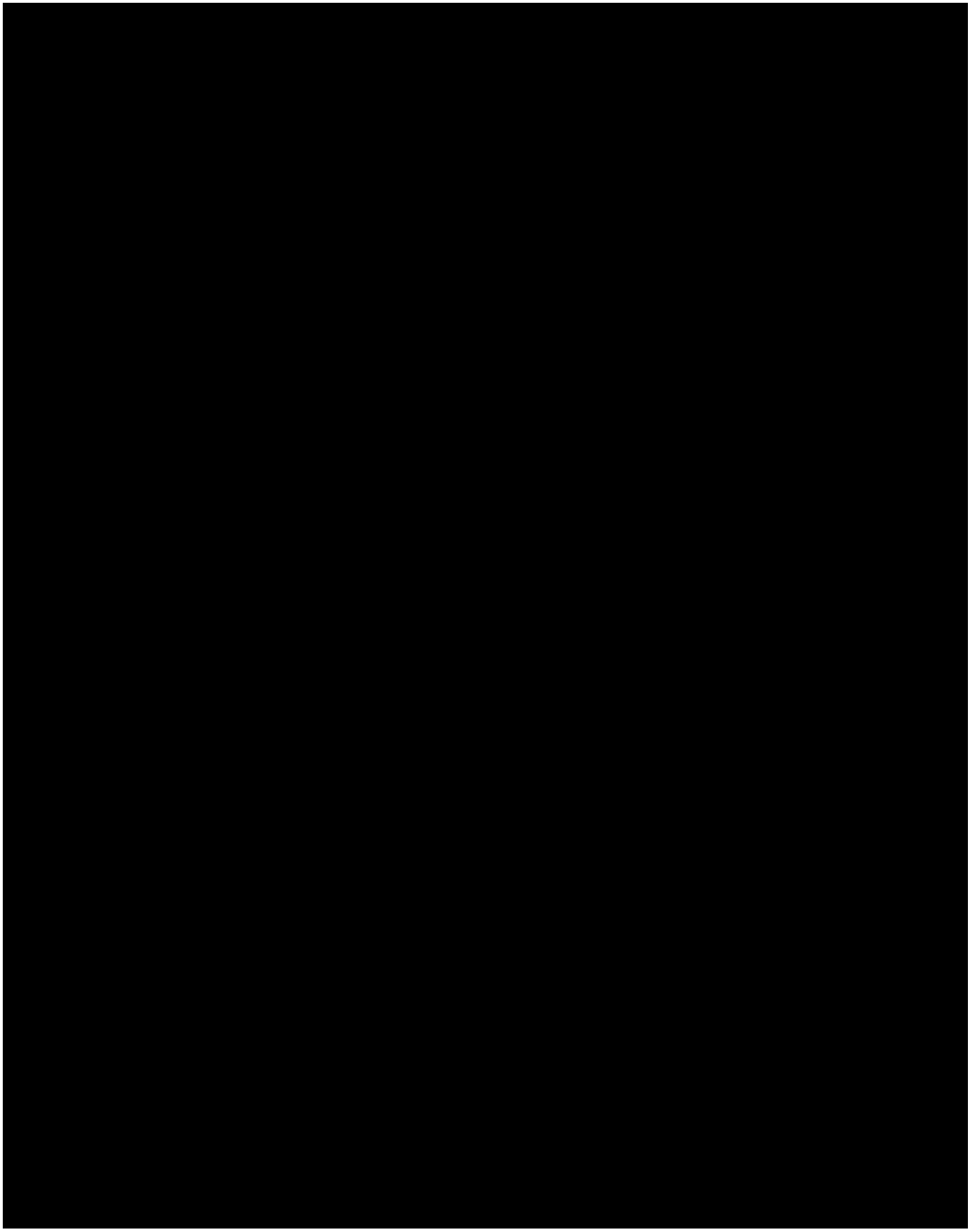


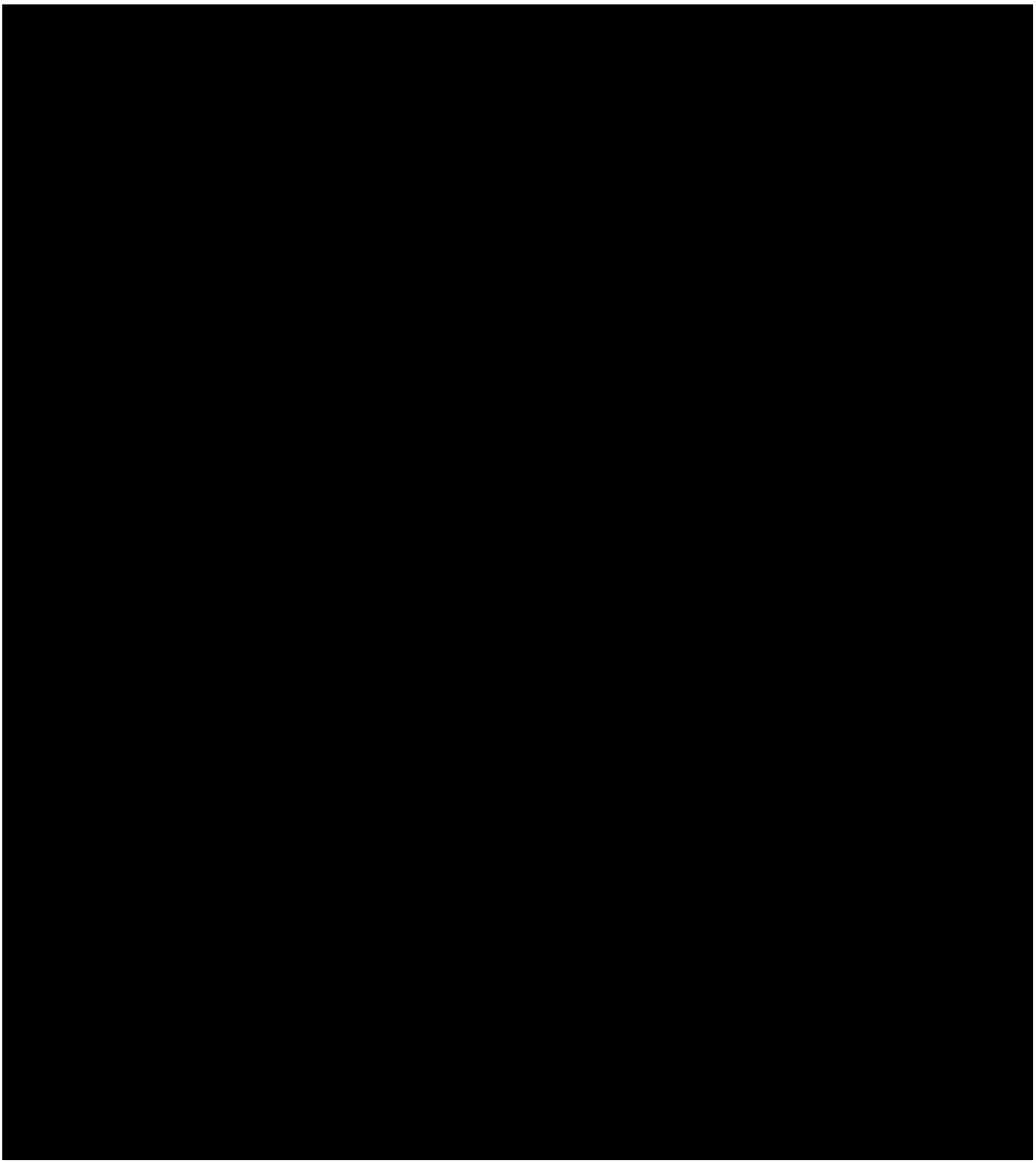


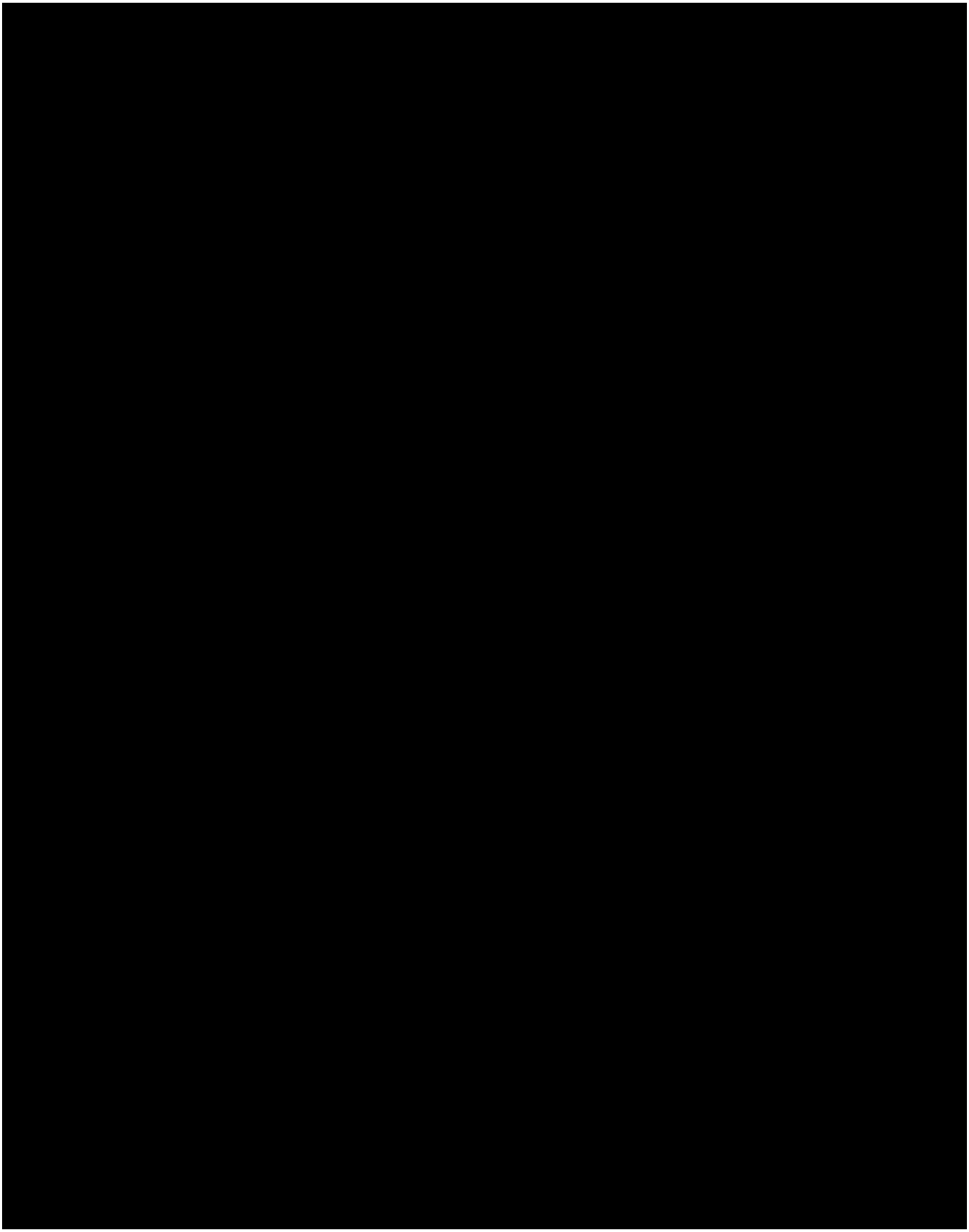


[redacted]

7.1 [redacted]



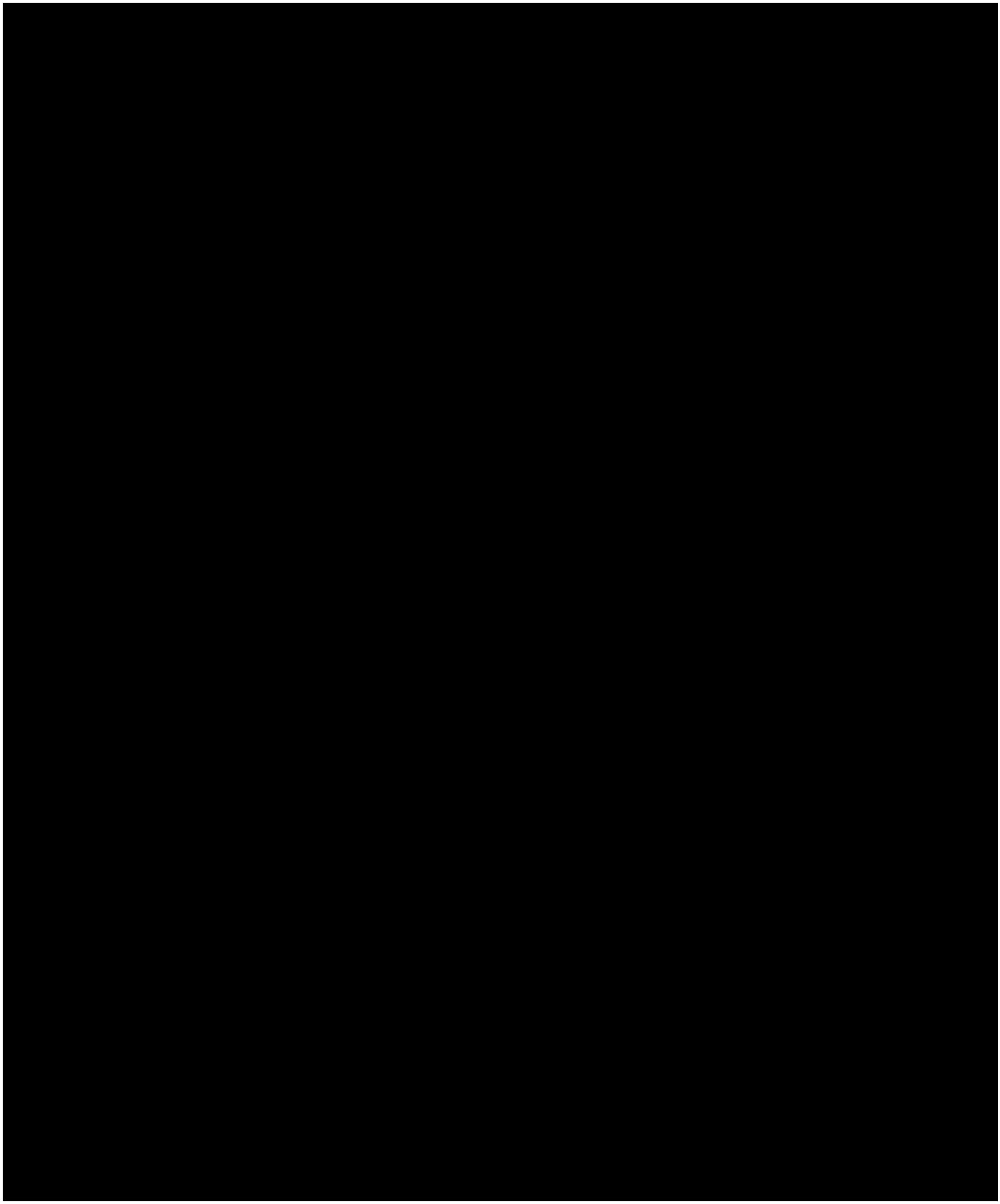


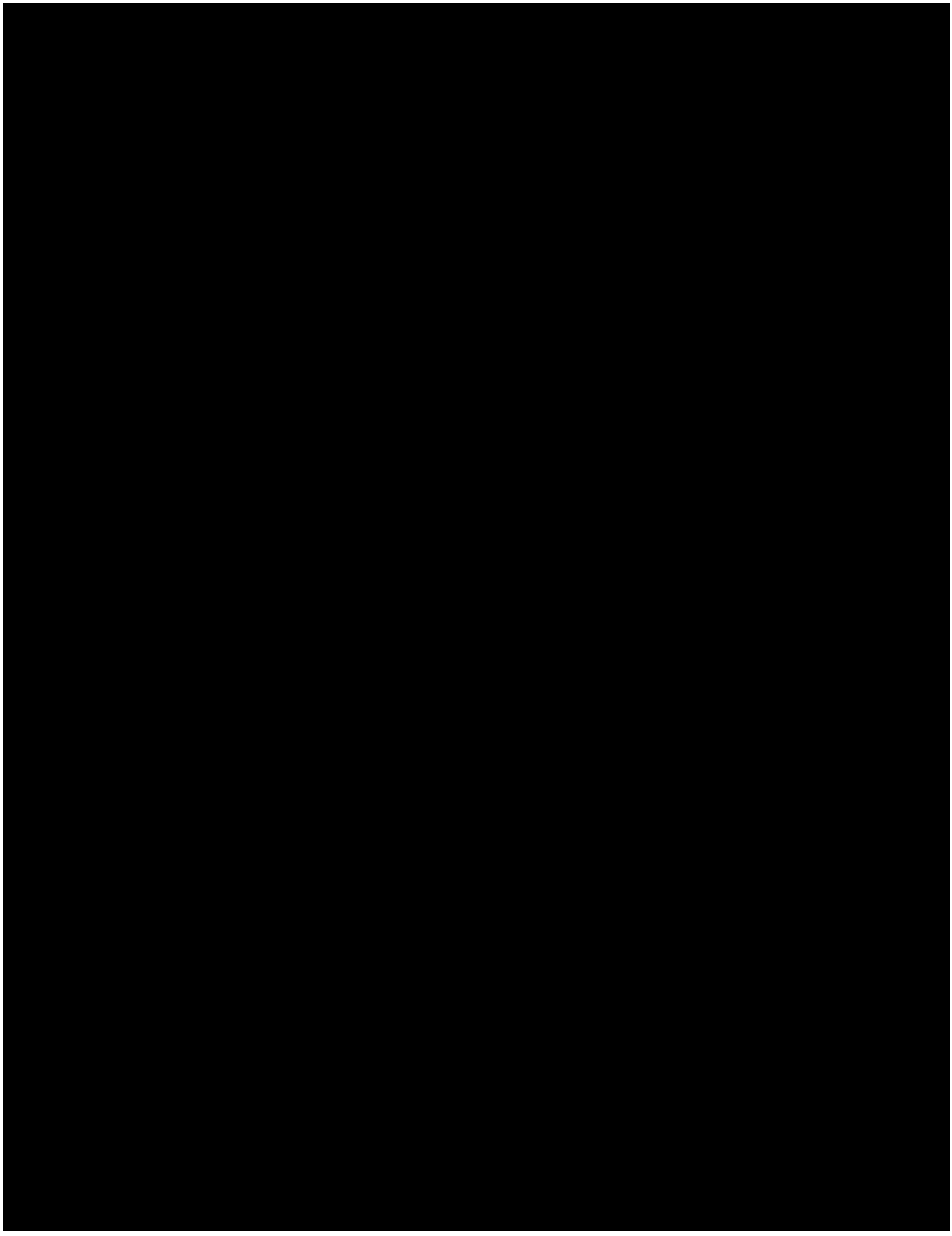


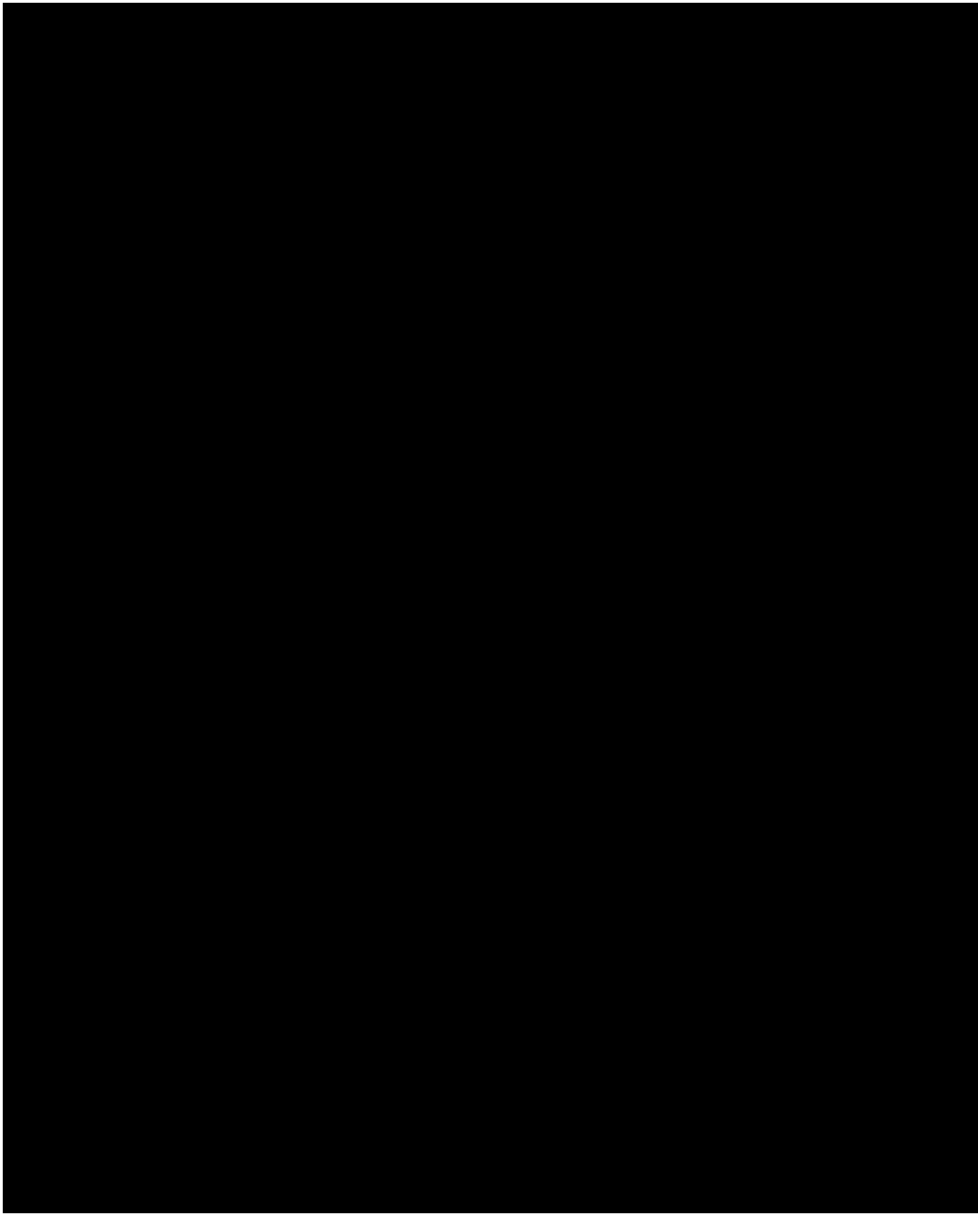
[redacted]

[redacted]

[redacted]



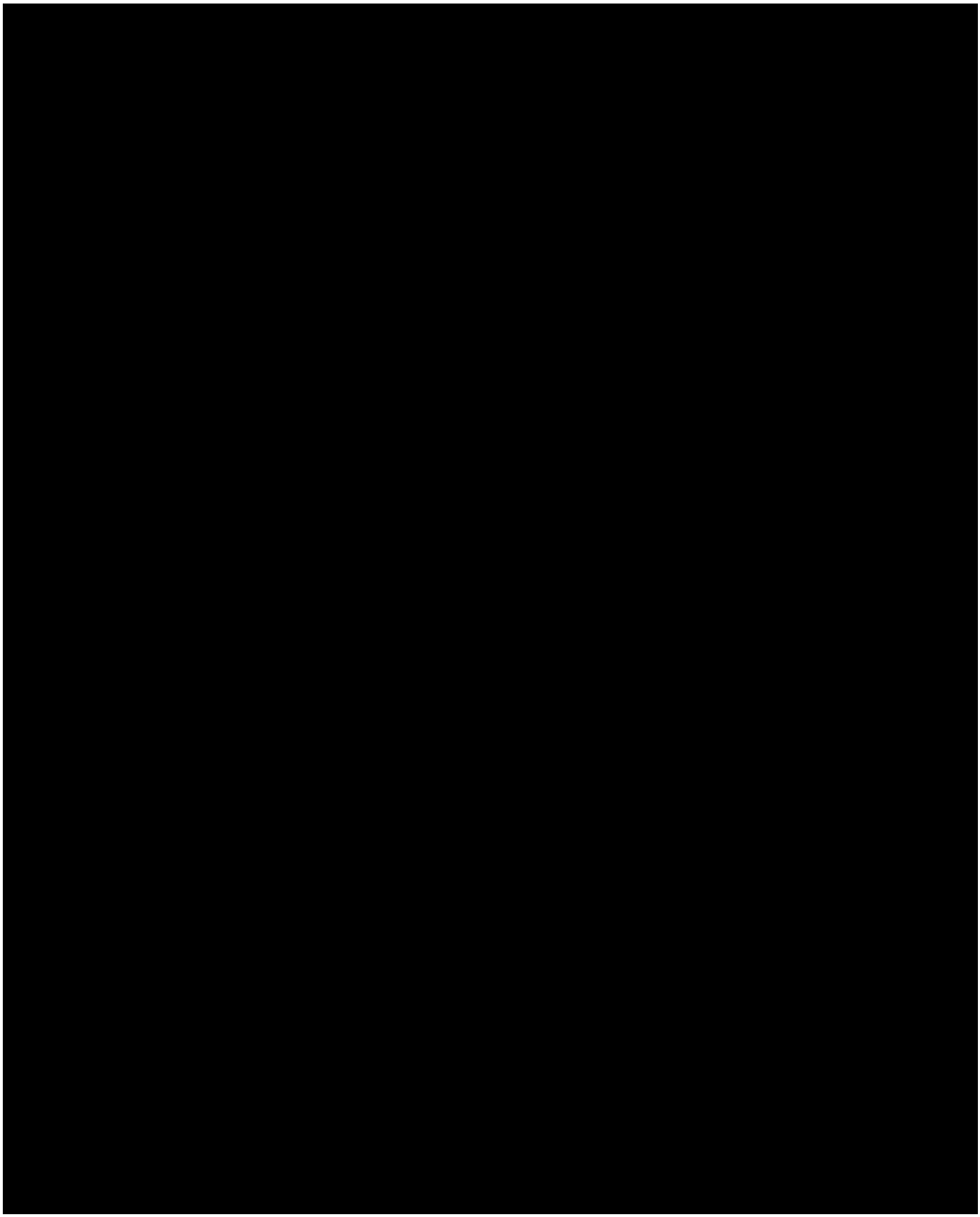


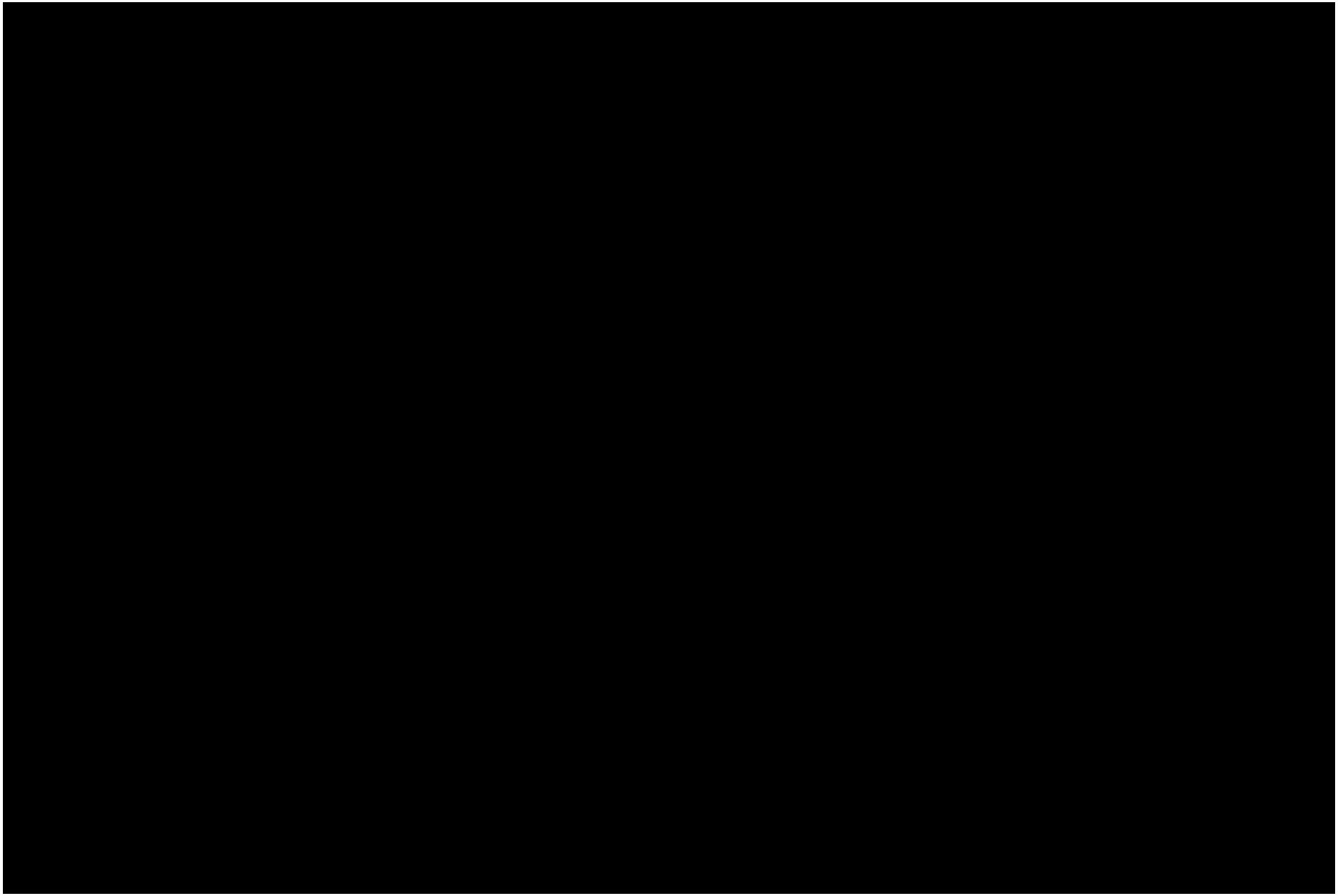


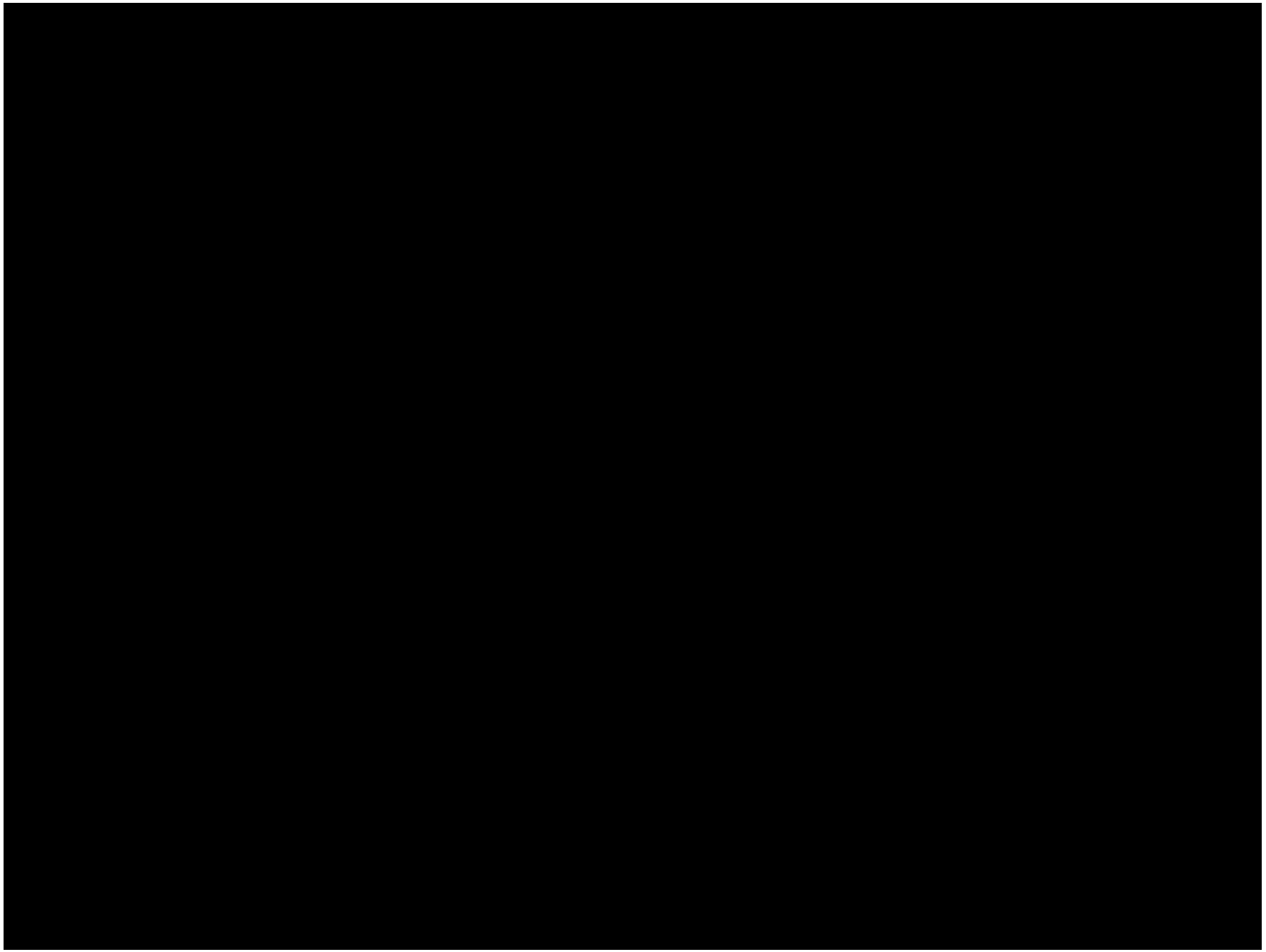
[redacted]

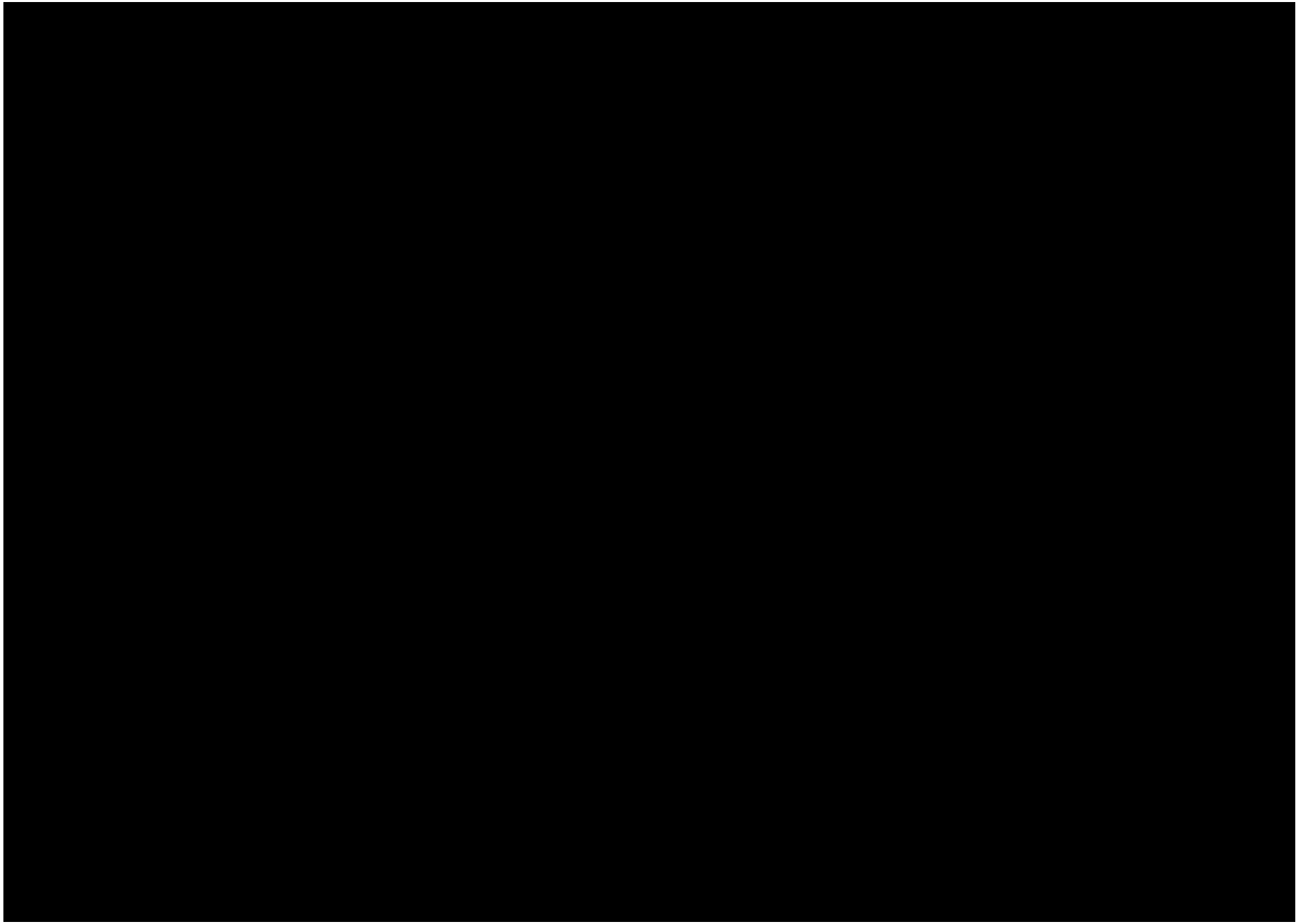
[redacted]

[redacted]



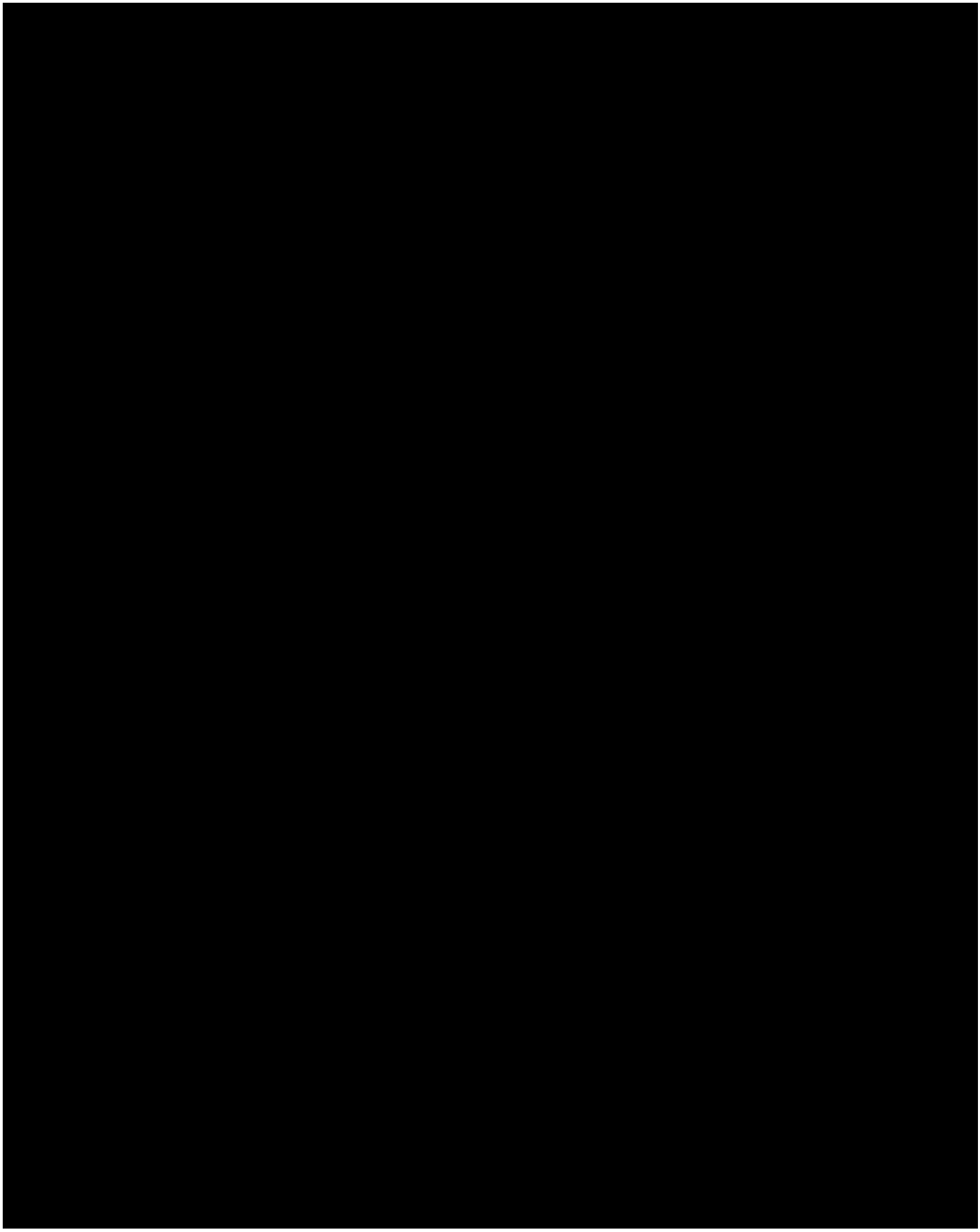






[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

13. STATISTICAL CONSIDERATIONS

Study Design:
This is a "safety and preliminary efficacy" study of Ribociclib administered orally once daily for 3 weeks, off one week every 28 days following radiation therapy for up to 12 courses in children with newly-diagnosed diffuse intrinsic pontine glioma (DIPG) and RB+ high grade gliomas (HGG). The study design requires 24 patients evaluable for feasibility (12 in both the DIPG and HGG groups). Patients not evaluable for feasibility will be replaced, therefore, the enrollment sample size may be greater than 24. DIPG patients will have the option to have diagnostic biopsy to evaluate RB status. Patients with RB negative DIPG and HGG tumors will have the opportunity to enroll on other DIPG or HGG protocols as directed by the family and their treating physician. Patients with DIPG who do not consent to biopsy will be offered Ribociclib maintenance since over 70% of patients with DIPG have been reported to have an intact RB. RB status will be identified pre-treatment on tumor tissue by immunohistochemistry.

We will start with the recommended phase II dose (RP2D) 350 mg/m^2/day once daily for 3 weeks, off 1 week every 28 days and monitor for safety and toxicity for up to 12 courses upon completion of radiation therapy. One intra-patient dose de-escalation is allowed in subsequent courses to 280 mg/m^2 /day once daily for 3 weeks, off one week every 28 days.

The primary endpoint of feasibility**,** the two strata (DIPG and HGG) will be considered together. This is done since it is not expected that the two groups will differ with respect to the feasibility. The primary feasibility endpoints are a) toxic death or individual toxicities related to study drug resulting in discontinuation of study drug b) the incidence of significant delays (> 2 weeks) in the start of any course of maintenance therapy or discontinuation of the protocol therapy even after appropriate dose modification. Dose-modifying toxicities for maintenance therapy will be monitored. The primary endpoint for the early phase II study will be the 1-year overall survival (OS) of the two strata separately, DIPG and HGG. Early efficacy will be measured by the overall survival distribution will be evaluated and compared to historical controls. Pharmacokinetic analysis will be stratified according to age groups: patients ≤ 21 years of age and >21 years of age.

13.1 **Study Design/Endpoints**.

13.1.1 Feasibility

To address the **endpoint of feasibility,** the two strata (DIPG and HGG) will be considered together. This is done since it is not expected that the two groups will differ with respect to the feasibility.

The primary feasibility endpoints are:
a) Toxic death or individual toxicities especially Grade 3 or 4 related to study drug resulting in discontinuation of study drug
b) The incidence of significant delays (> 2 weeks) in the start of any course of maintenance therapy or removal from protocol therapy over any course of maintenance or discontinuation of the protocol therapy even after appropriate dose modification.

For a patient surviving 6 months after the start of maintenance, if 5 out of 6 courses out of the first 6 months

are completed the drug will be deemed feasible for this patient. This includes up to one intra-patient de-escalation to 280 mg/m^2/day once daily for 3 weeks and off one week every 28 days in this time period. If **more than 2** out of the first 12 enrolled evaluable patients are infeasible, the study will stop and the drug will be considered infeasible at the RP2D (350 mg/m^2/day) for this patient population. If after 24 patients there are **fewer than 5** patients for whom the drug is infeasible the drug will be considered feasible at the RP2D (350mg/ m^2/day). If infeasible for 6 evaluable patients enrolled at any point, the study will stop. Enrollment will continue after the first 12 participants are enrolled while evaluability is being determined. In the event of early shut down of the study, < 25% of patients with dose modifying toxicities after one dose level modification will be considered feasible.

We anticipate enrollment of 12 DIPG patients and 12 HGG patients at the RP2D 350 mg/m^2/day once daily for 3 weeks and off one week every 28 days for patients ≤ 21 years of age and 600 mg orally once daily for 3 weeks and off one week every 28 days for DIPG patients > 21 years of age and evaluate the feasibility at 6 months post completion of radiation therapy up to 12 courses of therapy.

13.1.2 Definition of Evaluable Patient (Feasibility)

Patients who receive at least 80% (5/6 courses) of the treatment regimen or are removed from treatment for toxicity after the dose-modification are evaluable for estimating the safety and feasibility of Ribociclib as long as no additional anti-cancer therapy or supportive care that would confound the interpretation of any observed toxicity or side effect is given.

Patients who receive at least 80% of prescribed therapy during the 6 month feasibility period but who progress prior to completing the 12 months of therapy may be considered evaluable for safety and feasibility, as long as no additional anti-cancer therapy or supportive care that would confound the interpretation of any observed toxicity or side effect is given. Patients should have completed all of the clinical and laboratory monitoring requirements specified by the protocol up to the time of disease progression for them to be considered evaluable for safety and feasibility.

Patients who receive less than 80% of the protocol specified therapy and who go off treatment for reasons other than toxicity (e.g. progressive disease, withdrawal of consent etc.) will be considered in evaluable for estimating the safety and feasibility and will be replaced.

Patients who complete all therapy during the 6 month feasibility period but who fail to comply with all the specified clinical and laboratory monitoring requirements for the dose finding period may be considered inevaluable by the study chair for estimating the feasibility and may be replaced.

13.2 **Early Efficacy**

The 1-year overall survival (OS) of the two strata will be considered separately. For each, the 1-year OS will be estimated and 95% confidence intervals will be given. All patients enrolled will be considered eligible for the estimation of the 1-year OS. In our most recent HGG-01 study, OS was approximately 35% and 80% for DIPG and HGG, respectively. Available data report OS is 7-17 months and 12-24 months for DIPG and HGG respectively. [2,26,100] Conservatively assuming only 12 patients per group, this will yield confidence intervals with width 46% and 55%, respectively. In addition to the 1-year OS, Kaplan-Meier curves will be generated for each stratum. The primary objective of this part of the study will be assessed based on the intent-to-treat (ITT) hypothesis. That is, any eligible patient who receives any Ribociclib will be included in the primary analysis

13.2.1 Progression-free survival (PFS) is a secondary endpoint and is defined as the time from initiation of treatment to the earliest date of failure (disease progression, death from any cause, or second malignancy) for patients who fail and to the last assessment date for patients who have not failed. Patients who start other anti-cancer therapy prior to disease progression will be censored in the Kaplan-Meier estimate of PFS as of the date the alternative therapy began. Patients who have not failed (died) at the time of analyses will be censored at their last date of contact in the Kaplan-Meier estimate of the PFS (overall survival) distribution.

13.2.2 Definition of an Evaluable Patient (Efficacy)

All eligible patients who receive at least 1 dose of Ribociclib are evaluable for assessing overall survival, as well as for evaluating progression free survival and objective response rates

13.3 **Projected Accrual Rate and Study Duration**

[redacted]

REFERENCES

1. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. *Lancet Oncol.* 2006;7(3):241-248.
2. Jansen MH, van Vuurden DG, Vandertop WP, Kaspers GJ. Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. *Cancer Treat Rev.* 2012;38(1):27-35.
3. Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. Cyclin D as a therapeutic target in cancer. *Nat Rev Cancer.* 2011;11(8):558-572.
4. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet.* 2012;44(3):251-253.
5. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature.* 2012;482(7384):226-231.
6. Buczkowicz P, Hoeman C, Rakopoulos P, et al. Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. *Nat Genet.* 2014.
7. Fontebasso AM, Papillon-Cavanagh S, Schwartzentruber J, et al. Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma. *Nat Genet.* 2014.
8. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell.* 2013;155(2):462-477.
9. Paugh BS, Broniscer A, Qu C, et al. Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. *J Clin Oncol.* 2011;29(30):3999-4006.
10. Taylor KR, Mackay A, Truffaux N, et al. Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma. *Nat Genet.* 2014.
11. Grill J, Puget S, Andreiuolo F, Philippe C, MacConaill L, Kieran MW. Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. *Pediatr Blood Cancer.* 2012;58(4):489-491.
12. Guillamo JS, Monjour A, Taillandier L, et al. Brainstem gliomas in adults: prognostic factors and classification. *Brain.* 2001;124(Pt 12):2528-2539.
13. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *N Engl J Med.* 1993;328(24):1725-1731.
14. Caretti V, Bugiani M, Freret M, et al. Subventricular spread of diffuse intrinsic pontine glioma. *Acta Neuropathol.* 2014;128(4):605-607.
15. Buczkowicz P, Bartels U, Bouffet E, Becher O, Hawkins C. Histopathological spectrum of paediatric diffuse intrinsic pontine glioma: diagnostic and therapeutic implications. *Acta Neuropathol.* 2014;128(4):573-581.
16. Massimino M, Spreafico F, Biassoni V, et al. Diffuse pontine gliomas in children: changing strategies, changing results? A mono-institutional 20-year experience. *J Neurooncol.* 2008;87(3):355-361.
17. Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD. Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. *Neurosurgery.* 1993;33(6):1026-1029;

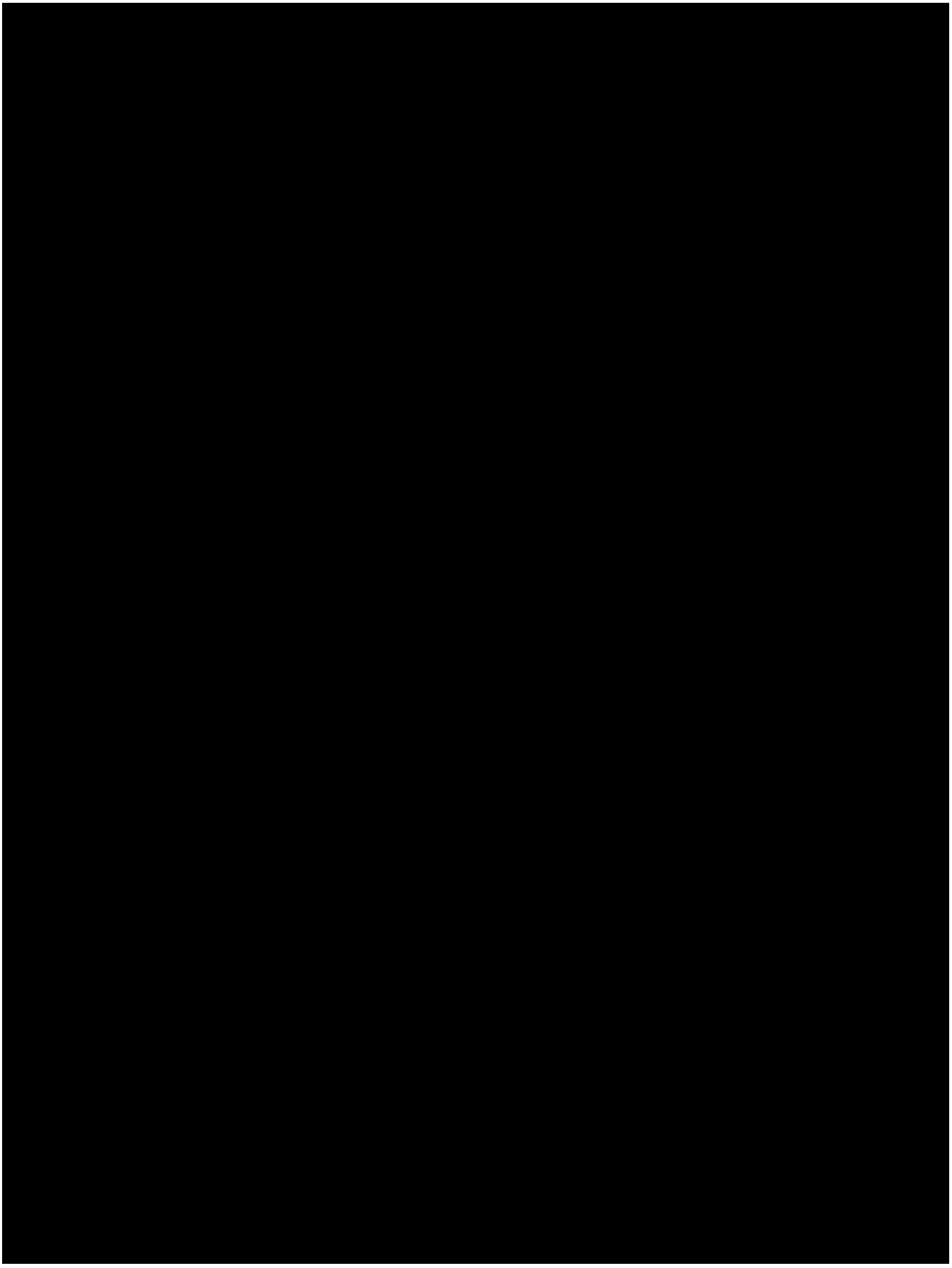
discussion 1029-1030.
18. Roujeau T, Machado G, Garnett MR, et al. Stereotactic biopsy of diffuse pontine lesions in children. *J Neurosurg.* 2007;107(1 Suppl):1-4.
19. Puget S, Philippe C, Bax DA, et al. Mesenchymal transition and PDGFRA amplification/mutation are key distinct oncogenic events in pediatric diffuse intrinsic pontine gliomas. *PLoS One.* 2012;7(2):e30313.
20. Grill J, Puget S, Andreiuolo F, Philippe C, MacConaill L, Kieran MW. Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. *Pediatr Blood Cancer.* 2012;58(4):489-491.
21. Robison NJ, Kieran MW. Diffuse intrinsic pontine glioma: a reassessment. *J Neurooncol.* 2014;119(1):7-15.
22. Broniscer A, Baker JN, Baker SJ, et al. Prospective collection of tissue samples at autopsy in children with diffuse intrinsic pontine glioma. *Cancer.* 2010;116(19):4632-4637.
23. Angelini P, Hawkins C, Laperriere N, Bouffet E, Bartels U. Post mortem examinations in diffuse intrinsic pontine glioma: challenges and chances. *J Neurooncol.* 2011;101(1):75-81.
24. Alabran JL, Hooper JE, Hill M, et al. Overcoming autopsy barriers in pediatric cancer research. *Pediatr Blood Cancer.* 2013;60(2):204-209.
25. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2008. Source: Central Brain Tumor Registry of the United States, Hinsdale, IL. website: http://www.cbtrus.org2012/.
26. Broniscer A, Gajjar A. Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist. *Oncologist.* 2004;9(2):197-206.
27. Cohen KJ, Heideman RL, Zhou T, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. *Neuro Oncol.* 2011;13(4):410-416.
28. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.
29. Paugh BS, Qu C, Jones C, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol.* 2010;28(18):3061-3068.
30. Ivanchuk SM, Rutka JT. The cell cycle: accelerators, brakes, and checkpoints. *Neurosurgery.* 2004;54(3):692-699; discussion 699-700.
31. Choi YJ, Anders L. Signaling through cyclin D-dependent kinases. *Oncogene.* 2013.
32. Lange CA, Yee D. Killing the second messenger: targeting loss of cell cycle control in endocrine-resistant breast cancer. *Endocr Relat Cancer.* 2011;18(4):C19-24.
33. Grasso CS, Tang Y, Truffaux N, et al. Functionally defined therapeutic targets in diffuse intrinsic pontine glioma. *Nat Med.* 2015.
34. Barrow J, Adamowicz-Brice M, Cartmill M, et al. Homozygous loss of ADAM3A revealed by genome-wide analysis of pediatric high-grade glioma and diffuse intrinsic pontine gliomas. *Neuro Oncol.* 2011;13(2):212-222.
35. the St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome P. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genet.* 2014.
36. Goldhoff P, Clarke J, Smirnov I, et al. Clinical stratification of glioblastoma based on

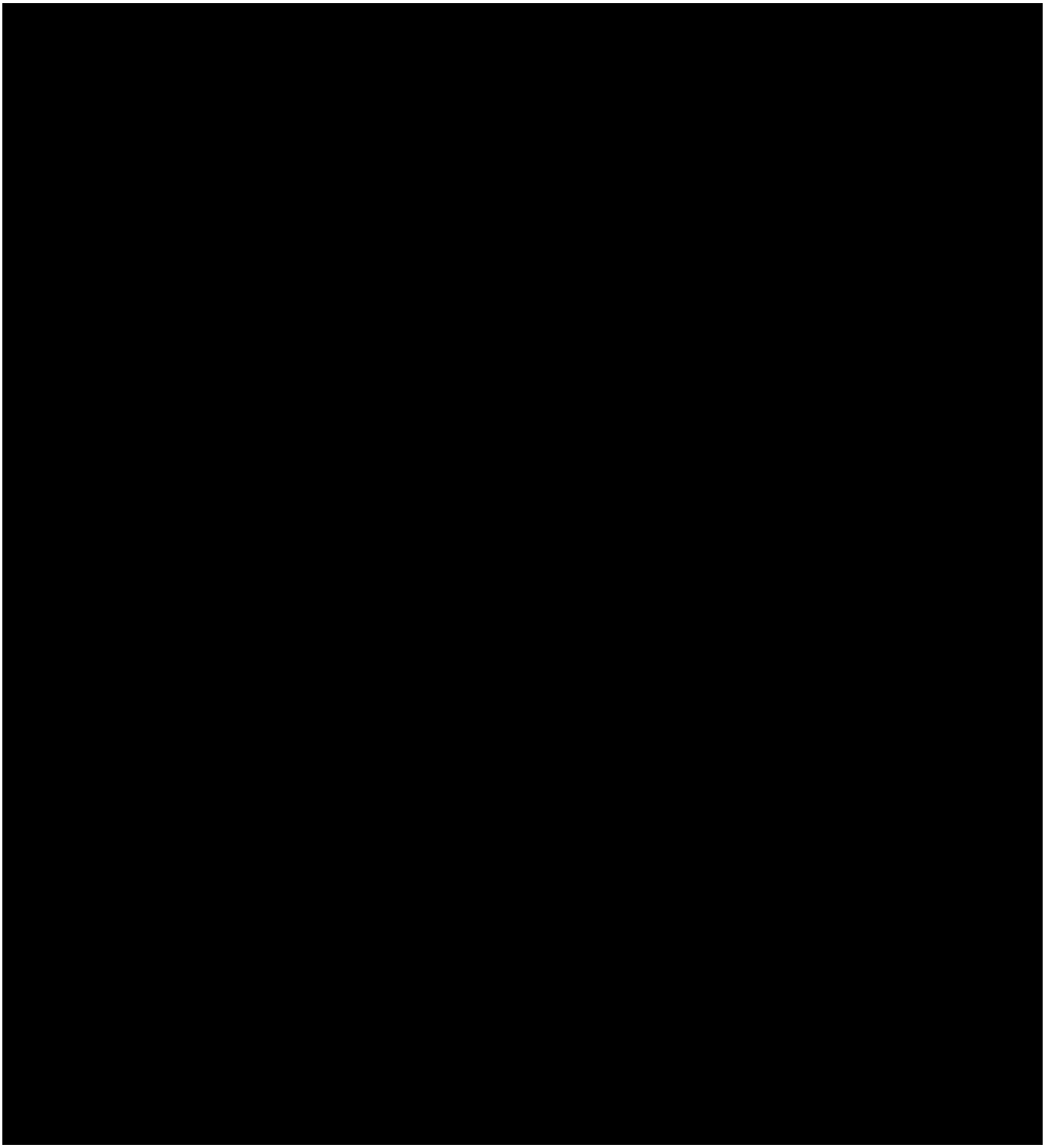
alterations in retinoblastoma tumor suppressor protein (RB1) and association with the proneural subtype. *J Neuropathol Exp Neurol.* 2012;71(1):83-89.
37. Aoki Y, Hashizume R, Ozawa T, et al. An experimental xenograft mouse model of diffuse pontine glioma designed for therapeutic testing. *J Neurooncol.* 2012;108(1):29-35.
38. Barton KL, Misuraca K, Cordero F, et al. PD-0332991, a CDK4/6 inhibitor, significantly prolongs survival in a genetically engineered mouse model of brainstem glioma. *PLoS One.* 2013;8(10):e77639.
39. Paugh BS, Qu C, Jones C, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol.* 2010;28(18):3061-3068.
40. Stroink AR, Hoffman HJ, Hendrick EB, Humphreys RP. Diagnosis and management of pediatric brain-stem gliomas. *J Neurosurg.* 1986;65(6):745-750.
41. Epstein F, McCleary EL. Intrinsic brain-stem tumors of childhood: surgical indications. *J Neurosurg.* 1986;64(1):11-15.
42. Kramm CM, Butenhoff S, Rausche U, et al. Thalamic high-grade gliomas in children: a distinct clinical subset? *Neuro Oncol.* 2011;13(6):680-689.
43. Wang ZJ, Rao L, Bhambhani K, et al. Diffuse intrinsic pontine glioma biopsy: a single institution experience. *Pediatr Blood Cancer.* 2015;62(1):163-165.
44. Cage TA, Samagh SP, Mueller S, et al. Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children. *Childs Nerv Syst.* 2013;29(8):1313-1319.
45. Dellaretti M, Reyns N, Touzet G, et al. Stereotactic biopsy for brainstem tumors: comparison of transcerebellar with transfrontal approach. *Stereotactic and functional neurosurgery.* 2012;90(2):79-83.
46. Rajshekhar V, Moorthy RK. Status of stereotactic biopsy in children with brain stem masses: insights from a series of 106 patients. *Stereotactic and functional neurosurgery.* 2010;88(6):360-366.
47. Pirotte BJ, Lubansu A, Massager N, Wikler D, Goldman S, Levivier M. Results of positron emission tomography guidance and reassessment of the utility of and indications for stereotactic biopsy in children with infiltrative brainstem tumors. *J Neurosurg.* 2007;107(5 Suppl):392-399.
48. Pincus DW, Richter EO, Yachnis AT, Bennett J, Bhatti MT, Smith A. Brainstem stereotactic biopsy sampling in children. *J Neurosurg.* 2006;104(2 Suppl):108-114.
49. Samadani U, Judy KD. Stereotactic brainstem biopsy is indicated for the diagnosis of a vast array of brainstem pathology. *Stereotactic and functional neurosurgery.* 2003;81(1-4):5-9.
50. Warren KE, Patronas N, Aikin AA, Albert PS, Balis FM. Comparison of one-, two-, and three-dimensional measurements of childhood brain tumors. *J Natl Cancer Inst.* 2001;93(18):1401-1405.
51. Warren KE, Poussaint TY, Vezina G, et al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the response assessment in pediatric neuro-oncology (RAPNO) working group. *Pediatr Blood Cancer.* 2013;60(9):1397-1401.
52. Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* 1990;8(7):1277-1280.

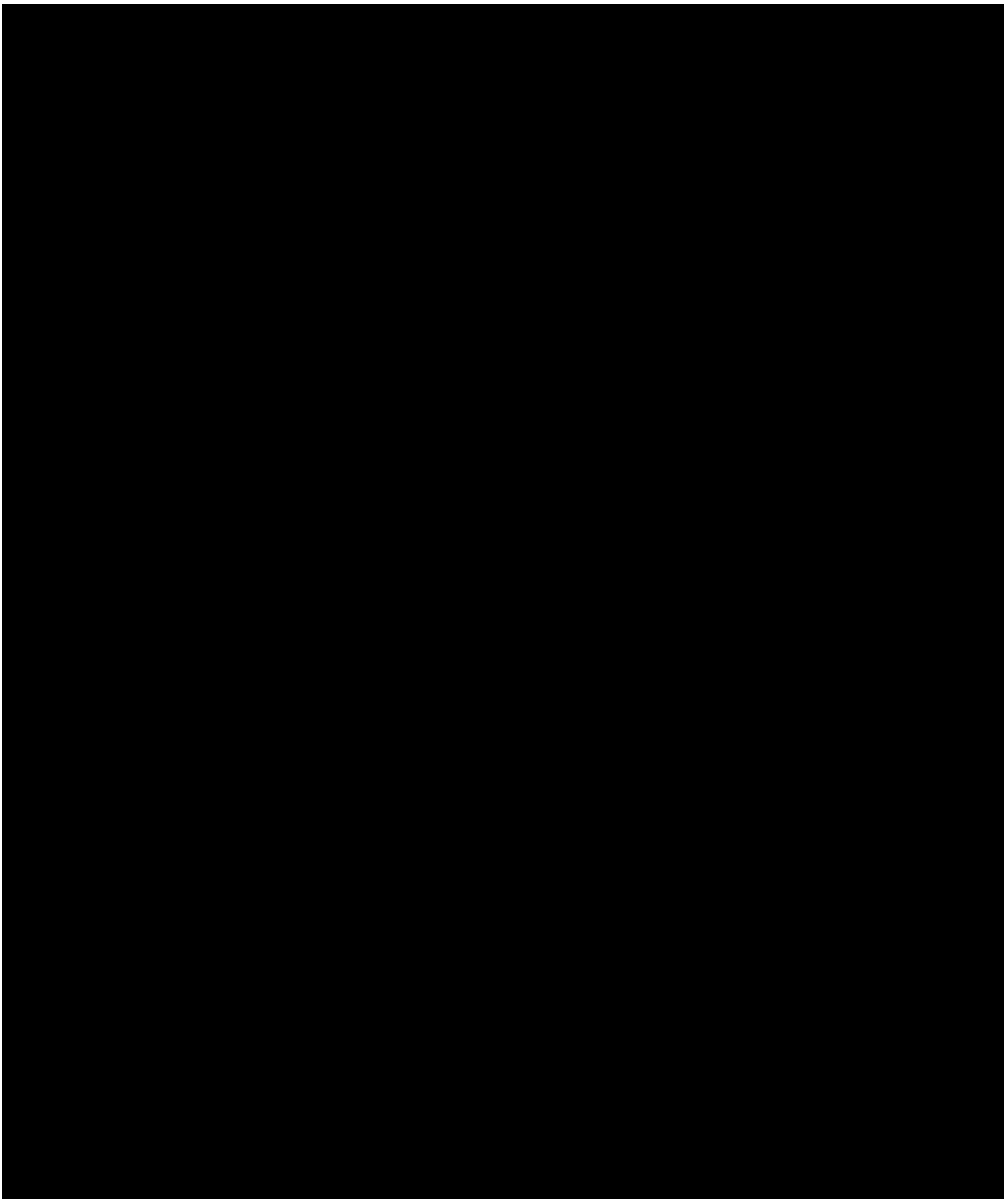
53. Fink J, Born D, Chamberlain MC. Pseudoprogression: relevance with respect to treatment of high-grade gliomas. *Curr Treat Options Oncol.* 2011;12(3):240-252.
54. Mangla R, Singh G, Ziegelitz D, et al. Changes in Relative Cerebral Blood Volume 1 Month after Radiation-Temozolomide Therapy Can Help Predict Overall Survival in Patients with Glioblastoma 1. *Radiology.* 2010;256(2):575-584.
55. Prabhu SP, Ng S, Vajapeyam S, et al. DTI assessment of the brainstem white matter tracts in pediatric BSG before and after therapy. *Child's Nervous System.* 2011;27(1):11-18.
56. Chen H, Panigrahy A, Dhall G, Finlay J, Nelson M, Blüml S. Apparent diffusion and fractional anisotropy of diffuse intrinsic brain stem gliomas. *American Journal of Neuroradiology.* 2010;31(10):1879-1885.
57. Sturm D, Bender S, Jones DT, et al. Paediatric and adult glioblastoma: multiform (epi)genomic culprits emerge. *Nat Rev Cancer.* 2014;14(2):92-107.
58. Mueller S, Phillips J, Onar-Thomas A, et al. PTEN promoter methylation and activation of the PI3K/Akt/mTOR pathway in pediatric gliomas and influence on clinical outcome. *Neuro Oncol.* 2012;14(9):1146-1152.
59. Liang J, Slingerland JM. Multiple roles of the PI3K/PKB (Akt) pathway in cell cycle progression. *Cell Cycle.* 2003;2(4):339-345.
60. Khuong-Quang DA, Buczkowicz P, Rakopoulos P, et al. K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas. *Acta Neuropathol.* 2012;124(3):439-447.
61. Bender S, Tang Y, Lindroth AM, et al. Reduced H3K27me3 and DNA hypomethylation are major drivers of gene expression in K27M mutant pediatric high-grade gliomas. *Cancer Cell.* 2013;24(5):660-672.
62. Mishina Y, Crombie R, Bradley A, Behringer RR. Multiple roles for activin-like kinase-2 signaling during mouse embryogenesis. *Dev Biol.* 1999;213(2):314-326.
63. Kishigami S, Yoshikawa S, Castranio T, Okazaki K, Furuta Y, Mishina Y. BMP signaling through ACVRI is required for left-right patterning in the early mouse embryo. *Dev Biol.* 2004;276(1):185-193.
64. Song GA, Kim HJ, Woo KM, et al. Molecular consequences of the ACVR1(R206H) mutation of fibrodysplasia ossificans progressiva. *J Biol Chem.* 2010;285(29):22542-22553.
65. Kaplan FS, Xu M, Seemann P, et al. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. *Hum Mutat.* 2009;30(3):379-390.
66. Stevens MC, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. *Eur J Cancer.* 1998;34(5):694-698.
67. Landier W, Bhatia S. Cancer survivorship: a pediatric perspective. *Oncologist.* 2008;13(11):1181-1192.
68. Nandagopal R, Laverdière C, Mulrooney D, Hudson MM, Meacham L. Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Horm Res.* 2008;69(2):65-74.
69. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009;101(13):946-958.
70. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology,

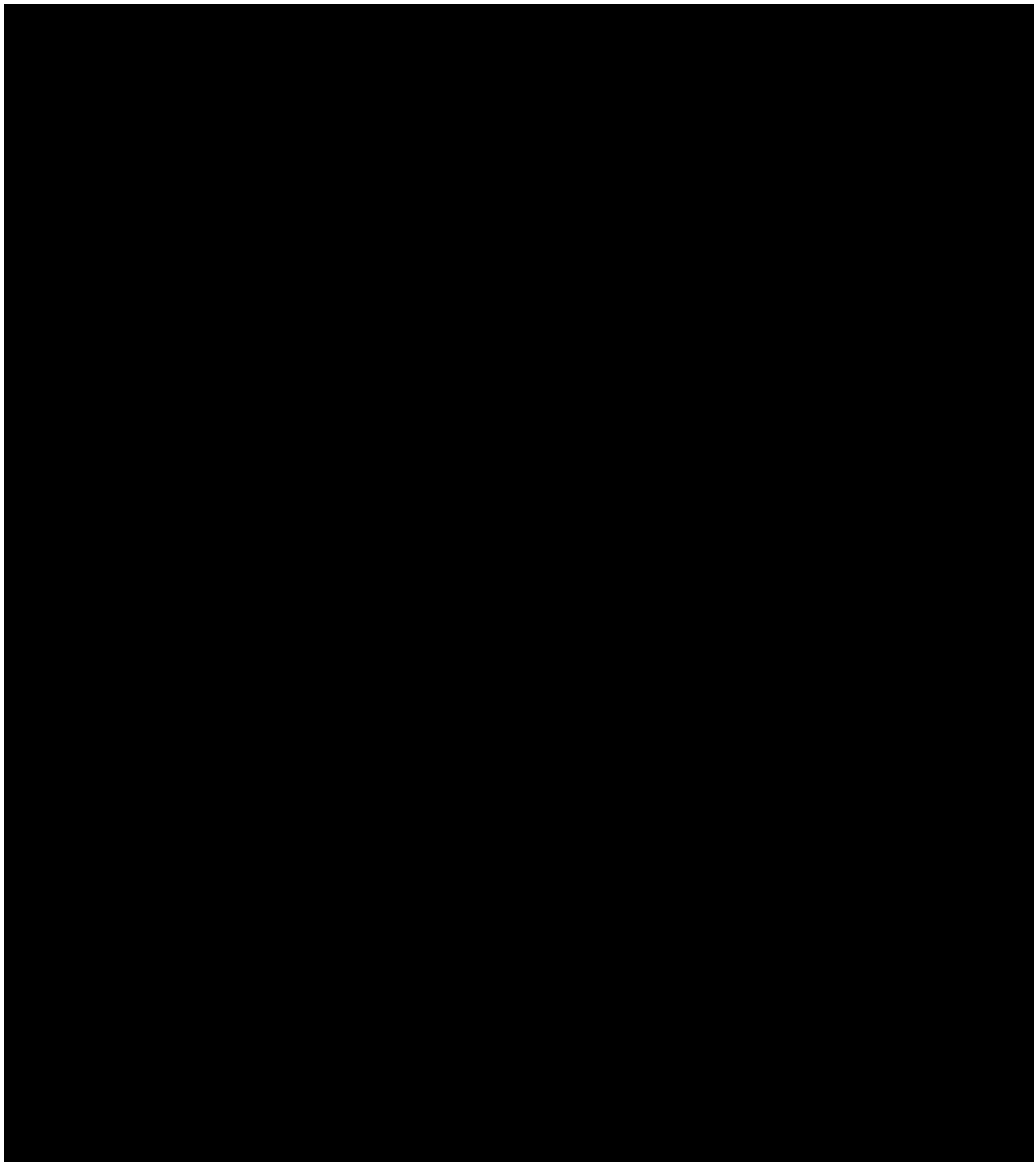
therapy, and late effects. *Semin Radiat Oncol.* 2010;20(1):58-66.
71. Haller MJ, Schatz DA. Endocrine complications of childhood cancer therapy: evaluation and management. *Pediatr Endocrinol Rev.* 2007;4(3):196-204.
72. Rose SR, Schreiber RE, Kearney NS, et al. Hypothalamic dysfunction after chemotherapy. *J Pediatr Endocrinol Metab.* 2004;17(1):55-66.
73. Darzy KH, Shalet SM. Hypopituitarism following Radiotherapy Revisited. *Endocr Dev.* 2009;15:1-24.
74. Fouladi M, Wallace D, Langston JW, et al. Survival and functional outcome of children with hypothalamic/chiasmatic tumors. *Cancer.* 2003;97(4):1084-1092.
75. Laughton S, Merchant T, Sklar C, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol.* 2008;26(7):1112-1118.
76. van Dijk IW, Cardous-Ubbink MC, van der Pal HJ, et al. Dose-effect relationships for adverse events after cranial radiation therapy in long-term childhood cancer survivors. *Int J Radiat Oncol Biol Phys.* 2013;85(3):768-775.
77. Merchant TE, Williams T, Smith JM, et al. Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. *Int J Radiat Oncol Biol Phys.* 2002;54(1):45-50.
78. Spoudeas HA. Growth and endocrine function after chemotherapy and radiotherapy in childhood. *Eur J Cancer.* 2002;38(13):1748-1759; discussion 1760-1741.
79. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab.* 1999;84(12):4472-4479.
80. Ricardi U, Corrias A, Einaudi S, et al. Thyroid dysfunction as a late effect in childhood medulloblastoma: a comparison of hyperfractionated versus conventionally fractionated craniospinal radiotherapy. *Int J Radiat Oncol Biol Phys.* 2001;50(5):1287-1294.
81. Spoudeas H, Charmandari E, Brook C. Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posterior fossa tumours. *Med Pediatr Oncol.* 2003;40(4):224-229.
82. Meirow D. Reproduction post-chemotherapy in young cancer patients. *Mol Cell Endocrinol.* 2000;169(1-2):123-131.
83. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA.* 2007;297(24):2705-2715.
84. Rosendahl M, Andersen CY, la Cour Freiesleben N, Juul A, Lossl K, Andersen AN. Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age. *Fertil Steril.* 2010;94(1):156-166.
85. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? *Lancet Oncol.* 2005;6(4):209-218.
86. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer.* 1999;86(4):697-709.
87. La Marca A, Sighinolfi G, Radi D, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). *Hum Reprod Update.* 2010;16(2):113-130.
88. van Rooij IA, Broekmans FJ, Scheffer GJ, et al. Serum antimullerian hormone levels best

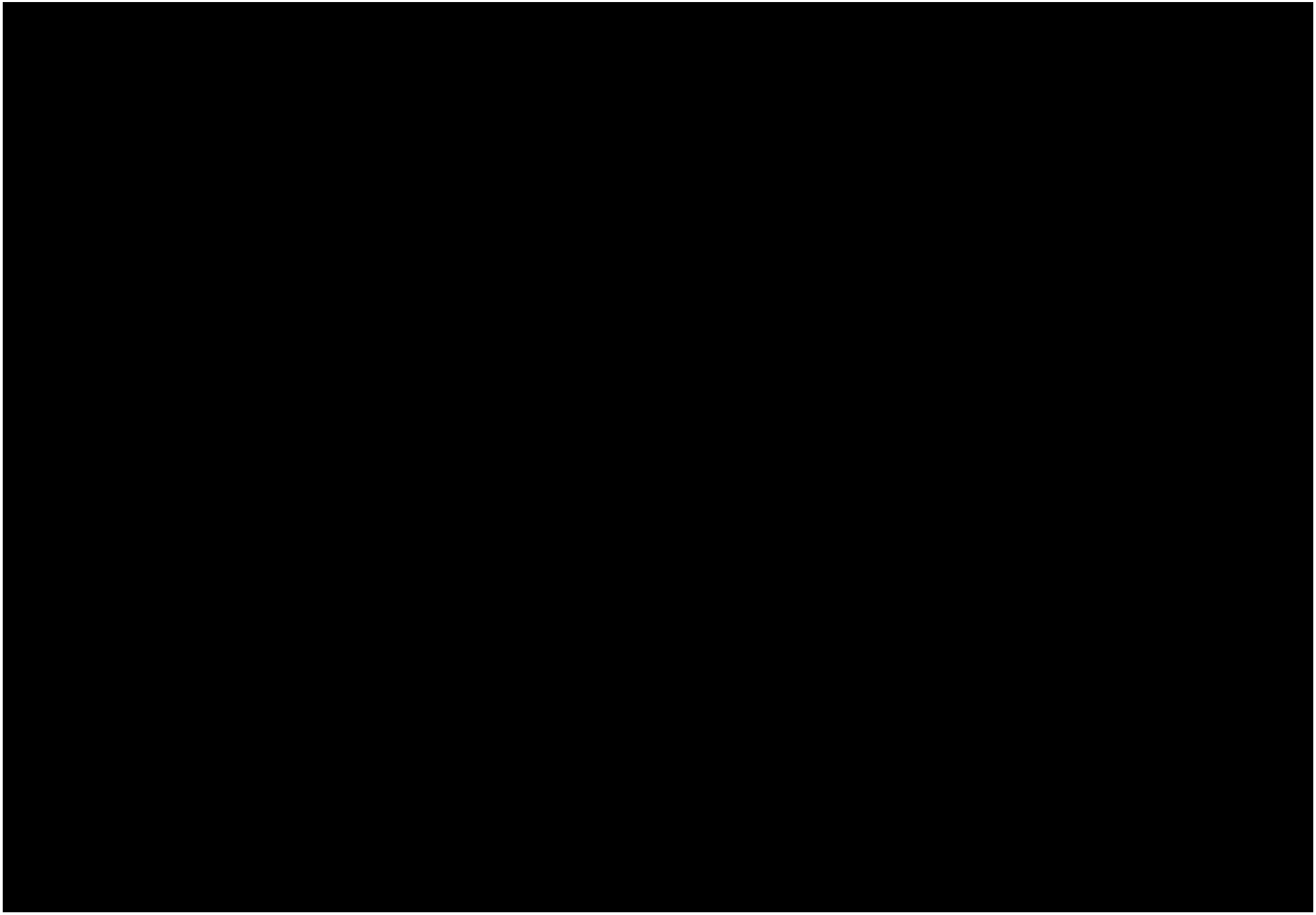
reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. *Fertil Steril.* 2005;83(4):979-987.
89. Hagen CP, Aksglaede L, Sorensen K, et al. Serum levels of anti-Mullerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. *J Clin Endocrinol Metab.* 2010;95(11):5003-5010.
90. Pui CH, Gajjar AJ, Kane JR, Qaddoumi IA, Pappo AS. Challenging issues in pediatric oncology. *Nat Rev Clin Oncol.* 2011;8(9):540-549.
91. Jacobson CJ, Farrell JE, Kashikar-Zuck S, Seid M, Verkamp E, Dewitt EM. Disclosure and self-report of emotional, social, and physical health in children and adolescents with chronic pain--a qualitative study of PROMIS pediatric measures. *Journal of pediatric psychology.* 2013;38(1):82-93.
92. Hinds PS, Nuss SL, Ruccione KS, et al. PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. *Pediatr Blood Cancer.* 2013;60(3):402-408.
93. Gipson DS, Selewski DT, Massengill SF, et al. Gaining the PROMIS perspective from children with nephrotic syndrome: a Midwest pediatric nephrology consortium study. *Health Qual Life Outcomes.* 2013;11:30.
94. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care.* 2007;45(5 Suppl 1):S3-S11.
95. Irwin DE, Gross HE, Stucky BD, et al. Development of six PROMIS pediatrics proxy-report item banks. *Health Qual Life Outcomes.* 2012;10:22.
96. DeWitt EM, Stucky BD, Thissen D, et al. Construction of the eight-item patient-reported outcomes measurement information system pediatric physical function scales: built using item response theory. *Journal of clinical epidemiology.* 2011;64(7):794-804.
97. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(6):803-820.
98. Selewski DT, Collier DN, MacHardy J, et al. Promising insights into the health related quality of life for children with severe obesity. *Health Qual Life Outcomes.* 2013;11:29.
99. Thissen D, Varni JW, Stucky BD, Liu Y, Irwin DE, Dewalt DA. Using the PedsQL 3.0 asthma module to obtain scores comparable with those of the PROMIS pediatric asthma impact scale (PAIS). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2011;20(9):1497-1505.
100. Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro Oncol.* 2011;13(3):317-323.

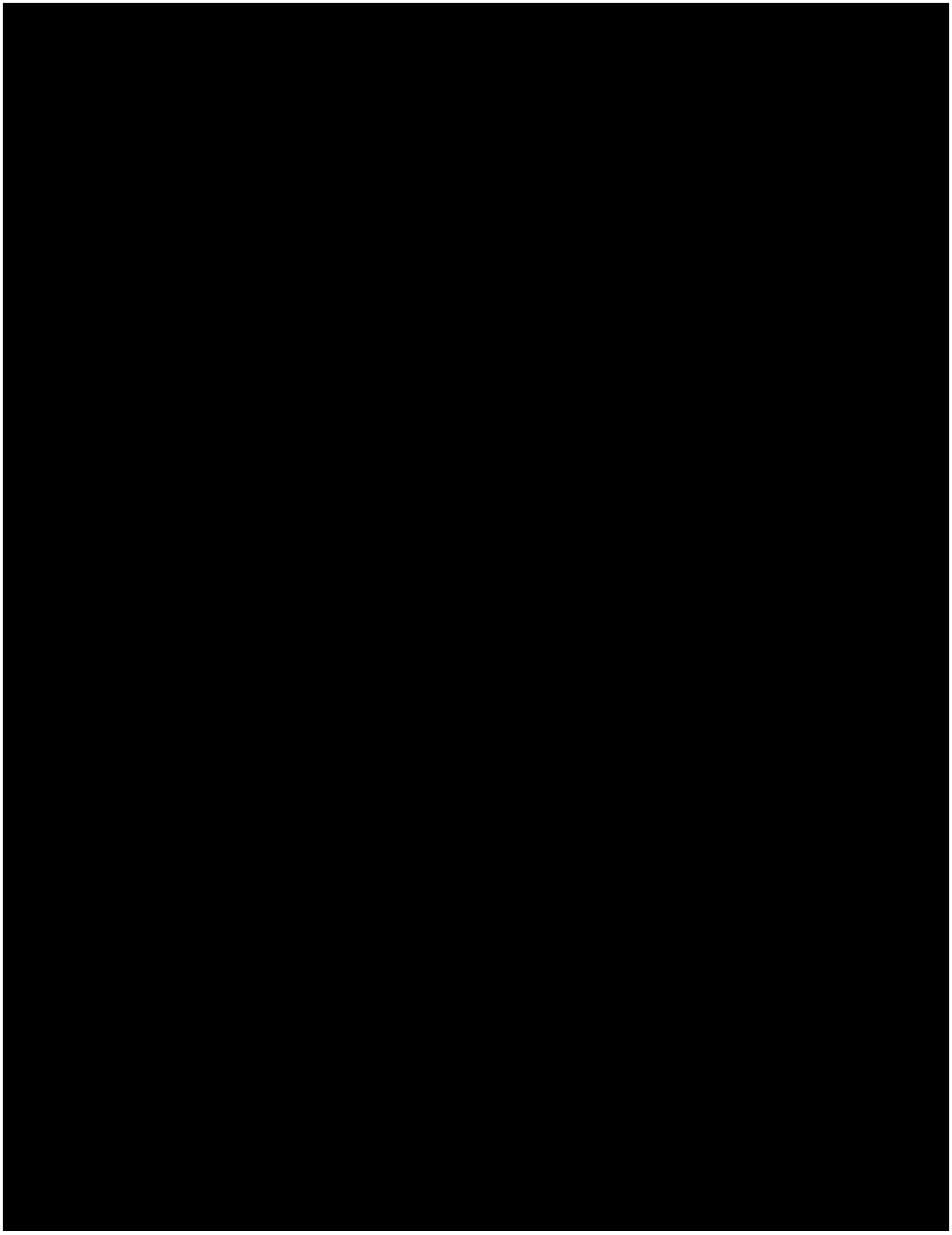


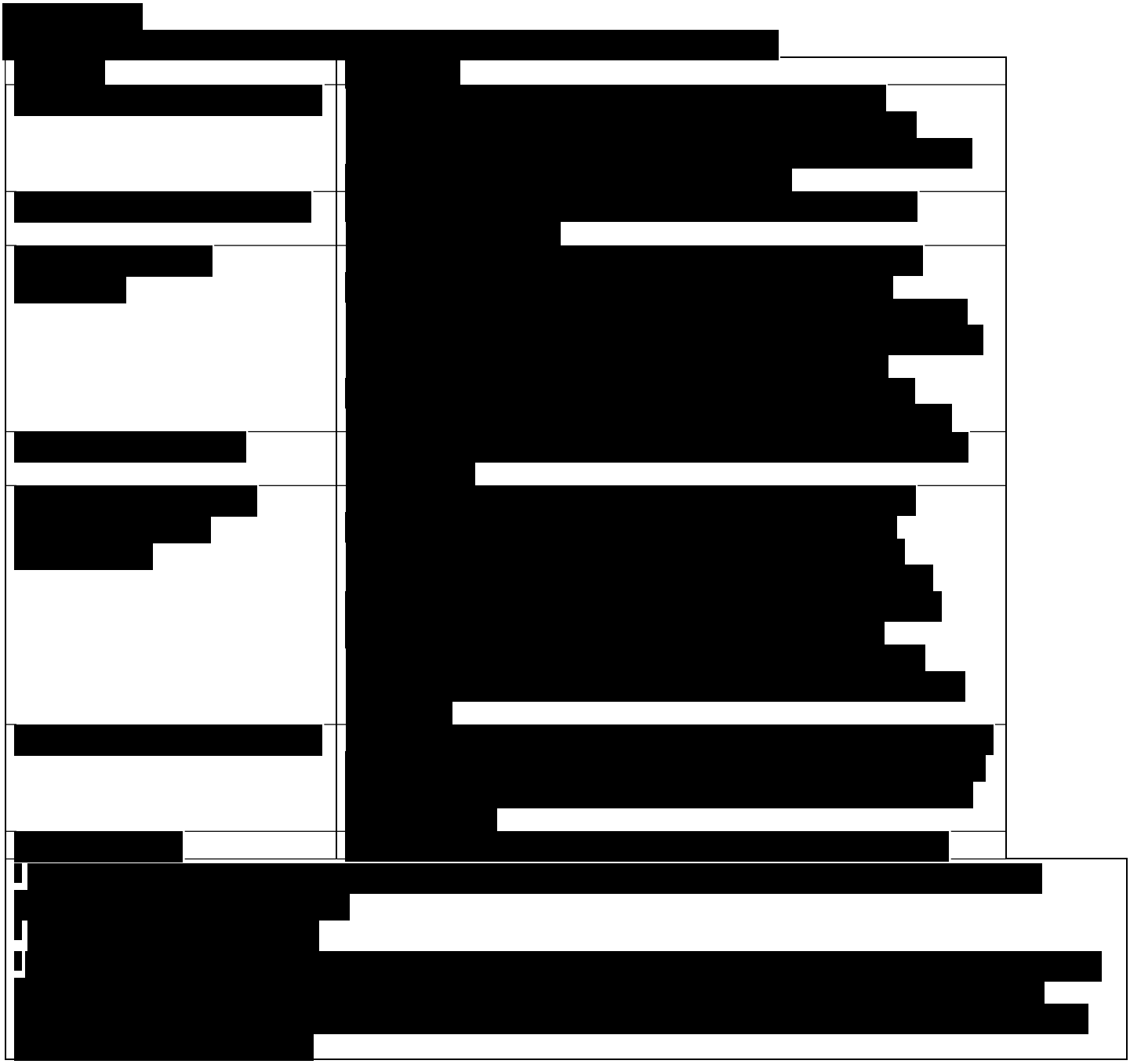




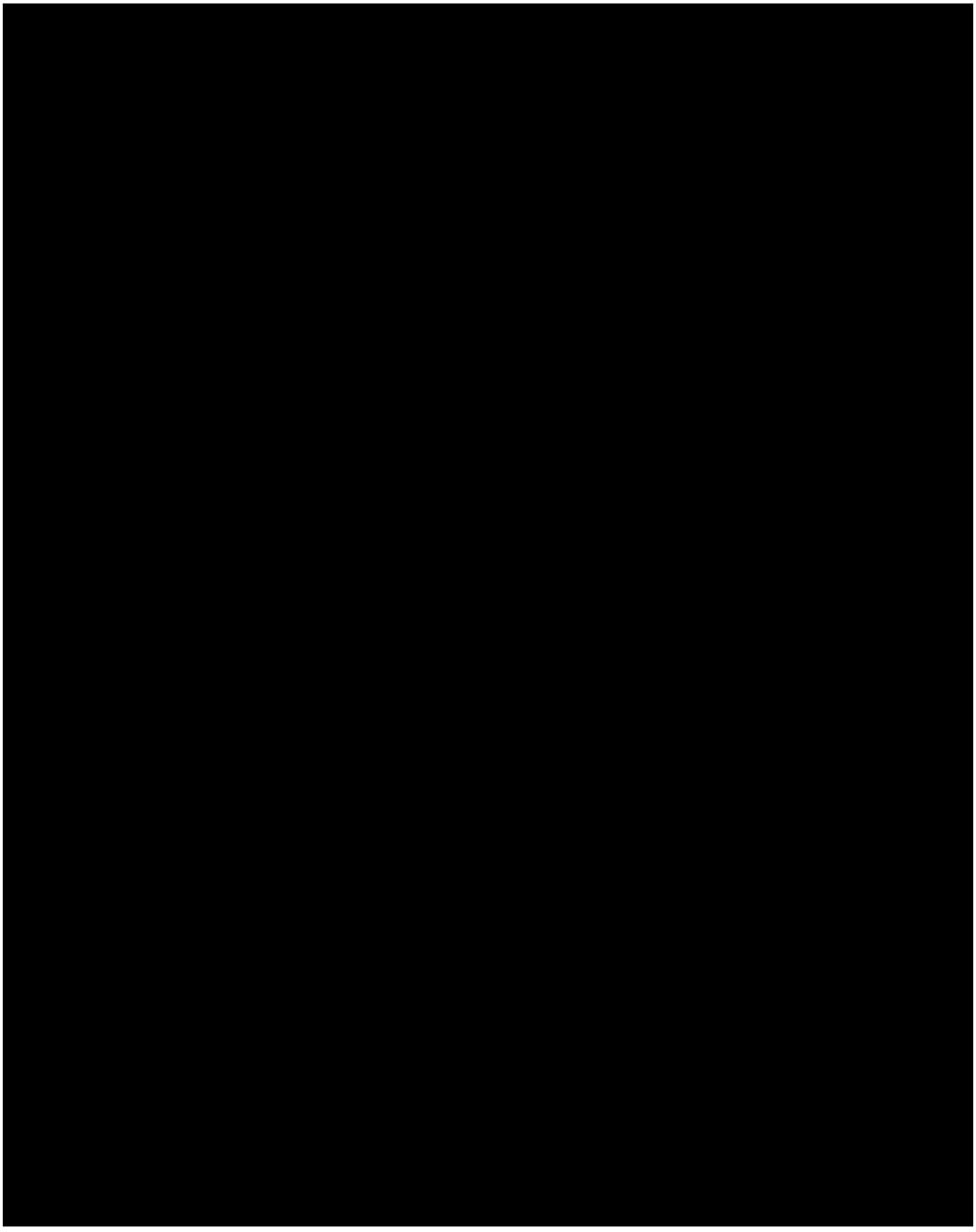


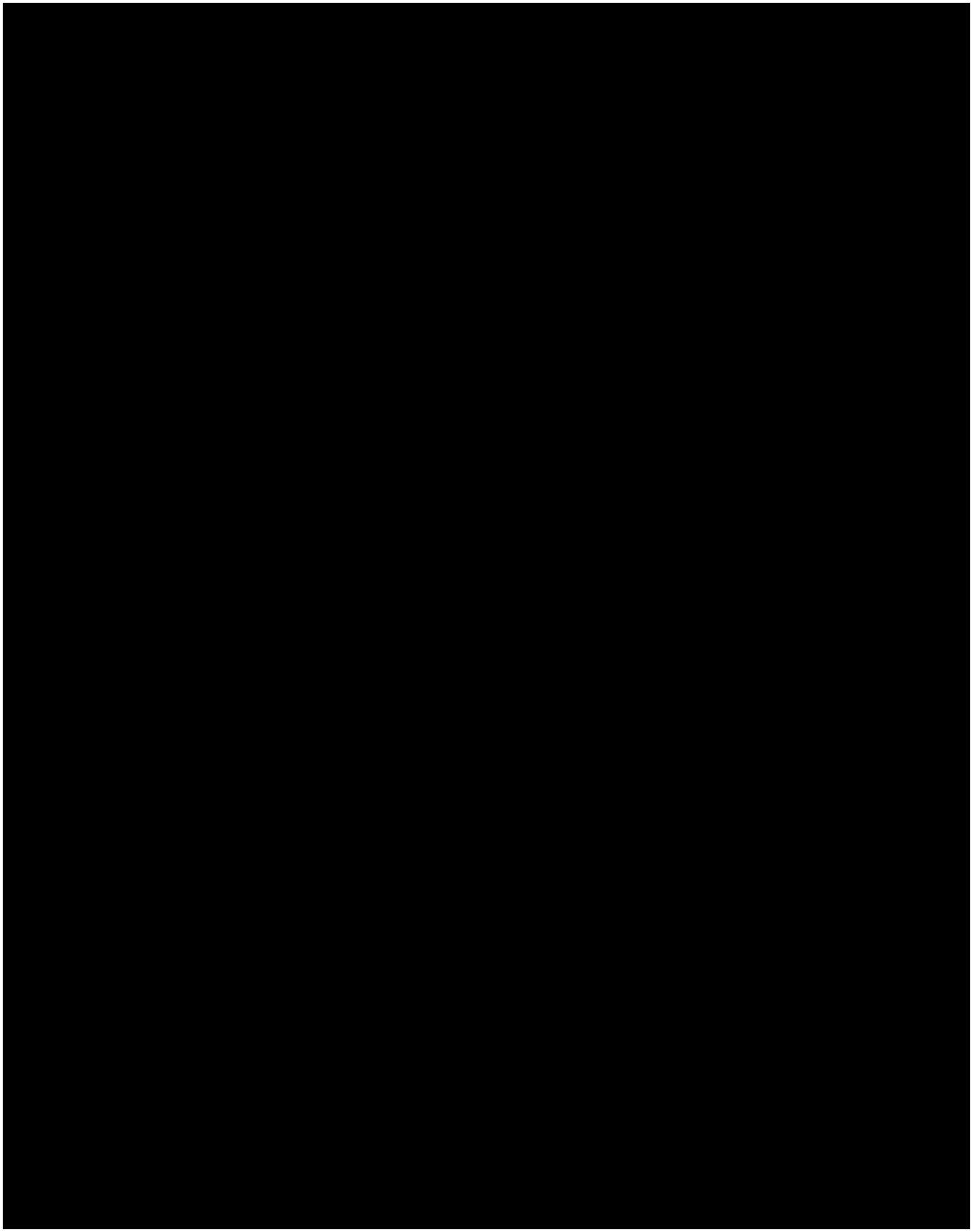






[redacted]





[redacted]