Medicinrådet

Bilag til Medicinrådets anbefaling vedr. nivolumab kombineret med gemcitabin og cisplatin til førstelinjebehandling af lokalavanceret eller metastatisk urotelialt karcinom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab kombineret med gemcitabin og cisplatin
2. Forhandlingsnotat fra Amgros vedr. nivolumab kombineret med gemcitabin og cisplatin
3. Ansøgers endelige ansøgning vedr. nivolumab kombineret med gemcitabin og cisplatin

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Virum d. 23.09.24

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab kombineret med gemcitabin og cisplatin til førstelinjebehandling af lokalavanceret eller metastatisk urotelialt karcinom.

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. nivolumab i kombination med cisplatin og gemcitabin er indiceret til førstelinjebehandling af voksne patienter med inoperabelt eller metastatisk urotelialt karcinom planlagt til 23. oktober 2024.

Indledningsvist vil BMS anerkende Medicinrådet for det store arbejde, der er gjort med at nedbringe sagsbehandlingstiden, samt at sagsbehandlingen for denne anbefaling er holdt indenfor de forventede 14 uger.

BMS har dog 2 væsentlige kommentarer til den foreliggende vurderingsrapport, relateret til afsnittet omkring komparator og opsummeringen af den samlede sag:

1) **Vedr. Medicinrådets opsummering omkring effekt på overlevelse (OS)**

BMS finder det nødvendigt at fremhæve Medicinrådets sammenligning af CheckMate-901 studiet med IMvigor130 og Keynote-361, som i vurderingsrapporten fremstår ufuldstændig og potentielt vildledende.

I opsummeringen skriver Medicinrådet:

”*To andre lignende RCTs kunne ikke påvise statistisk signifikant effekt på overlevelse af tillæg af immunterapi (pembrolizumab og atezolizumab) til standard platinbaseret kemoterapi i første linje*.”

Denne sætning står i kontrast til den vurdering Medicinrådet selv laver senere i rapporten, hvor det konkluderes, at studierne ikke er direkte sammenlignelige på grund af flere, betydelige forskelle. Der er især en afgørende forskel i patientpopulationer mellem studierne, da CheckMate-901 kun inkluderede cisplatin-egnede og ikke både cisplatin-egnede og -uegnede. Det betyder, at patienterne i Checkmate-901 udelukkende behandles med gemcitabine plus cisplatin (GemCis), hvor de to andre studier behandler med enten GemCis eller gemcitabine plus carboplatin (GemCarbo; i alt 56%[1] og 70%[2] af patienterne). Idet kemoterapibehandlingen ikke er den samme mellem de pågældende studier og Checkmate 901, kan resultaterne ikke direkte sammenlignes. BMS fremhæver desuden i ansøgningen netop, at der i en eksplorativ analyse af IMvigor130 blev fundet en overlevelsesgevinst for subgruppen af patienter, der modtog kombinationen af atezolizumab og GemCis sammenlignet med GemCis alene (HR = 0,73; 95% CI, 0,54, 0,98) versus atezolizumab kombineret med GemCarbo sammenlingnet med GemCarbo alene (HR = 0,91 95% CI, 0,75; 1,10)[3].

Resultaterne fra IMvigor130 underbygger således robustheden af resultatet fra CheckMate-901 og ikke modsat, som det fremgår af vurderingsrapporten.

BMS undrer sig over, at denne essentielle del af sammenligningen mellem studieresultaterne er udeladt af vurderingsrapporten, da den fremgår af ansøgningen og Galsky et al. artiklen[3] refereres.

2) Vedr. Medicinrådets vurdering af komparator.

Medicinrådet påpeger, at frekvensen af vedligeholdelsesbehandling i Checkmate-901 er ca. 10-15% point lavere i studiet end i dansk klinisk praksis, som Medicinrådet derimod mener er bedre afspejlet i EV-302[4]. Medicinrådet mener, at denne forskel kan betyde, at især overlevelsesraten (OS) i Checkmate-901 underestimeres i komparatorarmen relativt til dansk klinisk praksis. BMS påpeger, at på trods af, at der i Checkmate-901 rigtigt nok er færre patienter (27,6%), der modtager vedligeholdelsesbehandling med PD-1/PDL-1-hæmmer sammenlignet med EV-302 (41,6%), så viser studierne en median OS i komparatorarmene på 18,9 mdr. i Checkmate-901 og 18,4 mdr. i EV-302, når man ser på cisplatin-eligible patienter alene[5]. Altså, en forskel på 14 dage. BMS mener derfor, at det er yderst spekulativt om OS i Checkmate-901 komparatorarmen skulle være underestimeret, på trods af den lavere rate af vedligeholdelsesbehandling relativt til dansk klinisk praksis. Tværtimod peger sammenligningen af studierne på, at den højere rate af vedligeholdelsesbehandling i EV-302 ikke giver anledning til en forbedring af OS i komparatorarmen sammenlignet med Checkmate-901.

Vi håber, Medicinrådet vil tage vores kommentarer i betragtning og justere vurderingsrapporten i overensstemmelse hermed for at sikre en retvisende og fuldstændig evaluering af nivolumab i kombination med cisplatin og gemcitabine.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Danmark

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[1] Powles T,Csőszi T, Özgüroğlu M, Matsubara N et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomized, open-label, phase 3 trial. Lancet Oncol 2021; 22:391-45. DOI: http://doi.org/10.1016/S1470-2045(21)00152-2.

[2] Galsky MD, Arija JAA, Bamias A, Davis ID et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomized, placebo-controlled phase 3 trial. Lancet 2020; 395:1547-57. DOI: http://doi.org/10.1016/S0140-6736(20)30230-0

[3]Galsky MD, Guan X, Rishipathak D, Rapaport AS, Shehata HM, Banchereau R, et al. Immunomodulatory effects and improved outcomes with cisplatin- versus carboplatinbased chemotherapy plus atezolizumab in urothelial cancer. Cell Rep Med. 2024 Jan 17:101393. DOI: http://dx.doi.org/10.1016/j.xcrm.2024.101393.

[4] Powles T, Valderrama BP, Gupta S, Bedke J et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med 2024;309:875-888. DOI: http://doi.org/10.1056/NEJMoa2312117.

[5] Supplement to: Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med 2024;390:875-88. DOI: http://doi.org/10.1056/NEJMoa2312117, Figure S4.

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23.09.2024
KLE/CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.10.2024
Leverandør	BMS
Lægemiddel	Opdivo (nivolumab)
Ansøgt indikation	Nivolumab kombineret med gemcitabin og cisplatin til førstelinjebehandling af lokalavanceret eller metastatisk urotelialt karcinom
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Opdivo (nivolumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP, (DKK)	Rabatprocent ift. AIP
Opdivo	100 mg/10 ml	1 stk.	8.523,80	[redacted]	[redacted]
Opdivo	120 mg/12 ml	1 stk.	10.228,57	[redacted]	[redacted]
Opdivo	240 mg/24 ml	1 stk.	20.457,13	[redacted]	[redacted]
Opdivo	40 mg/4 ml	1 stk.	3.431,27	[redacted]	[redacted]

Aftaleforhold

Amgros har en aftale på Opdivo, som er en del af et dynamisk udbud sammen med Keytruda (pembolizumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Bavencio (avelumab) og Imfinzi (durvalumab). I den nuværende aftale er der mulighed for prisregulering når Amgros vurderer det som fordelagtigt.

Konkurrencesituationen

Opdivo i kombination med cisplatin og gemcitabin er den først immunterapi, som vurderes til 1. linje behandling til inoperabelt eller metastatisk urotelialt karcinom.

Tabel 2 viser lægemiddeludgifter pr patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Opdivo	100 mg/10 ml	1 stk.	4,5 mg/kg hver 3 uge, IV	[redacted]	[redacted]

*Gennemsnitvægt på 78,8 kg

Status fra andre lande

Tabel 1: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of nivolumab (OPDIVO®) in combination with gemcitabine and cisplatin chemotherapy for the first-line treatment of adults with unresectable or metastatic urothelial carcinoma

Contains confidential information

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

Contact information

Contact information	
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Table of contents

Tables and figures

Abbreviations

Abbreviation	Term
1L	first line
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System

Abbreviation	Term
BICR	blinded independent central review
BMS	Bristol Myers Squibb
cHL	classical Hodgkin lymphoma
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dCTP	deoxynucleoside triphosphate
dFdCDP	gemcitabine diphosphate
dFdCTP	gemcitabine triphosphate
DKK	Danish krone
DMC	Danish Medicines Council
dMMR	mismatch repair deficient
DoCR	duration of complete response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core)
GC	gemcitabine-cisplatin
GEJC	gastro-oesophageal junction cancer
GFR	glomerular filtration rate
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio

Abbreviation	Term
ICH	International Council for Harmonisation
IMAE	immune-mediated adverse event
IQR	interquartile range
ITT	intention to treat
IV	intravenous
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIUC	muscle-invasive urothelial carcinoma
MPM	malignant pleural mesothelioma
MSI-H	microsatellite instability-high
mUC	metastatic urothelial carcinoma
NA	not applicable
NCT	National Clinical Trial
NIVO	nivolumab
NME	not meaningful estimate
NR	not relevant or not reported
NSCLC	non–small cell lung cancer
NYHA	New York Heart Association
OC	oesophageal cancer
OR	odds ratio
ORR	objective response rate
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
PD	progressive disease
PD-1	programmed cell death protein 1

Abbreviation	Term
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PR	partial response
PS	performance status
QALY	quality-adjusted life-year
QoL	quality of life
QxW	every x weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCCHN	squamous cell cancer of the head and neck
SD	stable disease
SoC	standard of care
TNM	tumour-node-metastasis
TTCR	time to complete response
TTR	time to objective response
UE	unevaluable

1 Regulatory information on the medicine

Overview of the medicine	
Proprietary name	OPDIVO®
Generic name	Nivolumab

Overview of the medicine	
Therapeutic indication as defined by EMA	OPDIVO in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
Marketing authorization holder in Denmark	Bristol Myers Squibb Hummeltoftevej 49 2830 Virum Denmark
ATC code	L01FF01
Combination therapy and/or co-medication	Yes: combined with gemcitabine-cisplatin chemotherapy
(Expected) Date of EC approval	May 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	**Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival and overall survival for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. **Adjuvant treatment of melanoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. **Non–small cell lung cancer (NSCLC)** OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation. OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.

Overview of the medicine	
	Neoadjuvant treatment of NSCLC OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%. **Malignant pleural mesothelioma (MPM)** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable MPM. **Renal cell carcinoma (RCC)** OPDIVO as monotherapy is indicated for the treatment of advanced RCC after prior therapy in adults. OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC. OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced RCC. **Classical Hodgkin lymphoma (cHL)** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant and treatment with brentuximab vedotin. **Squamous cell cancer of the head and neck (SCCHN)** OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic SCCHN in adults progressing on or after platinum-based therapy. **Urothelial carcinoma** OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. **Adjuvant treatment of urothelial carcinoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle-invasive urothelial carcinoma (MIUC) with tumour-cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC. **Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)** OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with dMMR or MSI-H metastatic CRC after prior fluoropyrimidine-based combination chemotherapy. **Oesophageal squamous cell carcinoma (OSCC)** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or

Overview of the medicine	
	metastatic oesophageal squamous cell carcinoma with tumour-cell PD-L1 expression ≥ 1%. OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC with tumour-cell PD-L1 expression ≥ 1%. OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy. **Adjuvant treatment of oesophageal cancer (OC) or gastro-oesophageal junction cancer (GEJC)** OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with OC or GEJC who have residual pathologic disease following prior neoadjuvant chemoradiotherapy. **Gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma** OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor 2–negative advanced or metastatic gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5.
Other indications that have been evaluated by the DMC (yes/no)	Yes
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Each millilitre of concentrate for solution for infusion contains 10 mg of nivolumab. One vial of 4 mL contains 40 mg of nivolumab. One vial of 10 mL contains 100 mg of nivolumab. One vial of 12 mL contains 120 mg of nivolumab. One vial of 24 mL contains 240 mg of nivolumab.

ATC = Anatomical Therapeutic Chemical Classification System; PD-L1 = programmed death-ligand 1.

2 Summary table

Summary	
Therapeutic indication relevant for the assessment	Same as the EMA indication (nivolumab in combination with gemcitabine and cisplatin (GC) chemotherapy for the first-line treatment of adults with unresectable or metastatic urothelial carcinoma)
Dosage regiment and administration	360 mg nivolumab administered intravenously over 30 minutes in combination with GC chemotherapy every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes or at 480 mg every 4 weeks over 30 minutes.
Choice of comparator	The comparator is GC chemotherapy in the 1L treatment of patients with unresectable or metastatic urothelial carcinoma. In spite of not being part of the study protocol because this was not SoC when the study was initiated, maintenance treatment with immunotherapy (including avelumab) was given to some patients with no disease progression who were undergoing 1L GC chemotherapy. This aligns with treatment guidelines for Denmark. GC chemotherapy is given every 3 weeks, for up to 6 cycles: ▪ Gemcitabine: 1,000 mg/m^2 (day 1 and day 8) ▪ Cisplatin: 70 mg/m^2 (day 1)
Prognosis with current treatment (comparator)	▪ GC chemotherapy, when patients are eligible to receive cisplatin, is the 1L treatment of patients with unresectable or metastatic urothelial carcinoma. In case of no disease progression within 4-10 weeks of last dose of chemotherapy, maintenance treatment with avelumab is possible. ▪ According to Danish real-world treatment endpoints, the median OS of patients receiving 1L GC chemotherapy was 14 months in the era before immunotherapy.[1] ▪ Addition of avelumab maintenance therapy improved OS for the subset of patients with no disease progression within 4-10 weeks of 1L chemotherapy and therefore has been recommended in Denmark.[2] ▪ Two separate contemporary phase 3 trials within 1L urothelial carcinoma show comparable survival results of 1L GC in the era of immunotherapies. The median OS of 18.9 months for the GC arm of CheckMate-901 is similar to the 18.4-month OS of participants treated with GC in EV302.[3,4] Although the CheckMate-901 trial was initiated in the era before avelumab maintenance, this did not seem to affect the external validity of the CheckMate-901 results since survival results mirror those reported in EV302.[4] Despite the advances associated with the addition of avelumab to the care pathway, there is an unmet need in the 1L setting for

Summary	
	treatments that provide deep and durable responses, increase patients' survival, and improve patients' HRQoL.
Type of evidence for the clinical evaluation	Head-to-head comparison of nivolumab (OPDIVO) plus GC chemotherapy vs. GC chemotherapy.

Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	▪ OS: HR, 0.78; 95% CI, 0.63-0.96; *P* = 0.0171 — OS, 24 months – NIVO+GC: 46.9 months (95% CI, 40.7-52.8); GC: 40.7 months (95% CI, 34.6-46.7) ▪ PFS: HR, 0.72; 95% CI, 0.59-0.88; *P* = 0.0012 — PFS: 24 months – NIVO+GC: 23.5 months (95% CI, 18.3-29.0); GC: 9.6 months (95% CI, 5.6-15.0) ▪ Objective response rate: OR, 1.81; 95% CI, 1.31-2.50 — Complete response: NIVO+GC: 21.7%; GC: 11.8% — Partial response: NIVO+GC 35.9%; GC 31.3% ▪ Median duration of complete response: — NIVO+GC: 37.1 months; 95% CI, 18.1 months to not evaluable — GC: 13.2 months; 95% CI, 7.3-18.4 months
Most important serious adverse events for the intervention and comparator	SAEs observed in ≥ 1% of participants in any treatment arm are summarised below: [redacted]
Impact on health-related quality of life	Clinical documentation: HRQoL measured using the EORTC QLQ-C30 remained stable in both treatment arms.
Type of economic analysis that is submitted	A fast-track submission is requested; economic analysis is not required.

SAEs, n (%)	NIVO+GC (n = 304)	GC (n = 288)
[redacted]		

Summary	
Data sources used to model the clinical effects	Not applicable
Data sources used to model the health-related quality of life	Not applicable
Life years gained	Not applicable
QALYs gained	Not applicable
Incremental costs	Not applicable
ICER (DKK/QALY)	Not applicable
Uncertainty associated with the ICER estimate	Not applicable
Number of eligible patients in Denmark	DMC estimates that 150 patients per year receive 1L treatment for Urothelial Carcinoma,[2] and real-world data show that 46.2% of 1L patients initiate standard GC chemotherapy.[1] Correspondingly, approximately 70 patients per year are estimated to be eligible. Prevalence data are not relevant to this indication because the treatment is for incident cases.
Budget impact (in year 5)	Not applicable

1L = first line; CI = confidence interval; DKK = Danish krone; EMA = European Medicines Agency; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); GC = gemcitabine-cisplatin; HR = hazard ratio; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NIVO = nivolumab; OR = odds ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; SAE = serious adverse event; SoC = standard of care.

3 The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

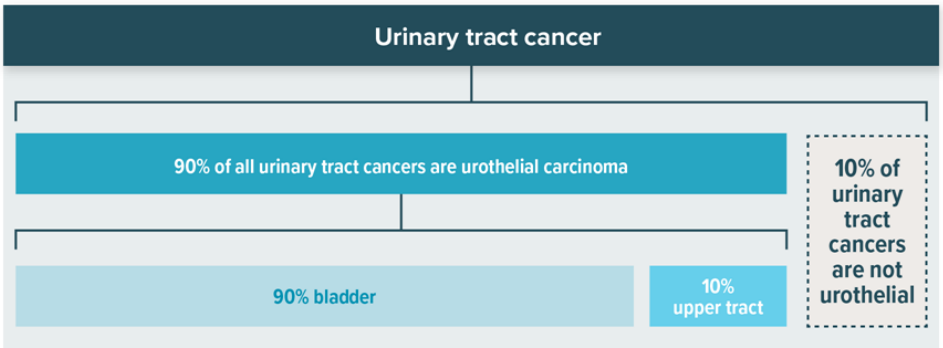
3.1.1 Disease background

Urothelial carcinoma is a type of urinary tract cancer that begins in the urothelium that lines the lower urinary tract (including the urethra and bladder) and the upper urinary tract (including the ureter and renal pelvis).[5]

Urothelial carcinoma is the most common type of urinary tract cancer. Approximately 90% of urinary tract cancers are urothelial carcinoma, with the remaining 10% being squamous cell carcinoma, small cell carcinoma, and adenocarcinoma.[6]

In 90% to 95% of cases, urothelial carcinoma develops in the bladder; in approximately 5% to 10% of cases, urothelial carcinoma develops in the upper urinary tract (Figure 1).[7-9]

Figure 1. Types of urinary tract cancer



3.1.1.1 Presentation

The symptoms of urothelial carcinoma vary depending on its location. Individuals with bladder cancer typically present with painless gross haematuria (visible blood in the urine),[7,10] increased urinary frequency, urgency, nocturia, and dysuria.[10,11] If bladder cancer reaches an advanced stage, individuals may present with an inability to urinate, lower back pain on one side, pelvic or bone pain, reduced appetite and weight loss, weakness and fatigue, or pedal oedema.[10] The similarity of these symptoms to those of benign disorders (e.g., urinary tract infection, cystitis, prostatitis) and the potentially intermittent nature of symptoms may delay diagnosis of bladder cancer, which can lead to worse endpoints.[12,13] The main risk factors for bladder cancer are cigarette smoking,

exposure to benzene derivatives and aromatic amines, and chronic irritative conditions of the bladder.[14]

People with cancer in the upper urinary tract (renal pelvis and ureter) often have no symptoms and the cancer is identified incidentally.[15] Individuals who do have symptoms may present with macroscopic haematuria.[15] If the tumour causes an obstruction, it may cause hydronephrosis and kidney infections.[7] Most of the risk factors identified with cancer in the upper urinary tract are identical to the risk factors for bladder cancer. In addition, exposure to plants containing aristolochic acid is another specific risk factor for cancer in the upper urinary tract.[15]

3.1.1.2 Disease staging and progression

Once diagnosed, urothelial carcinomas are most often staged using the tumour-node-metastasis (TNM) staging system,[10,11,16-18] which characterises cancers according to the size of the primary tumour (T, or Tis if the tumour is in situ), the degree of involvement of regional lymph nodes (N), and the presence of distant metastases (M)[15,19,20] (Table 1). This dossier focuses on unresectable (T4b) and metastatic urothelial carcinoma.

Table 1. Clinical classification and TNM staging of bladder cancer

Clinical classification	T	N	M	Description
Non–muscle invasive	Ta/Tis/T1	0	0	Non-invasive, carcinoma in situ, or invades lamina propria; no regional lymph node metastases
Muscle invasive, rejectable	T2a/T2b/T3a/T3b/T4a	0-1[a]	0	Invades superficial muscularis propria, deep muscularis propria, or perivesical tissue; no regional lymph node metastases (0) or single regional lymph node metastasis in true pelvis (1)
Locally advanced, unresectable	T4b	0	0	Invades pelvis or abdominal wall, no regional lymph node metastases
Metastatic	Any	Any	1	Distant metastases

TNM = tumour-node-metastasis.

Note: The staging of muscle-invasive urothelial carcinoma in the upper urinary tract is broadly similar to staging of bladder cancer, whereby T2 indicates the tumour is invading the muscularis propria, T3 indicates the tumour is invading the periureteric or peripelvic fat, and T4 indicates the tumour is invading adjacent organs or into perinephric fat.[21]

[a] In some cases, individuals with ≥ 2 lymph nodes in the true pelvis (N2) or lymph node metastasis to common iliac lymph nodes (N3) may also have resectable disease.

Sources: American Joint Committee on Cancer[22]; Cancer Research UK[23]

First-line therapy for unresectable and metastatic urothelial carcinoma is intended to slow the spread and growth of cancer, extend survival for as long as possible, and maintain a patient's quality of life (QoL).[14,24,25] For individuals who are cisplatin eligible, cisplatin-containing chemotherapy is considered a standard-of-care (SoC) treatment in the first-line setting.[11,19,20] Approximately 40% to 50% of patients respond to treatment;

however, durable responses are rare.[26,27] Analyses of real-world survival endpoints in Denmark in the era before immunotherapy have shown 5 year survival of approximately 13% to 15% for individuals who are cisplatin eligible and approximately 5% for individuals who are cisplatin ineligible.[1]

Individuals with metastatic bladder cancer have a particularly challenging experience given the advanced stage of the disease and the limited treatment options available.[14,28] As such, this patient population is subject to reductions in baseline QoL due to high symptomatic burden and poor prognosis.[29,30] The metastatic stage is associated with greater pain, fatigue, nausea/vomiting, emotional distress, and urinary/sexual dysfunction than earlier or more localised stages of bladder cancer.[31] First-line treatment options have historically provided limited durability of response or prolonged survival. Considering the poor prognosis associated with metastatic bladder cancer, differentiated agents that can provide a durable response and prolong survival while maintaining QoL remain a key unmet need for people with metastatic bladder cancer.

3.2 Patient population

In Denmark, approximately 2,000 new cases of bladder cancer are diagnosed each year, approximately 50% will be invasive, and half of those will also be muscle invasive.[18] Bladder cancer occurs in both female and male patients most frequently from 50 through 80 years of age, with a peak at approximately 70 years of age.[18] The median age of individuals with metastatic urinary tract cancer initiating first-line chemotherapy at Danish oncology departments has been reported to be 67 years of age (interquartile range, 61-71 years) for gemcitabine-cisplatin (GC)–treated patients.[1]

Omland et al.[1] reported the incidence of GC-eligible patients with unresectable and metastatic urothelial carcinoma in Denmark. According to this study, 440 patients received GC over a 6.25-year period from 1 January 2010 to 31 March 2016[1] (i.e., approximately 70 patients per year); we assume this number is stable (see estimates for 2019-2023 in Table 2).

Table 2. Incidence and prevalence (5 years) of GC-eligible unresectable and metastatic urothelial carcinoma in Denmark (2019-2023)

Year	2019	2020	2021	2022	2023
Incidence in Denmark	70	70	70	70	70
Prevalence in Denmark	NR	NR	NR	NR	NR

1L = first line; GC = gemcitabine-cisplatin; NR = not relevant.

Note: Given that the intervention is only relevant for the patients initiating 1L therapy, the prevalence is not relevant to the case.

The estimated number of patients eligible for treatment based on the full indication of this application is presented in Table 3. Danish Medicines Council (DMC) estimates that 150 patients per year receive first-line treatment for urothelial carcinoma,[2] and real-world data from Omland et al.[1] show that 46.2% of first-line patients initiate standard GC

chemotherapy. Correspondingly, approximately 70 patients per year are estimated to be eligible.

Table 3. Estimated number of patients eligible for treatment

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years	70	70	70	70	70

Data from Omland et al.[1] show that in Denmark, in the era before immunotherapy, median overall survival (OS) following first-line treatment of locally advanced, unresectable, and metastatic urinary tract cancer was approximately 11.7 months overall. For patients eligible for GC, median OS was 13.0 to 14.0 months, and 5-year OS was approximately 13% to 15% (Table 4).

Table 4. Overall survival in Denmark following first-line treatment of locally advanced, unresectable, and metastatic urinary tract cancer)

Population	Median OS, months	5-year OS, %
Treatment		
GC (for cisplatin-eligible patients with creatinine clearance > 60 mL/min)	14.0	15%
Gemcitabine-cisplatin split course (for cisplatin-eligible patients with creatinine clearance 50-60 mL/min)	13.0	13%
Carboplatin and gemcitabine (for cisplatin-ineligible patients)	9.8	5%
Gemcitabine (for platinum-ineligible patients)	7.5	3%
Carboplatin and etoposide (for patients with small cell neuroendocrine carcinoma)	13.5	20%
Males		
Aged ≥ 70 years	11.0	-
Aged < 70 years	12.4	-
Females		
Aged ≥ 70 years	10.5	-
Aged < 70 years	13.2	-

GC = gemcitabine-cisplatin; OS = overall survival.

Source: Omland et al.[1]

3.3 Current treatment options

In Denmark, the Danish Multidisciplinary Cancer Group (Danske Multidisciplinære Cancer Grupper) provides national guidelines for the treatment and follow-up of T4b (unresectable) and metastatic bladder cancer,[18] 90% of which is urothelial carcinoma and urothelial cancer in the upper urinary tract.[15,18] Table 5 presents the key recommendations for individuals with stage T4b and/or metastatic bladder cancer. First-line treatment consists of GC chemotherapy when individuals are eligible to receive cisplatin. In the case of no disease progression within 4 to 10 weeks of the last dose of chemotherapy, maintenance treatment with avelumab is possible.[18]

Table 5. Key recommendations for the treatment and follow-up of T4b and metastatic bladder cancer in Denmark

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
Systemisk onkologisk behandling bør tilbydes til patienter med T4b, N+ eller M+ sygdom samt til patienter med recidiv efter tidligere cystektomi eller inoperabelt recidiv efter strålebehandling	Systemic oncology treatment should be offered to patients with T4b, N+, or M+ disease as well as for patients with recurrence after previous cystectomy or inoperable recurrence after radiotherapy.	B
Systemisk onkologisk behandling kan ikke tilbydes ved: ▪ Betydeligt nedsat performance status (PS 3-4) ▪ Anden alvorlig påvirkning af patientens tilstand eller betydelig komorbiditet, hvor behandling ikke skønnes mulig	Systemic oncology treatment cannot be offered if: ▪ Significantly reduced PS (PS 3-4) ▪ Other serious impact on the patient's condition or significant comorbidity, where treatment is not deemed possible	D
Første linje behandling	**First-line treatment**	
Der anbefales kombinationskemoterapi frem for enkeltstofbehandling	Combination chemotherapy is recommended over single-agent treatment.	A
Ved valg af behandling skelnes mellem cisplatin-egnede og cisplatin-uegnede patienter Cisplatin-egnede patienter: ▪ Kombinationsbehandling med Gemcitabin og Cisplatin (GC) er standardbehandling og anbefales. Cisplatin-uegnede patienter: ▪ Er defineret ved nyrefunktion med GFR < 50 mL/min, PS > 1, signifikant hjertesygdom (NYHA klasse > 2), betydende høretab eller neuropati	When choosing treatment, a distinction is made between patients for whom cisplatin is suitable and for whom cisplatin is unsuitable. Cisplatin-eligible patients: ▪ Combination treatment with GC is standard treatment and is recommended Patients not eligible for cisplatin: ▪ Is defined by kidney function with GFR < 50 mL/min, PS > 1, significant heart disease (NYHA class > 2),	B

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
(> grad 2). Alder over 75 år betragtes også som relativ kontraindikation.	significant hearing loss, or neuropathy (> grade 2). Age > 75 years is also considered a relative contraindication.	
Vedligeholdelsesbehandling efter kemoterapi	**Maintenance treatment after chemotherapy**	
Behandling med PD-L1-hæmmeren avelumab skal tilbydes efter afsluttet 1. Linje platin-baseret kemoterapi for inoperabel eller metastatisk urothelialt karcinom hvis patienterne opfylder følgende: ▪ PS 0-1 ▪ Er uden progression ▪ Er immunterapi-egnede ▪ Ikke tidligere har modtaget immunterapi	Treatment with the PD-L1 inhibitor avelumab must be offered after completion of the first-line platinum-based chemotherapy for unresectable or metastatic urothelial carcinoma if patients meet the following criteria: ▪ Have a PS 0-1 ▪ Have not previously received immunotherapy ▪ Are without progression ▪ Are suitable for immunotherapy	A
Behandlingen bør opstartes indenfor 10 uger efter afsluttet kemoterapi	Treatment should be started within 10 weeks after completion of chemotherapy.	D
Behandling kan fortsættes til progression, uacceptabel tokscicitet eller max 2 års behandling. Behandling ud over 2 år kan dog individuelt diskuteres med patienten	Treatment can be continued until progression, unacceptable toxicity, or a maximum of 2 years of treatment. However, treatment beyond 2 years can be individually discussed with the patient.	D
Opfølgning efter systemisk onkologisk behandling	**Follow-up after systemic oncological treatment**	
Undersøgelser hos patienter efter behandling for metastatisk sygdom afhænger af sygdomsstatus og almentilstand ▪ Patienter i PS > 2 skal ikke følges, men tilbydes pallierende og understøttende foranstaltninger. ▪ Patienter, der vurderes egnet til behandling ved sygdomsprogression, bør følges regelmæssigt.	Investigations in patients after treatment of metastatic disease depend on disease status and general condition: ▪ Patients in PS > 2 do not have to be followed but are offered palliative care and supporting measures. ▪ Patients assessed as suitable for treatment in the event of disease progression should be followed up regularly.	D
Opfølgningen består i CT-scanning af thorax og abdomen hver 3.- 4. Måned i 2 år, herefter hver 6. Måned i yderligere 3 år	Follow-up consists of a CT scan of the thorax and abdomen every 3-4 months for 2 years, then every 6 months for a further 3 years.	D

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
Patienter med komplet respons, som ikke er cystektomeret, kankontrolleres med cystoskopi hver 4. Mdr i 2 år. Herefter årlig kontrol	Patients with complete response who have not been cystectomised can be monitored with cystoscopy every 4 months for 2 years. Thereafter, patients should have an annual check.	D

CT = computed tomography; GC = gemcitabine-cisplatin; GFR = glomerular filtration rate; NYHA = New York Heart Association; PD-L1 = programmed death-ligand 1; PS = performance status.

[a] Recommendations marked A are strongest, and recommendations marked D are weakest. Further information on the strength and evidence assessment can be found at oxford-levels-of-evidence-2009_dansk-v.1.1.pdf (dmcg.dk).

Source: Danish Bladder Cancer Group[18]

In the Danish real-world treatment study by Omland et al.,[1] 46.2% of patients initiated standard GC chemotherapy.[1]

In 2021, DMC recommended the addition of avelumab as a maintenance therapy for the subset of patients with no disease progression within 4 to 10 weeks of the first-line chemotherapy.[2] This was based on the results of the JAVELIN Bladder 100 trial.[3] Avelumab is only offered to patients eligible for immunotherapy and if there is no disease progression during or immediately after first-line chemotherapy. The Omland et al.[1] study showed that of the 440 patients initiating standard GC, 66 (15%) patients had a complete response (CR) to treatment, 160 (36%) patients had a partial response (PR), and 78 (18%) patients had stable disease (SD). Based on these results, it can be estimated that approximately 70% of patients in Denmark receiving first-line chemotherapy would be eligible to receive avelumab. However, far from all eligible patients end up receiving avelumab maintenance treatment. A clinical expert from Denmark estimates that approximately 35% of eligible patients actually receive avelumab.[32] Reasons may vary. Some patients experience disease progression during the 4- to 10-week gap between the end of chemotherapy and the start of avelumab treatment, some become ineligible for immunotherapy, and some simply opt out when offered further treatment. Thus, first-line treatments that provide deep and durable responses, increase patients' survival, and improve patients' health-related QoL (HRQoL) for more patients are needed.[27,33]

3.4 The intervention

Nivolumab is a human, monoclonal immunoglobulin G4 antibody that acts as a programmed cell death protein 1 (PD-1) inhibitor, blocking the interaction of PD-1 with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). Binding of PD-L1 and PD-L2 to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumour immune response, and helping to restore antitumour immune response.[34]

Nivolumab in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. Table 6 summarises the use of nivolumab in this indication. The summary of product characteristics[34] provides full details of the prescribing information.

Table 6. Description of nivolumab

Overview of intervention	Description
Therapeutic indication relevant for the assessment	Nivolumab in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
Method of administration	IV infusion
Dosing	360 mg nivolumab administered intravenously over 30 minutes in combination with GC chemotherapy every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously 480 mg every 4 weeks over 30 minutes.
Dosing in the health economic model (including relative dose intensity)	Not applicable
Should the medicine be administered with other medicines?	GC chemotherapy is given every 3 weeks, for up to 6 cycles: ▪ Gemcitabine: 1,000 mg/m^2 (day 1 and day 8) ▪ Cisplatin: 70 mg/m^2 (day 1)
Treatment duration / criteria for end of treatment	Treatment with OPDIVO should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).
Necessary monitoring, both during administration and during the treatment period	Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring.
Need for diagnostics or other tests (e.g., companion diagnostics). How are these included in the model?	No specific diagnostics or tests are required.
Package size(s)	Each millilitre of concentrate for solution for infusion contains 10 mg of nivolumab. One vial of 4 mL contains 40 mg of nivolumab. One vial of 10 mL contains 100 mg of nivolumab. One vial of 12 mL contains 120 mg of nivolumab. One vial of 24 mL contains 240 mg of nivolumab.

GC = gemcitabine-cisplatin; IV = intravenous.

Nivolumab in combination with GC chemotherapy followed by nivolumab monotherapy carries some significant advantages compared with current treatment options in Denmark. First, more patients will have the chance to achieve a response to PD-L1

therapy. Second, the dosing schedule for nivolumab monotherapy is more spaced out, with treatment schedules every 4 weeks instead of every second week as with avelumab. This allows for more cost-efficient administration due to the less frequent administration schedule. Third, the treatment is continuous with no need to first introduce the patient to chemotherapy, followed by a waiting period and assessment of progression before the additional maintenance treatment (avelumab). These patients spend a lot of time at the hospital, and the option to initiate one treatment (nivolumab and GC at the same time), taking away the need to later having to introduce a maintenance treatment, is seen as beneficial for the patient.

3.4.1 Combining immunotherapy with chemotherapy

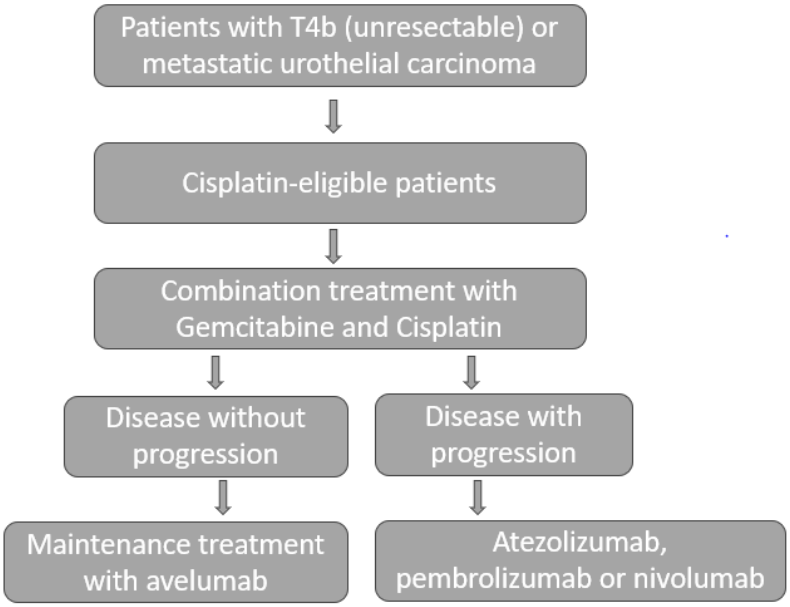
As stated in the Danish national guidelines of T4b (unresectable) and metastatic bladder cancer, the recommend first-line treatment is GC chemotherapy.[18] This recommendation is based on a large retrospective cohort study, evaluating OS based on type of first-line chemotherapy received by patients with advanced bladder cancer. The results showed that cisplatin was found to be an independent favourable factor for OS for patients who were eligible for cisplatin.[35]

In previous studies of immunotherapies in first-line settings, no significant improvements in OS were observed in studies combining immunotherapy with chemotherapy not distinguishing between cisplatin-containing regimens and non–cisplatin-containing regimes.[36-38] Thus, guidelines have historically recommended cisplatin-based chemotherapy alone, with immunotherapy used for maintenance or as second line or beyond treatment. In the IMVIGOR 130 trial, a subset of participants treated with immunotherapy and cisplatin-based chemotherapy showed improved OS.[38,39] This suggests that immunotherapy can be optimally combined with GC chemotherapy in the first-line setting, and are hence in line with the results seen in the CheckMate-901 trial.

3.4.2 The intervention in relation to Danish clinical practice

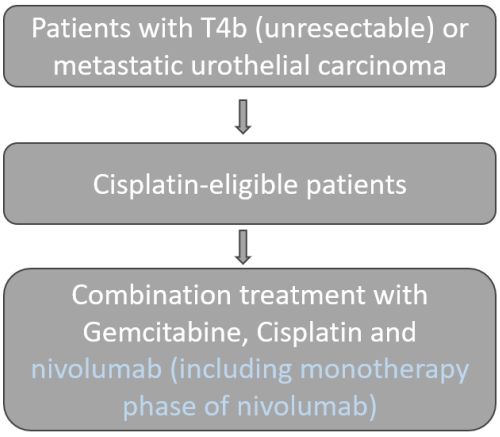
Nivolumab in combination with GC chemotherapy is positioned as first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. Figure 2 presents the current treatment pathway, and Figure 3 presents the proposed position of nivolumab in the treatment pathway.

Figure 2. **Current treatment pathway**



Source: Danish Bladder Cancer Group[18]

Figure 3. **Position of nivolumab in the treatment pathway**



Sources: Danish Bladder Cancer Group[18]; Opdivo SmPC[34]

3.5 Choice of comparator(s)

The comparator for first-line treatment of patients with unresectable or metastatic urothelial carcinoma is GC chemotherapy (Table 10 and Table 11), if the patient is eligible to receive it. For a subset of the population with no disease progression after GC chemotherapy, maintenance treatment with avelumab (Table 12) is recommended. This aligns with treatment guidelines for Denmark and the comparator in the pivotal CheckMate-901 trial.[4]

Although the CheckMate-901 trial was initiated in the era before avelumab maintenance was recommended, Bristol Myers Squibb (BMS) argues that immunotherapies, including avelumab, were used in the GC arm of the study before disease progression to an extent comparable with today's Danish treatment practice; therefore, the control arm of CheckMate-901 is a reasonable proxy for current Danish clinical practice. The actual use of avelumab in Danish clinical practice is unknown, but input from a clinical expert in Denmark suggests that 35% of eligible patients are offered avelumab.[32] In the CheckMate-901 trial, 217 of the 304 participants in the GC arm of the study had a CR, PR, or SD and would be eligible for subsequent immunotherapy (Table 7). A total of 60 participants received anti–PD-1/anti–PD-L1 before disease progression, corresponding to 27.6% of eligible participants (Table 8).[40] Furthermore, EV302, a contemporary phase 3 trial in first-line urothelial carcinoma, was initiated after the implementation of maintenance avelumab use.[3] A comparison of subsequent use of immunotherapy between CheckMate-901 and EV302 shows that both trials reflect Danish current practice with regard to immunotherapy use before disease progression. Table 7 presents the response rates for the chemotherapy arm of both trials. In the EV302 trial, 345 of 441 participants (78.2%) had a CR, PR, or SD.[3,4] Table 8 and Table 9 summarise subsequent therapy usage in the CheckMate-901 trial and the EV302 trial, respectively. In the CheckMate-901 trial, 60 of 217 participants (27.6%) received an anti–PD-1/anti–PD-L1 therapy before disease progression.[40] In the EV302 trial, 143 of 345 participants (41.4%) received any maintenance therapy before disease progression.[3] Hence, the suggested use of avelumab in Denmark (35%) is close to the use reported in the 2 trials (CheckMate-901 and EV302).

Additionally, looking at the endpoint in the comparator arms of the 2 studies, the median OS of participants treated with GC chemotherapy in the EV302 trial was 18.4 months.[3] This result is indistinguishable from the GC arm of CheckMate-901, which had a median OS of 18.9 months,[4] suggesting the 2 trials both reflect current Danish practice.

In the ITT population 26 (9%) in the nivolumab arm and 124 (41%) in the GC arm received received anti–PD-1/anti–PD-L1 at any point (not counting initial nivolumab treatment I the nivolumab arm.)

Table 7. CheckMate-901 and EV302: confirmed best overall response for the comparator arms (chemotherapy)

Category, no. of participants (%)	CheckMate-901[4]	EV302[3]
Participants receiving chemotherapy	304	441
Confirmed best overall response		
Complete response	36 (11.8)	55 (12.5)
Partial response	95 (31.2)	141 (32.0)
Stable disease	86 (28.3)	149 (33.8)

Category, no. of participants (%)	CheckMate-901[4]	EV302[3]
Progressive disease	39 (12.8)	60 (13.6)
Unevaluable	48 (15.8)	4 (0.9)
No assessment	Not applicable	32 (7.3)

Sources: van der Heijden et al.[4]; Powles et al.[3]

Table 8. CheckMate-901: subsequent immunotherapy received before disease progression in the comparator arm

Category, no. of participants (%)	GC (n = 304)
Any immune checkpoint inhibitor	60 (20)
Anti–PD-1	24 (8)
Pembrolizumab	17 (6)
Anti–PD-L1	36 (12)
Avelumab	27 (9)
Atezolizumab	6 (2)

GC = gemcitabine-cisplatin; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

Note: In all randomly assigned participants, subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if participant was never treated). Participants may have received more than 1 subsequent therapy. Subsequent therapies received in ≥ 1% of participants in either arm are listed.

Source: BMS data on file[40]

Table 9. EV302: summary of subsequent cancer therapies used in comparator arm

Category, no. of participants (%)	Chemotherapy arm (n = 444)
Participants who received subsequent anticancer therapies	313 (70.5)
First subsequent systemic therapy	294 (66.2)
Platinum-based therapy	17 (3.8)
PD-1/PD-L1 inhibitor–containing therapy	260 (58.6)
Maintenance therapy[a]	143 (32.2)
Avelumab	135 (30.4)
Other therapy	117 (26.4)

PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

[a] Included atezolizumab, avelumab, ipilimumab, M 6223, nivolumab, NKTR-255, and pembrolizumab. Maintenance therapy was permitted in the trial after platinum-based chemotherapy.

Source: Powles et al.[3]

Table 10. Description of gemcitabine

Overview of comparator	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Gemcitabine, which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by 2 mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce dCTPs for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).
Method of administration	Intravenous
Dosing	1,000 mg/m^2 (day 1 and day 8)
Dosing in the health economic model (including relative dose intensity)	Not applicable
Should the medicine be administered with other medicines?	Combination therapy, GC chemotherapy
Treatment duration/ criteria for end of treatment	GC chemotherapy is given every 3 weeks, for up to 6 cycles.
Need for diagnostics or other tests (i.e., companion diagnostics)	No specific diagnostics or tests are required.
Package size(s)	Gemzar 200 mg powder for solution for infusion Gemzar 1,000 mg powder for solution for infusion

ATC = Anatomical Therapeutic Chemical Classification System; dCTP = deoxynucleoside triphosphate; dFdCDP = gemcitabine diphosphate; dFdCTP = gemcitabine triphosphate; GC = gemcitabine-cisplatin.

Source: Gemzar SmPC[41]

Table 11. Description of cisplatin

Overview of comparator	
Generic name	Cisplatin
ATC code	L01XA01
Mechanism of action	Cisplatin has biochemical properties similar to those of bifunctional alkylating agents. Cisplatin inhibits DNA synthesis by producing intrastrand and interstrand cross-links in DNA. Protein and RNA synthesis are also inhibited to a lesser extent. Although the principal mechanism of action of cisplatin appears to be inhibition of DNA synthesis, other mechanisms, including enhancement of tumour immunogenicity, may be involved in its antineoplastic activity. Cisplatin also has immunosuppressive, radiosensitising, and antimicrobial properties.
Method of administration	Intravenous
Dosing	70 mg/m^2 (day 1)
Dosing in the health economic model (including relative dose intensity)	Not applicable
Should the medicine be administered with other medicines?	Combination therapy, GC chemotherapy
Treatment duration/ criteria for end of treatment	GC chemotherapy is given every 3 weeks, for up to 6 cycles.
Need for diagnostics or other tests (i.e., companion diagnostics)	No specific diagnostics or tests are required.
Package size(s)	Each 1 mL of concentrate for solution for infusion contains 1 mg of cisplatin. Each single vial of 10 mL concentrate for solution for infusion contains 10 mg of cisplatin. Each single vial of 50 mL concentrate for solution for infusion contains 50 mg of cisplatin. Each single vial of 100 mL concentrate for solution for infusion contains 100 mg of cisplatin.

ATC = Anatomical Therapeutic Chemical Classification System; GC = gemcitabine-cisplatin.

Source: Cisplatin SmPC[42]

Table 12. Description of avelumab

Overview of comparator	
Generic name	Avelumab
ATC code	L01FF04
Mechanism of action	Avelumab is a human immunoglobulin G1 monoclonal antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the PD-1 and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T cells, resulting in the restoration of antitumour T-cell responses. Avelumab has also shown to induce natural killer cell–mediated direct tumour-cell lysis via antibody-dependent cell-mediated cytotoxicity.
Method of administration	Intravenous
Dosing	Administered intravenously 10 mg/kg over 60 minutes every 2 weeks when used as monotherapy.
Dosing in the health economic model (including relative dose intensity)	Not applicable
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Treatment can be continued until progression, unacceptable toxicity, or a maximum of 2 years of treatment. However, treatment beyond 2 years can be individually discussed with the patient.
Need for diagnostics or other tests (i.e., companion diagnostics)	No specific diagnostics or tests are required.
Package size(s)	200 mg/10 mL, 1 vial

ATC = Anatomical Therapeutic Chemical Classification System; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

Sources: Bavencio SmPC[43]; Danish Bladder Cancer Group[18]

3.6 Cost-effectiveness of the comparator(s)

Not relevant as a fast-track submission is requested.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 13 presents the relevant endpoints necessary to evaluate the effect of nivolumab compared with Danish SoC.

Table 13. Efficacy endpoint measures relevant for the application

Efficacy measure and source	Time point[a]	Definition	How was the measure investigated/method of data collection
OS van der Heijden et al.[4]	Median follow-up, 33.6 months	OS was defined as the time from randomisation to the date of death from any cause.	For patients who are alive, their survival time was censored at the date of last contact (or "last known alive date"). OS was censored at the date of randomisation for patients who were randomly assigned but had no follow-up.
PFS van der Heijden et al.[4]	Median follow-up, 33.6 months	PFS by BICR was defined as the time from randomisation to the date of documentation of disease progression or death from any cause, whichever occurred first.	Patients receiving subsequent anticancer therapy before documented disease progression or death were censored at the last evaluable tumour assessment on or before the date of subsequent therapy in the PFS primary definition. However, the sensitivity analysis of PFS by BICR is **not censored** by subsequent anticancer therapy before progression of disease or death was performed (PFS secondary definition). This secondary definition is reflective of Danish clinical practice and therefore presented in Section 6.1.4.3.
ORR van der Heijden et al.[4]	Median follow-up, 33.6 months	The objective response was defined as a confirmed complete or partial response, according to RECIST, version 1.1.	All responses were assessed by BICR.
DoCR van der Heijden et al.[4]	Median follow-up, 33.6 months	DoCR.	All responses were assessed by BICR.

Efficacy measure and source	Time point[a]	Definition	How was the measure investigated/method of data collection
HRQoL van der Heijden et al.[4]	16 weeks	EORTC QLQ-C30 Global Health Status score.	Changes from baseline in HRQoL were measured using the EORTC QLQ-C30 version 3 Global Health Status/QoL score.

BICR = blinded independent central review; DoCR = duration of complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); HRQoL = health-related quality of life; ORR = overall response ratio; OS = overall survival; PFS = progression-free survival; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Timepoint for data collection used in analysis (follow-up time for time-to-event measures).

3.7.2 Validity of outcomes

Table 14 presents the validity of the relevant efficacy endpoints for this application.

Table 14. Validity of efficacy endpoint measures relevant for the application

Endpoint measure and source	Validity
OS van der Heijden et al.[4]	OS is the gold standard primary endpoint to evaluate the endpoint of any drug, biologic, intervention, or procedure that is assessed in oncologic clinical trials. OS is universally recognised as being unambiguous and unbiased, with a defined endpoint of paramount clinical relevance; positive results provide confirmatory evidence that a given treatment extends the life of a patient.[44]
PFS van der Heijden et al.[4]	The parameters used to assess the efficacy profile of nivolumab in combination with standard of care (OS, PFS, and objective response rate) are consistent with other studies exploring the use of other anticancer agents in this patient population. RECIST v1.1 criteria were used by investigators and BICR to assess tumour response and PFS.[45]
ORR van der Heijden et al.[4]	ORR is a measure of how a specific treatment impacts tumour burden in a patient with a history of solid tumours. ORR is a good measure of antitumour activity. The World Health Organization was the first to develop criteria to evaluate ORR in clinical trials of cancer treatments.[46]
DoCR van der Heijden et al.[4]	DoCR is useful in assessing treatments that promise durable response and delay disease progression as opposed to treatments that provide a temporary remission without lasting benefit.[46]
HRQoL van der Heijden et al.[4]	The EORTC QLQ-C30 is the most commonly used quality-of-life instrument in bladder oncology trials, followed by the EQ-5D.[47] A significant change in EORTC QLQ-C30 scores can be interpreted as small, moderate, or large changes in QoL as reported by patients in a subjective significance questionnaire. For patients with little change,

Endpoint measure and source	Validity
	the mean change in scores is about 5-10, 10 for moderate, and 20 for very much.[48]

BICR = blinded independent central review; DoCR = duration of complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors.

4 Health economic analysis

Not relevant because a fast-track submission is requested.

5 Overview of literature

5.1 Literature used for the clinical assessment

The indication for nivolumab included in this submission is based on the pivotal head-to-head CheckMate-901 trial, with a comparator relevant to Danish clinical practice, as presented in Section 3.5. Therefore, a literature search was not performed because, at the time of submission, CheckMate-901 was the only study relevant to this indication. Table 15 summarises the relevant literature relating to CheckMate-901.

Table 15. Relevant literature included in the assessment of efficacy and safety

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med. 2023;389(19):1778-89. doi:http://dx.doi.org/10.1056/NEJMoa2309863.[4]	CheckMate-901	NCT03036098	Start: 30 January 2018 Completed: 9 May 2023	NIVO+GC vs. GC

GC = gemcitabine-cisplatin; NCT = National Clinical Trial; NIVO = nivolumab.

5.2 Literature used for the assessment of health-related quality of life

Not relevant because a fast-track submission is requested.

5.3 Literature used for inputs for the health economic model

Not relevant because a fast-track submission is requested.

6 Efficacy

6.1 Efficacy of nivolumab combined with gemcitabine-cisplatin chemotherapy compared to gemcitabine-cisplatin chemotherapy for the first-line treatment of patients with unresectable or metastatic urothelial carcinoma

6.1.1 Relevant studies

6.1.1.1 CheckMate-901

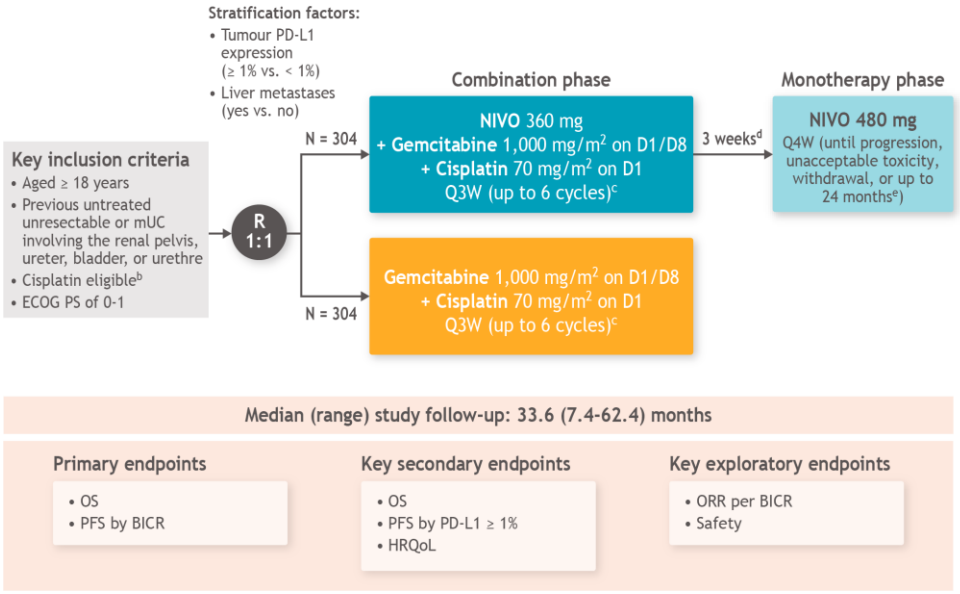
CheckMate-901 (NCT03036098) was an open-label, randomised, phase 3 trial evaluating intravenous nivolumab combined with GC chemotherapy compared with GC as first-line therapy in participants with unresectable or metastatic urothelial carcinoma who were eligible to receive cisplatin-based chemotherapy. Results from the final analysis of this study have been published by van der Heijden et al.[4]

The primary objectives were to compare the OS and progression-free survival (PFS) of nivolumab combined with GC versus GC. The secondary objectives were to evaluate whether PD-L1 expression is a predictive biomarker of efficacy (OS and PFS) of nivolumab combined with SoC chemotherapy as first-line therapy and to evaluate changes from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core) (EORTC QLQ-C30) Global Health Status score in order to assess cancer-specific HRQoL.[4]

Appendix A summarises the main characteristics of CheckMate-901. Figure 4 presents the study design.

Figure 4. CheckMate-901 (CA209901): study design

NIVO+GC vs. GC in cisplatin-eligible patients[a]



BICR = blinded independent central review; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine-cisplatin; GFR = glomerular filtration rate; HRQoL = health-related quality of life; mUC = metastatic urothelial carcinoma; NIVO = nivolumab; ORR = objective response rate; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; QxW = every x weeks; R = randomisation.

[a] Additional CheckMate-901 study design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098.

[b] Cisplatin eligibility was determined in the study population by a GFR ≥ 60 mL/min (assessed by direct measurement, i.e., creatinine clearance, or, if not available, using the Cockcroft-Gault formula), and absence of CTCAE v.4 grade ≥ 2 hearing loss and grade ≥ 2 peripheral neuropathy.

[c] Participants who discontinued cisplatin alone could be switched to GC for the remainder of the platinum doublet cycles (up to 6 cycles in total).

[d] NIVO monotherapy should begin 3 weeks after the last dose of NIVO+GC.

[e] Represents a maximum of 24 months from the first dose of NIVO administered as part of NIVO+GC.

Source: van der Heijden et al.[49]

6.1.2 Comparability of studies

A single head-to-head study, CheckMate-901, is included in this submission.

6.1.2.1 Comparability of patients across studies

Baseline demographic and disease characteristics for all randomly assigned participants, including those with tumour-cell PD-L1 expression level ≥ 1%, were generally well-balanced across the treatment groups and representative of the target patient population—cisplatin-eligible individuals with unresectable or metastatic urothelial carcinoma who have not received prior treatment.[4] Most randomly assigned participants had bladder as the tumour location, and approximately 20% of participants had liver metastases.[4]

Table 16 presents baseline characteristics of participants included in CheckMate-901.

Table 16. CheckMate-901: baseline characteristics of participants

	All randomly assigned participants	
	NIVO+GC (n = 304)	GC (n = 304)
Age, median (range), years	65 (32-86)	65 (35-85)
Age distribution, n (%)		
< 65 years	150 (49.3)	148 (48.7)
≥ 65 years	154 (50.7)	156 (51.3)
Sex, n (%)		
Female	68 (22.4)	70 (23.0)
Male	236 (77.6)	234 (77.0)
Race or ethnic group, n (%)		
American Indian or Alaska Native	1 (0.3)	1 (0.3)
Asian	75 (24.7)	63 (20.7)
Black or African American	0	2 (0.7)
White	211 (69.4)	225 (74.0)
Other	17 (5.6)	13 (4.3)
Geographic region, n (%)		
Asia	72 (23.7)	61 (20.1)
Europe	134 (44.1)	142 (46.7)
United States	19 (6.3)	21 (6.9)
Rest of the world	79 (26.0)	80 (26.3)
ECOG PS, n (%)		
0	162 (53.5)	162 (53.3)
1	140 (46.1)	142 (46.7)
> 1	2 (0.7)	0

	All randomly assigned participants	
	NIVO+GC (n = 304)	GC (n = 304)
Tumour type at initial diagnosis, n (%)		
Urinary bladder	235 (77.3)	219 (72.0)
Renal pelvis	33 (10.9)	44 (14.5)
Other	36 (11.8)	41 (13.5)
Time from initial diagnosis, median (range), years	0.51 (0.0-27.8)	0.36 (0.0-23.9)
Time from initial diagnosis distribution, n (%)		
< 1 year	179 (58.9)	199 (65.5)
≥ 1 year	125 (41.1)	105 (34.5)
Histological variant, n (%)		
None	150 (49.3)	142 (46.7)
Adenocarcinoma	53 (17.4)	50 (16.4)
Squamous cell carcinoma	20 (6.6)	23 (7.6)
Micropapillary	17 (5.6)	16 (5.3)
Other	62 (20.4)	71 (23.4)
Not reported	2 (0.7)	2 (0.7)
Disease stage, n (%)		
Metastatic	261 (85.9)	269 (88.5)
Locally unresectable or non-metastatic	41 (13.5)	33 (10.9)
Not reported	2 (0.7)	2 (0.7)
Tumour PD-L1 expression, n (%)		
≥ 1%	111 (36.5)	110 (36.2)
< 1%	193 (63.5)	194 (63.8)

	All randomly assigned participants	
	NIVO+GC (n = 304)	GC (n = 304)
Liver metastasis, n (%)		
Yes	64 (21.1)	64 (21.1)
No	240 (78.9)	240 (78.9)

ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine-cisplatin; NIVO = nivolumab; PD-L1 = programmed death-ligand 1.

Note: n is the number of participants.

Source: van der Heijden et al.[4]

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Danish patients with unresectable or metastatic urothelial carcinoma who are eligible for first-line treatment with nivolumab + GC are comparable to the patient population in the pivotal study CheckMate-901. For a subset of the population with no disease progression after GC chemotherapy, maintenance treatment with avelumab is recommended. Although the CheckMate-901 trial was initiated in the era before avelumab maintenance was recommended, immunotherapies, including avelumab, were used before disease progression in the trial to an extent comparable with Danish treatment practice, as discussed in Section 3.5. Table 17 summarises key patient characteristics as presented in the Danish real-world treatment endpoint study by Omland et al.[1] of patients with metastatic urinary tract cancer who had initiated first-line chemotherapy and the CheckMate-901 study.[4,45]

Table 17. Characteristics in the relevant Danish population and CheckMate-901

	Value in Danish population with metastatic urinary tract cancer who initiated GC first-line chemotherapy[1]	Value in CheckMate-901 ITT population[45]
Age, median (IQR), years	67 (61-71)	65 (32-86)
Sex, male %	77	77.3
ECOG PS, %		
0	46.6	53.5
1	29.3	46.4
2	7.7	0.3
3	0.2	

	Value in Danish population with metastatic urinary tract cancer who initiated GC first-line chemotherapy[1]	Value in CheckMate-901 ITT population[45]
Unknown	16.1	
Primary tumour location, %		
Upper urinary tract	10.7	NR
Ureter	NR	9.2
Renal pelvis	NR	12.7
Bladder	86.8	74.7
Urethra	2.0	2.6
Unknown/other	0.6	0.8

ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine-cisplatin; IQR = interquartile range; ITT = intention to treat; NR = not reported.

	Value in Danish population with metastatic urinary tract cancer who initiated GC first-line chemotherapy[1]	Value in CheckMate-901 SoC population[4]	Value in CheckMate-901 ITT population[45]
Age, median (IQR), years	67 (61-71)	65 (32-86)	65 (32-86)
Sex, male %	77	77	77.3
ECOG PS, %			
0	46.6	53.3	53.5
1	29.3	46.7	46.4
2	7.7	0	0.3
3	0.2		
Unknown	16.1		
Primary tumour location, %			
Upper urinary tract	10.7	NR	NR

	Value in Danish population with metastatic urinary tract cancer who initiated GC first-line chemotherapy[1]	Value in CheckMate-901 SoC population[4]	Value in CheckMate-901 ITT population[45]
Ureter	NR	NR	9.2
Renal pelvis	NR	14.5	12.7
Bladder	86.8	72	74.7
Urethra	2.0	NR	2.6
Unknown/other	0.6	13.5	0.8

ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine-cisplatin; IQR = interquartile range; ITT = intention to treat; NR = not reported; SoC = standard of care.

6.1.4 Efficacy: results per CheckMate-901

The results summarised in this submission are from the final analysis of CheckMate-901, based on a data cut on 9 May 2023 and database lock on 23 June 2023. Median study follow-up at the final analysis was 33.6 months, with a minimum follow-up of 7.4 months.[4]

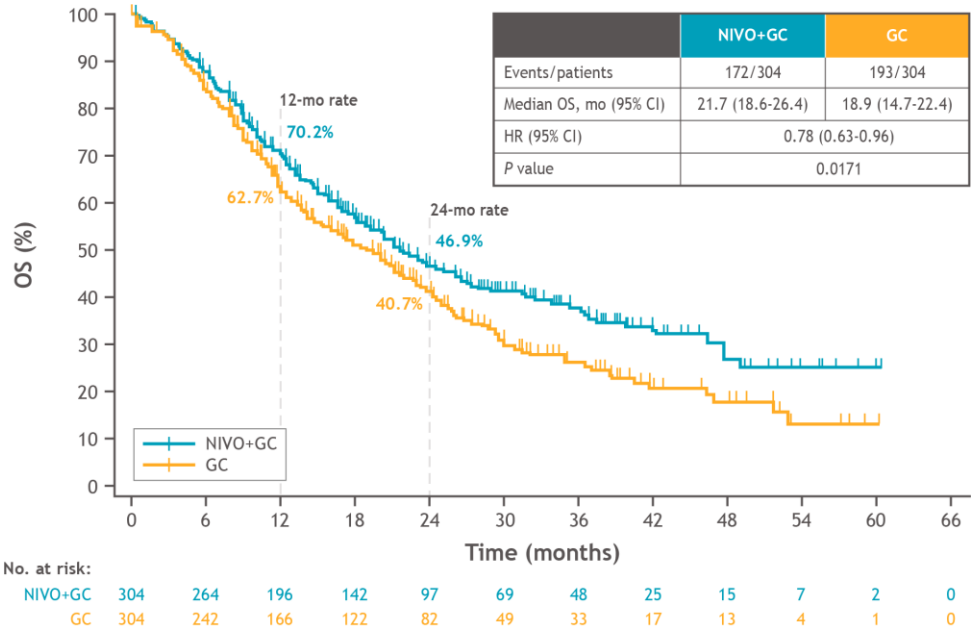
Results from the final analysis are reported in the following publications:

- van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med. 2023;389(19):1778-89. doi:http://dx.doi.org/10.1056/NEJMoa2309863.[4]

6.1.4.1 Overall survival in all randomly assigned participants

CheckMate-901 met its primary endpoint of statistically improved OS with nivolumab + GC versus GC at the final analysis.[4] Nivolumab + GC showed a statistically significant and clinically meaningful improvement in OS versus GC in the all–randomly assigned participant population, with a median OS of 21.7 months for nivolumab + GC versus 18.9 months for GC (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.63-0.96; *P* = 0.0171).[4] At 12 months and 24 months, the OS rate among participants receiving nivolumab + GC was 70.2% and 46.9%, respectively, compared with 62.7% and 40.7% of participants receiving GC (Figure 5).[4]

Figure 5. CheckMate-901: overall survival (all randomly assigned participants)



CI = confidence interval; GC = gemcitabine-cisplatin; HR = hazard ratio; NIVO = nivolumab; OS = overall survival.

Note: Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomly assigned participants and defined as time from randomisation to death from any cause. For participants without documented death, OS was censored on the last date the participant was known to be alive. For randomly assigned participants with no follow-up, OS was censored at randomisation.

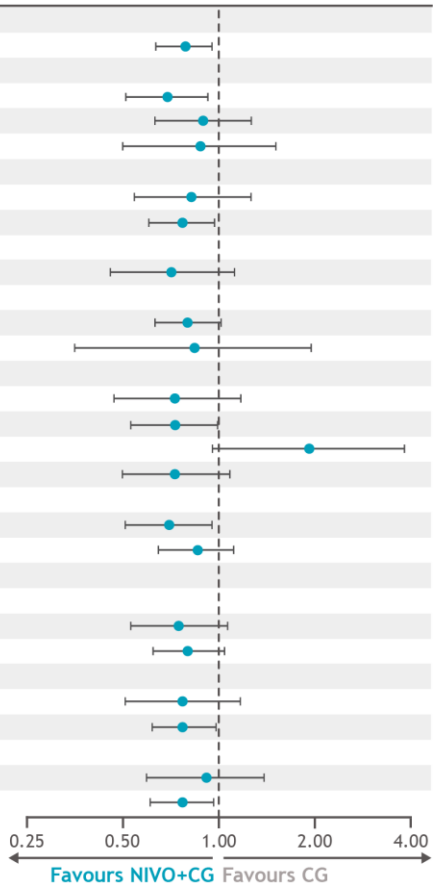
Source: van der Heijden et al.[4]

6.1.4.2 Subgroup analyses of overall survival for all randomly assigned participants

In subgroup analyses of OS, HRs favoured nivolumab + GC over GC across most subgroups that were analysed (HR < 1).[4] Although the United States region subgroup demonstrated an HR > 1, these analyses were not robust due to the small sample size of 40, limiting the reliability of this particular result.[4] Overall, subgroup analysis forest plots are descriptive in nature and not powered to draw conclusions from; therefore, subgroup results should be interpreted with caution (Figure 6).[49]

Figure 6. CheckMate-901: overall survival (subgroup analysis for all randomly assigned participants)

Subgroup	HR[a] (95% CI)
Overall	
All randomised (N = 608)	0.78 (0.63-0.95)
Age categorisation (years)	
< 65 (n = 298)	0.69 (0.51-0.92)
≥ 65 to < 75 (n = 236)	0.89 (0.63-1.26)
≥ 75 (n = 74)	0.86 (0.49-1.52)
Sex	
Female (n = 138)	0.82 (0.54-1.26)
Male (n = 470)	0.76 (0.60-0.97)
Race	
Asian (n = 138)	0.71 (0.45-1.12)
Black or African American (n = 2)	NME[b]
White (n = 436)	0.80 (0.63-1.02)
Other (n = 32)	0.84 (0.35-1.97)
Geographic region	
Asia (n = 133)	0.73 (0.46-1.17)
Europe (n = 276)	0.73 (0.53-0.99)
United States (n = 40)	1.92 (0.95-3.88)
Rest of the world (n = 159)	0.73 (0.49-1.08)
Baseline ECOG PS score	
0 (n = 324)	0.70 (0.51-0.95)
1 (n = 282)	0.85 (0.64-1.11)
> 1 (n = 2)	NME[b]
PD-L1 expression[b]	
PD-L1 ≥ 1% (n = 221)	0.75 (0.53-1.06)
PD-L1 < 1% or indeterminate (n = 387)	0.80 (0.62-1.04)
Liver metastases[b]	
Yes (n = 128)	0.77 (0.51-1.16)
No (n = 480)	0.77 (0.61-0.98)
Previous systemic cancer therapy	
Yes (n = 156)	0.90 (0.59-1.38)
No (n = 452)	0.76 (0.60-0.96)



CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine-cisplatin; HR = hazard ratio; NIVO = nivolumab; NME = not meaningful estimate; PD-L1 = programmed death-ligand 1.

Note: HR is not computed for subset (except age, race, geographic region, and sex) category with < 10 participants per treatment arm.

[a] Unstratified hazard model.

[b] Evaluated with the use of interactive response technology.

Source: van der Heijden et al.[49]

6.1.4.3 Progression-free survival per BICR in all randomly assigned participants

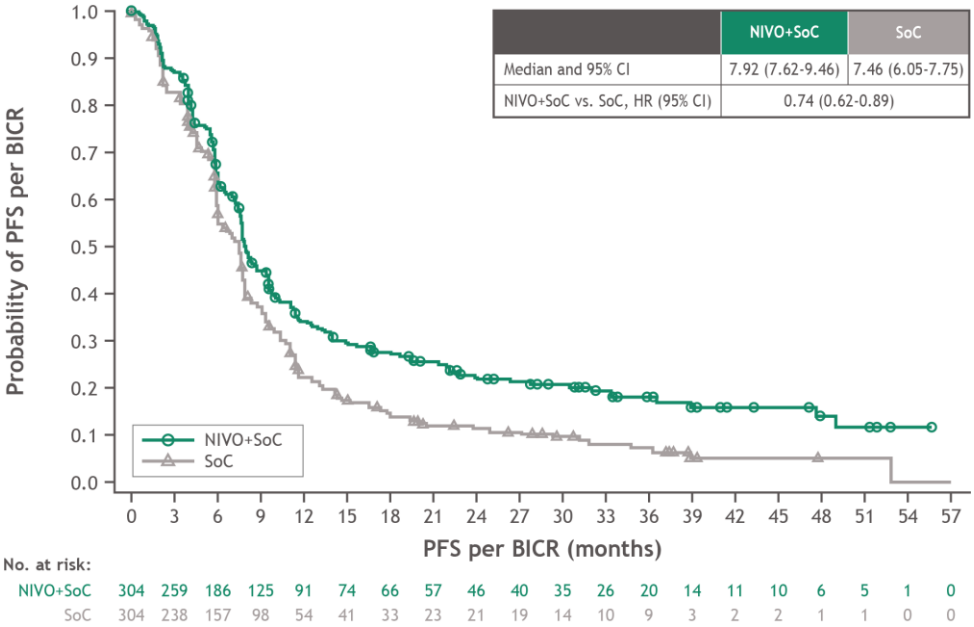
The analysis of PFS per blinded independent central review (BICR) was based on 2 definitions of PFS:[45]

- Primary definition: patients receiving subsequent anticancer therapy before disease progression *were* censored from the analysis.
- Secondary definition: data from patients receiving subsequent anticancer therapies before disease progression *were not* censored from the analysis.

The secondary definition reflects Danish clinical practice and is summarised below.

Nivolumab + GC showed a statistically significant improvement in PFS per BICR (based on the secondary definition) versus GC in the all–randomly assigned participant population, with a median PFS of 7.92 months (95% CI, 7.62-9.46) nivolumab + GC versus 7.46 months (95% CI, 6.05-7.75) for GC alone (HR, 0.74; 95% CI, 0.62-0.89),[45] as shown in Figure 7.

Figure 7. CheckMate-901: Kaplan-Meier plot of progression-free survival per BICR, secondary definition: all randomised participants



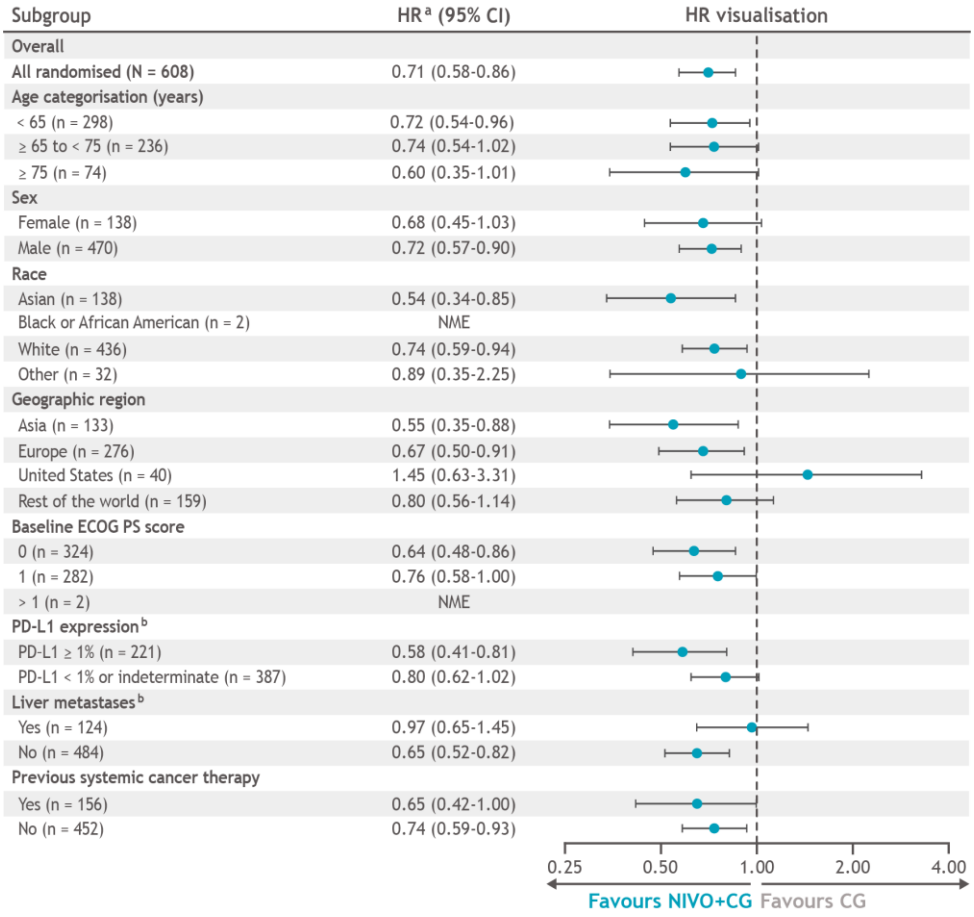
BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; SoC = standard of care.

Source: BMS data on file[45]

6.1.4.4 Subgroup analysis: progression-free survival per BICR in all randomly assigned participants

In subgroup analyses of PFS (according to the primary definition), HRs favoured nivolumab + GC over GC across most subgroups that were analysed (HR < 1) (Figure 8).[49] Although the United States region subgroup demonstrated an HR > 1, these analyses were not robust due to the small sample size of 40, limiting the reliability of this particular result.[4] Overall, subgroup analysis forest plots are descriptive in nature and not powered to draw conclusions from; therefore, subgroup results should be interpreted with caution.[4]

Figure 8. CheckMate-901: progression-free survival (primary definition) (subgroup analysis for all randomly assigned participants)



CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine-cisplatin; HR = hazard ratio; NIVO = nivolumab; NME = not meaningful estimate; PD-L1 = programmed death-ligand 1.

Note: HR is not computed for subset (except age, race, geographic region, and sex) category with < 10 participants per treatment arm.

[a] Unstratified hazard model.

Source: van der Heijden et al.[4] (supplement 3)

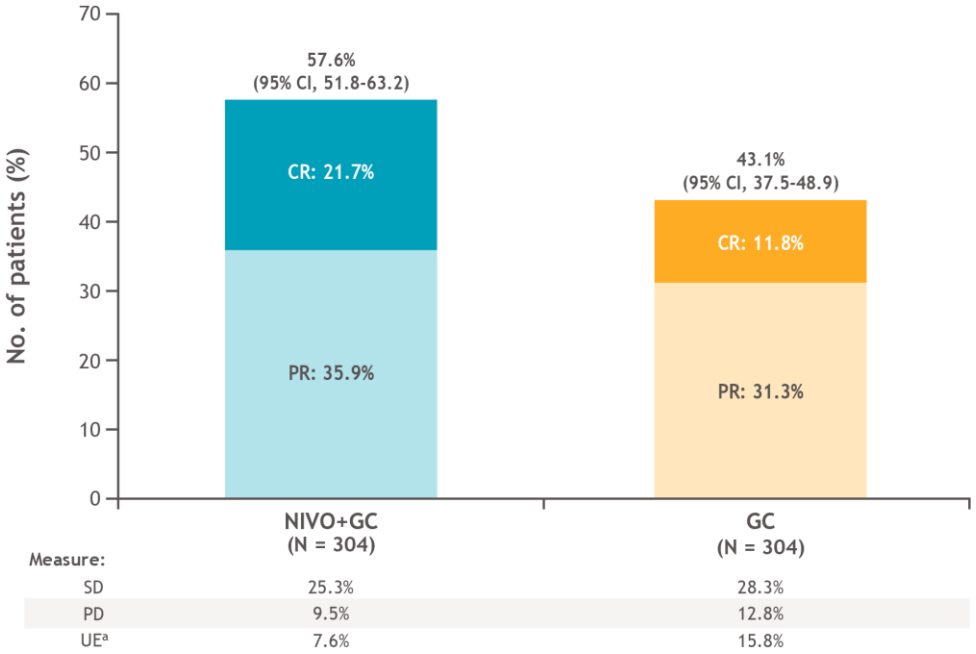
6.1.4.5 Objective response rate in all randomly assigned participants

Nivolumab + GC resulted in a substantially increased objective response rate (ORR) than GC, with a median ORR of 57.6% (95% CI, 51.8%-63.2%) and 43.1% (95% CI, 37.5%-48.9%), respectively,[4] resulting in an odds ratio of 1.81 (95% CI, 1.31-2.50)[45] (Figure 9). Additionally, nivolumab + GC nearly doubled CR rate compared with GC (21.7% vs. 11.8%, respectively).[4] 7,6 % of the patients in the nivolumab arm and 15,8% in the GC arm were unevaluable. [redacted]

[redacted]

[redacted]

Figure 9. CheckMate-901: objective response rate and best overall response per BICR (all randomly assigned participants)



Measure:	NIVO+GC (N = 304)	GC (N = 304)
SD	25.3%	28.3%
PD	9.5%	12.8%
UE[a]	7.6%	15.8%

BICR = blinded independent central review; CR = complete response; GC = gemcitabine-cisplatin; NIVO = nivolumab; PD = progressive disease; PR = partial response; SD = stable disease; UE = unevaluable.

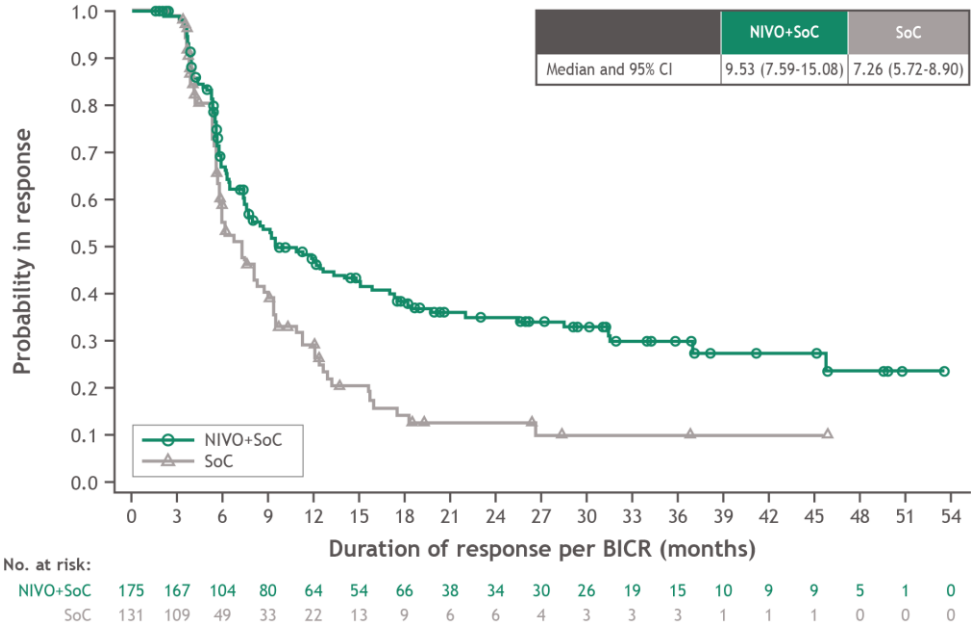
[a] The most common reasons for UE response included death before first tumour assessment, withdrawal of consent, treatment stopped due to toxicity, participant never treated, and receipt of subsequent anticancer therapy before first tumour assessment.

Source: van der Heijden et al.[49]

6.1.4.6 Duration of response and duration of complete response in all randomly assigned participants

Median time to objective response per BICR was the same (2.10 months) for all confirmed participants in both the nivolumab + GC and GC arms; however, the median duration of response was longer for all confirmed participants treated with nivolumab +GC (9.53 months [95% CI, 7.59-15.08]) than with GC (7.26 months [95% CI, 5.72-8.90]), with CIs not including the median of the other arm (Figure 10). Overall, 67% and 56% of participants in the nivolumab + GC and GC arms, respectively, had a duration of response of at least 6 months.

Figure 10. CheckMate-901: Kaplan-Meier plot of duration of response per BICR (all randomly assigned participants)



BICR = blinded independent central review; CI = confidence interval; NIVO = nivolumab; SoC = standard of care.

Source: BMS data on file[45]

Nivolumab + GC nearly tripled the duration of CR (DoCR), with a median DoCR of 37.1 months (95% CI, 18.1 months to not estimable) versus 13.2 months (95% CI, 7.3-18.4 months) with GC (Table 18).[4]

Table 18. CheckMate-901: duration of complete response (all randomly assigned participants)

Any objective response[a]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0-2.3)	2.1 (2.0-2.2)
CR[b]	**NIVO+GC (n = 66)**	**GC (n = 36)**
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1 to not estimable)	13.2 (7.3-18.4)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DoCR = duration of complete response; GC = gemcitabine-cisplatin; NIVO = nivolumab; PR = partial response; TTCR = time to complete response; TTR = time to objective response.

[a] Based on participants with an objective response per BICR (PR or CR as best overall response).

[b] Based on participants with a CR per BICR.

Source: van der Heijden et al.[49]

6.1.4.7 Patient-reported endpoints

CheckMate-901 demonstrated that nivolumab + GC maintained baseline HRQoL as measured by the EORTC QLQ-C30 over the course of treatment and during follow-up.[4] More than 90% of participants in both the nivolumab + GC and GC treatment arms

completed the EORTC QLQ-C30 survey at baseline; completion ranged from 78% to 86% through week 10, after which completion decreased to 40% in the nivolumab + GC group and 66% in the GC group (Table 19).[4]

Table 19. CheckMate-901: completion rate of EORTC QLQ-C30 for the 4 timepoints per arm

	NIVO+GC	GC
Baseline	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 10	[redacted]	[redacted]
Week 16	[redacted]	[redacted]

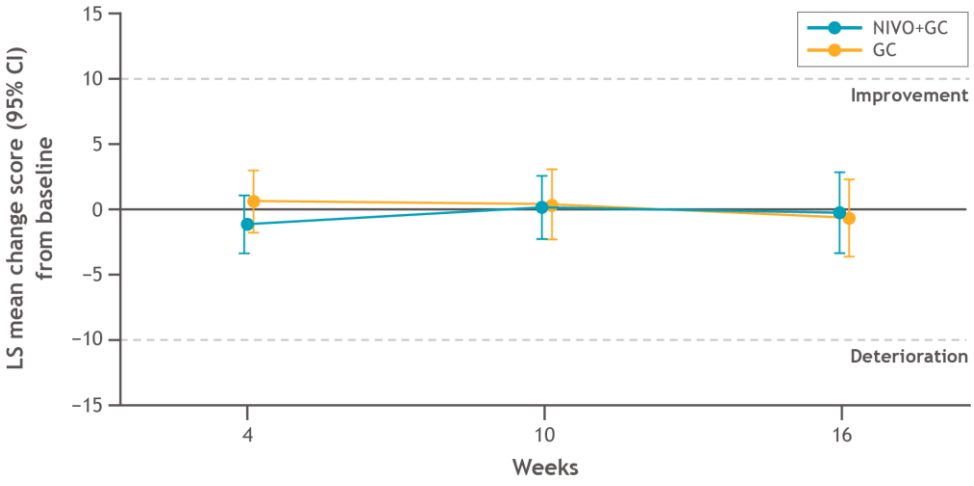
EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); GC = gemcitabine-cisplatin; NIVO = nivolumab.

Completion rate = number of participants who filled the questionnaire/number of available participants still enrolled in the trial (% of participants).

Source: BMS data on file[50]

A significant change in EORTC QLQ-C30 scores can be interpreted as small, moderate, or large changes in QoL as reported by patients in a subjective significance questionnaire. For patients with little change, the mean change in scores is approximately 5 to 10, 10 for moderate, and 20 for very much.[48] EORTC QLQ-C30 Global Health Status was stable in both treatment arms, with no change of more than 10 points from baseline in either direction through week 16, indicating that there was no meaningful difference in deterioration in baseline QoL between randomly assigned participants who received nivolumab + GC and those who received GC (Figure 11).[49]

Figure 11. CheckMate-901: mean change from baseline in EORTC QLQ-C30 Global Health Status score (all randomly assigned participants)



CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); GC = gemcitabine-cisplatin; HRQoL = health-related quality of life; LS = least squares; NIVO = nivolumab; PD-L1 = programmed death-ligand 1.

Note: In the EORTC QLQ-C30–evaluable population, participants included are those who completed ≥ 1 of the 15 domains/scales at baseline and ≥ 1 evaluable assessment at postbaseline visits based on the EORTC QLQ-C30. Changes from baseline were used as the dependent variable. The analysis was performed using all HRQoL data assessed during the treatment period through week 16. A mixed-effects repeated measure model was used assuming unstructured covariance and included a random intercept/slope and fixed effects by treatment group, time (i.e., week as a categorical variable), PD-L1 expression level, cisplatin eligibility (ineligible vs. eligible), liver metastasis (yes vs. no), baseline score, baseline score by time interaction, and treatment by time interaction.

Source: van der Heijden et al.[4] (supplement 3)

More data than presented in figure 11 is available. This data has, however, not been analysed with a mixed-effects repeated measure model similar to the one presented above. Hence, the numbers presented in figure 12 are unadjusted.

7 Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

Table 20 presents results from the comparative analyses.

Table 20. CheckMate-901: results from the comparative analysis of nivolumab + gemcitabine-cisplatin versus gemcitabine-cisplatin (all randomly assigned participants)

Endpoint measure	NIVO+GC (n = 304)	GC (n = 304)	Result	Source
OS, median	21.7 months (95% CI, 18.63-26.38 months)	18.9 months (95% CI, 14.72-22.44 months)	HR, 0.78 (95% CI, 0.63-0.96); *P* = 0.0171	van der Heijden et al.[4]
OS rate at 24 months	46.9% (95% CI, 40.7%-52.8%)	40.7% (95% CI, 34.6%-46.7%)		
PFS per BICR (secondary definition), median	7.9 months (95% CI, 7.62-9.46 months)	7.5 months (95% CI, 6.05-7.75 months)	HR, 0.74 (95% CI, 0.62-0.89); *P* = 0.0012	BMS data on file[45]
PFS rate per BICR (secondary definition) at 24 months	23.5 % (95% CI, 18.3%-29.0%)	9.6 % (95% CI, 5.6%-15.0%)		
Objective response rate	57.6% (95% CI, 51.8%-63.2%)	43.1% (95% CI, 37.5%-48.9%)	OR, 1.81 (95% CI, 1.31-2.50)	BMS data on file[45]
CR rate	21.7%	11.8%	—	van der Heijden et al.[4]
Duration of CR, median	37.1 months (95% CI, 18.1 months to not evaluable)	13.2 months (95% CI, 7.3-18.4 months)	—	van der Heijden et al.[4]
HRQoL (EORTC QLQ-C30), proportion of participants with a mean change of score rating from baseline reaching the minimal important difference of 10[48]	0	0	—	van der Heijden et al.[4]

BICR = blinded independent central review; CI = confidence interval; CR = complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); GC = gemcitabine-cisplatin; HR = hazard ratio; HRQoL = health-related quality of life; NIVO = nivolumab; OR = odds ratio; OS = overall survival; PFS = progression-free survival.

7.1.4 Efficacy – results per outcome measure

Not applicable.

8 Modelling of efficacy in the health economic analysis

Not relevant because a fast-track submission is requested.

9 Safety

9.1 Safety data from the clinical documentation

Safety results are based on data from the all-treated population (n = 592). This includes all participants who received any dose of study drug.[45]

Overall, 304 participants in the nivolumab + GC arm and 288 participants in the GC arm were included in the safety analysis. The median duration of therapy was 7.4 months (range, 0-47.9 months) for nivolumab + GC and 3.7 months (range, 0-14.3 months) for GC.

First-line treatment with nivolumab + GC demonstrated a manageable and acceptable safety profile, consistent with the known safety profiles of each drug in the regimen, and no new safety signals or toxicities were identified.[4]

Table 21 presents adverse events (AEs) (all-causality AEs) and adverse reactions (treatment-related AEs). Although the overall frequencies of AEs and adverse reactions leading to discontinuation were numerically higher in the nivolumab + GC arm compared with the GC arm, the difference can be attributed to the longer duration of therapy in the nivolumab + GC arm (7.4 months; range, 0-47.9 months) versus the GC arm (3.7 months; range, 0-14.3 months). In addition, adverse reactions were generally manageable with standard protocols, and most were grade 1 or 2.[4] The most common adverse reactions were anaemia, nausea, and neutropenia across treatment arms.[4] Table 22 summarises adverse reactions occurring in > 10% of participants across study groups.

Table 21. CheckMate-901: overview of safety events within 30 days of last dose (all-treated population; median study follow-up, 33.6 months)

	NIVO+GC (n = 304)	GC (n = 288)	Source
Number of AEs			

	NIVO+GC (n = 304)	GC (n = 288)	Source
Number and proportion of participants with ≥ 1 AE, n (%)	[redacted]	[redacted]	BMS data on file[45]
Number of SAEs[a]			
Number and proportion of participants with ≥ 1 SAE,[b] n (%)	[redacted]	[redacted]	BMS data on file[45]
Number of CTCAE grade ≥ 3 events[c]			
Proportion of participants with ≥ 1 CTCAE grade ≥ 3 events,[c] %	76.6	67.7	van der Heijden et al.[4]
Number of adverse reactions[d]			
Number and proportion of participants with ≥ 1 adverse reaction,[d] n (%)	296 (97.4)	267 (92.7)	van der Heijden et al.[4]
Number and proportion of participants who had a dose reduction, n (%)	[redacted]	[redacted]	BMS data on file[45]
Number and proportion of participants who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	BMS data on file[45]
Number and proportion of participants who discontinue treatment due to AEs, n (%)	[redacted]	[redacted]	BMS data on file[45]

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; GC = gemcitabine-cisplatin; ICH = International Council for Harmonisation; NIVO = nivolumab; SAE = serious adverse event.

[a] AEs are defined as all-causality AEs.

[b] An SAE is an event or reaction that, at any dose, results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

[c] CTCAE v. 4.0.

[d] Adverse reactions defined as treatment-related AEs of any grade.

Table 22. CheckMate-901: adverse reactions in ≥ 10% of participants in any treatment arm (all-treated population)

		NIVO+GC (n = 304)		GC (n = 288)	
		Any grade	Grade 3-4	Any grade	Grade 3-4
Blood and lymphatic system	Anaemia	57.2%	22.0%	47.6%	17.7%
	Neutropenia	30.6%	18.8%	29.9%	15.3%
	Thrombocytopenia	14.8%	6.6%	12.2%	4.5%

		NIVO+GC (n = 304)		GC (n = 288)	
		Any grade	Grade 3-4	Any grade	Grade 3-4
	Leukopenia	12.5%	2.3%	11.5%	1.7%
Gastrointestinal	Nausea	46.7%	0.3%	47.9%	1.0%
	Vomiting	18.1%	1.3%	16.7%	2.1%
	Constipation	14.5%	0	13.9%	0.3%
	Diarrhoea	13.2%	1.3%	8.7%	0
Investigations	Decreased neutrophil count	24.7%	14.5%	20.8%	11.1%
	Decreased platelet count	21.7%	7.6%	14.9%	4.9%
	Decreased white blood cell count	21.1%	9.9%	13.9%	3.8%
	Increased blood creatinine	12.8%	0.3%	12.2%	0
General	Fatigue	24.3%	2.0%	24.0%	1.4%
	Decreased appetite	22.4%	1.3%	15.6%	0.3%
	Asthenia	15.5%	1.0%	16.0%	1.7%
Skin and subcutaneous tissue	Pruritus	14.5%	0.7%	2.8%	0
	Rash	13.5%	0.7%	3.5%	0.3%
Endocrine	Hypothyroidism	13.2%	0	0	0

GC = gemcitabine-cisplatin; NIVO = nivolumab.

Note: An adverse reaction is any treatment-related adverse event reported between the first dose of a trial medication and 30 days after the end of the treatment period.

Source: van der Heijden et al.[4]

Table 23 summarises serious AEs (SAEs) with a frequency of ≥ 1%. Appendix E provides information about all SAEs observed in the study.

[redacted]

SAE, n (%)	NIVO+GC (n = 304) Number of participants with AE	GC (n = 288) Number of participants with AE
[redacted]		

A fast-track assessment is requested; therefore, Table 24 has not been completed.

Table 24. Adverse events used in the health economic model

AEs	Intervention Frequency used in economic model for intervention	Comparator Frequency used in economic model for comparator	Source	Justification
AE, n (%)				
[Add a new row for each AE included in the model]				

AE = adverse event.

9.1.1 Additional safety data from CheckMate-901

Only 21.1% of participants in the nivolumab + GC group discontinued therapy as a result of adverse reactions (compared with 17.4% in the GC group), further demonstrating the overall tolerability of nivolumab + GC (Table 25).[4] One participant in the nivolumab + GC arm died due to sepsis, and 1 participant in the GC arm died due to acute kidney injury (Table 25).[4]

Table 25. CheckMate-901: safety summary of adverse reactions (all-treated population)

	NIVO+GC (n = 304)		GC (n = 288)		
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Source
Any adverse reaction,[a] n (%)	296 (97.4)	188 (61.8)	267 (92.7)	149 (51.7)	van der Heijden et al.[4]
Adverse reactions leading to discontinuation,[a] n (%)	64[b] (21.1)	34[b] (11.2)	50[b] (17.4)	22[b] (7.6)	van der Heijden et al.[4]
Adverse reactions leading to dose delay or reduction,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	BMS data on file[45]
Treatment-related deaths,[a] n (%)	[redacted]		[redacted]		BMS data on file[45]

GC = gemcitabine-cisplatin; NIVO = nivolumab.

[a] Includes events reported between the first dose and 30 days after the last dose of the study therapy.

[b] Number of events calculated from percentages reported in the source.

Immune-mediated AEs were reported more frequently in the nivolumab + GC arm than in the GC arm; Table 26 presents the most common immune-mediated AEs.[4]

Table 26. CheckMate-901: immune-mediated adverse events in ≥ 1% of all randomly assigned participants in any treatment arm (all-treated population)

	NIVO+GC (n = 304)		GC (n = 288)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine,[a] n (%)				
Hypothyroidism	39 (12.8)	0	0	0
Hyperthyroidism	22 (7.2)	1 (0.3)	0	0
Adrenal insufficiency	3 (1.0)	1 (0.3)	0	0
Skin and subcutaneous tissue, n (%)				
Rash	13 (4.3)	1 (0.3)	1 (0.3)	0

	NIVO+GC (n = 304)		GC (n = 288)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Maculopapular rash	4 (1.3)	1 (0.3)	1 (0.3)	0
Investigations, n (%)				
ALT increased	3 (1.0)	2 (0.7)	0	0
AST increased	3 (1.0)	1 (0.3)	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GC = gemcitabine-cisplatin; IMAE = immune-mediated adverse event; NIVO = nivolumab.

Note: All-causality IMAEs reported between first dose and 100 days after the trial treatment period.

[a] Endocrine events were considered IMAEs regardless of immune-modulating medication use.

Source: van der Heijden et al.[4]

9.2 Safety data from external literature applied in the health economic model

Not relevant because a fast-track submission is requested.

10 Documentation of health-related quality of life (HRQoL)

Not relevant because a fast-track submission is requested.

11 Resource use and associated costs

Not relevant because a fast-track submission is requested.

12 Results

Not relevant because a fast-track submission is requested.

13 Budget impact analysis

Not relevant because a fast-track submission is requested.

14 List of experts

Name	Job function	Workplace
[redacted]	[redacted]	[redacted]

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Appendix A. Main characteristics of studies included

Table 27. Main characteristic of studies included

Aspect of trial	CheckMate-901 (CA209901)
Sample size (n)	608 participants were randomly assigned into 2 treatment groups in a 1:1 ratio [4]
Study design	A phase 3, international, open-label, randomised trial. Cisplatin-eligible participants with unresectable or metastatic urothelial carcinoma were randomly assigned 1:1 to receive either nivolumab combined with GC) or GC and stratified by tumour PD-L1 expression (≥ 1% vs. < 1%) and presence of liver metastases (yes vs. no).[4]
Location	135 sites in 29 countries (Argentina, Australia, Brazil, Canada, Chile, China, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Japan, Mexico, Netherlands, Norway, Peru, Poland, South Korea, Romania, Russian Federation, Singapore, Spain, Sweden, Switzerland, Taiwan, Turkey, and United States)[45]
Patient population	Eligible participants were at least 18 years of age with histologically confirmed unresectable or metastatic urothelial carcinoma involving the renal pelvis, ureter, bladder, or urethra. Participants had measurable disease according to RECIST, version 1.1, and had an ECOG PS score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability). All the participants had undergone tumour biopsy of the primary site or a metastatic site. Participants had to be eligible to receive cisplatin therapy, which included adequate renal function (glomerular filtration rate, ≥ 60 mL per minute). Previous systemic chemotherapy for unresectable or metastatic urothelial carcinoma was not permitted. Previous intravesical therapy was permitted if the treatment had been completed at least 4 weeks before the initiation of the trial treatment. Previous neoadjuvant therapy, radiation, or adjuvant platinum-based chemotherapy was permitted with recurrence 12 months or more after the completion of therapy.[4]
Assessment of PD-L1 status	PD-L1 expression was determined by the percentage of positive tumour-cell membrane staining in a minimum of 100 evaluable tumour cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.[4]
Intervention(s)	Nivolumab treatment: Nivolumab (360 mg, 30 min IV infusion, day 1) + gemcitabine (1,000 mg/m^2, 30 min IV infusion, Days 1 and 8) + cisplatin (70 mg/m^2, 30-120 min IV infusion, day 1) every 3 weeks for up to 6 cycles, followed by nivolumab (480 mg, 30 min IV infusion, day 1) every 4 weeks for up to 2 years or until disease progression, unacceptable toxicity, or withdrawal.[4]
Comparator(s)	GC control treatment: gemcitabine (1,000 mg/m^2, 30 min IV infusion, Days 1 and 8) + cisplatin (70 mg/m^2, 30-120 min IV infusion, day 1) every 3 weeks for up to 6 cycles.[4]
Follow-up period	Study duration: 24 months Median study follow-up was 33.6 months, with a minimum follow-up of 7.4 months Final analyses (23 June 2023 database lock; data cut 9 May 2023)[45]
Is the study used in the health economic model?	NA – fast-track assessment is requested
Reasons for use/non-use of the study in model	NA – fast-track assessment is requested

Aspect of trial	CheckMate-901 (CA209901)
Primary endpoints reported	Primary endpoints assessed in all participants who underwent randomisation (ITT population) and among those with a tumour-cell PD-L1 expression ≥ 1%[4]: ▪ OS was defined as the time from randomisation to the date of death from any cause. ▪ PFS per BICR was defined as the time from randomisation to the date of the first documented disease progression or death from any cause, whichever occurred first.
Other endpoints reported	Secondary endpoints assessed in all participants who underwent randomisation (ITT population) and among those with a tumour-cell PD-L1 expression ≥ 1%[4]: ▪ OS in participants with tumour PD-L1 expression ≥ 1% defined according to the percentage of positive staining of tumour-cell membrane that could be evaluated with the use of an immunohistochemical assay for PD-L1 ▪ PFS per BICR in participants with tumour PD-L1 expression ≥ 1% defined according to the percentage of positive staining of tumour-cell membrane that could be evaluated with the use of an immunohistochemical assay for PD-L1 ▪ Change from baseline in EORTC QLQ-C30 Global Health Status score in order to assess cancer-specific HRQoL Key exploratory endpoints[4]: ▪ Objective response rate per BICR defined as a confirmed complete or partial response according to RECIST assessment. ▪ Duration of response. ▪ Duration of complete response. ▪ Safety analysis including all participants who had received at least 1 dose of a trial drug. ▪ Adverse events in each treatment group were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v.4.0). ▪ Immune-mediated AEs were defined as AEs that were consistent with an immune-mediated mechanism or component for which a noninflammatory cause (e.g., infection or tumour) had been ruled out and for which immune-modulating medication had been initiated including all participants who had received at least 1 dose of a trial drug.

BICR = blinded independent central review; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); GC = gemcitabine-cisplatin; ITT = intention to treat; IV = intravenous; NA = not applicable; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Source: van der Heijden et al.[4]

Appendix B. Efficacy results per study

Results per study

Table 28. Results per study: CheckMate-901 (NCT03036098) (all randomly assigned participants)

Endpoint	Study arm	No. of participants[a]	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS	NIVO+GC	172/304	21.7 (18.6-26.4) months	—	—	—	HR = 0.78	0.63-0.96	0.0171	[redacted]	van der Heijden et al.[4]; BMS data on file[45]
	GC	193/304	18.9 (14.7-22.4) months								
PFS (secondary definition)	NIVO+GC	211/304	7.9 (7.6-9.5) months	—	—	—	[redacted]		NR	Based on secondary definition that does not censor participants receiving subsequent anticancer therapies before disease progression from the analysis. [redacted]	van der Heijden et al.[4]; BMS data on file[45]
	GC	191/304	7.5 (6.1-7.8) months								

Endpoint	Study arm	No. of participants[a]	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value	[redacted]	
ORR	NIVO+GC	175/304	57.6% (51.8%-63.2%)	[redacted]						van der Heijden et al.[4] Calculation based on BMS data on file[45]	
	GC	131/304	43.1% (37.5%-48.9%)								
CR rate	NIVO+GC	66/304	21.7%	[redacted]						Calculation based on methods in Deeks and Higgins[51]	van der Heijden et al.[4]
	GC	36/304	11.8%								
DoCR	NIVO+GC	66/304	37.1 (18.1 to not estimable) months	—	—	—	NR	NR	NR	NR	van der Heijden et al.[4]
	GC	36/304	13.2 (7.3-18.4) months								
	NIVO+GC	0	—	—	—	—	NR	NR	NR	NR	

Endpoint	Study arm	No. of participants[a]	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
HRQoL, proportion of participants with a mean change of score rating from baseline that reached the minimal important difference of 10	GC	0	—								

CI = confidence interval; CR = complete response; DoCR = duration of complete response; GC = gemcitabine-cisplatin; HR = hazard ratio; HRQoL = health-related quality of life; NIVO = nivolumab; NR = not reported; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SoC = standard of care.

[a] n/N represents the number of participants in each arm/total number of participants in study.

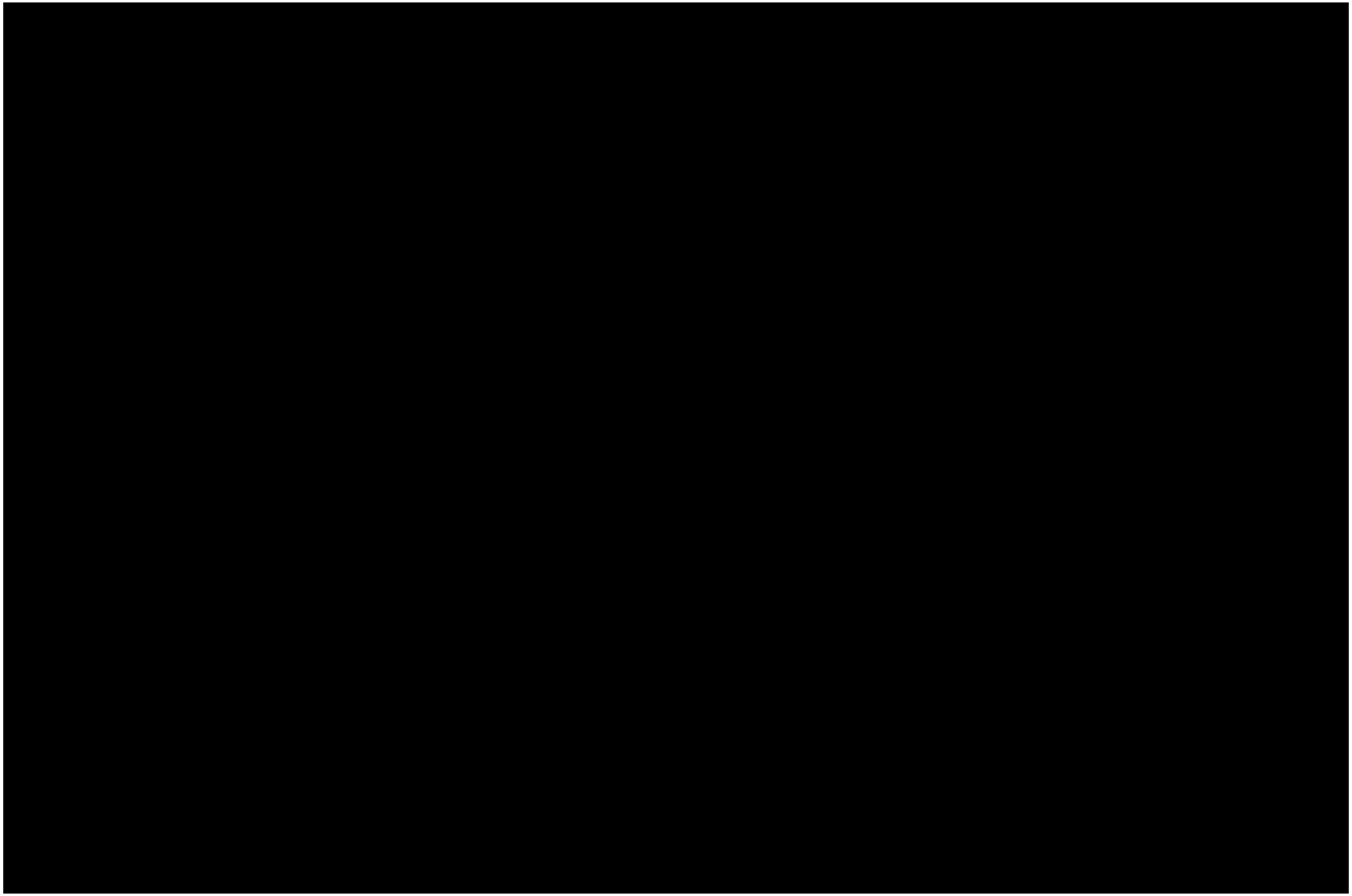
Appendix C. Comparative analysis of efficacy

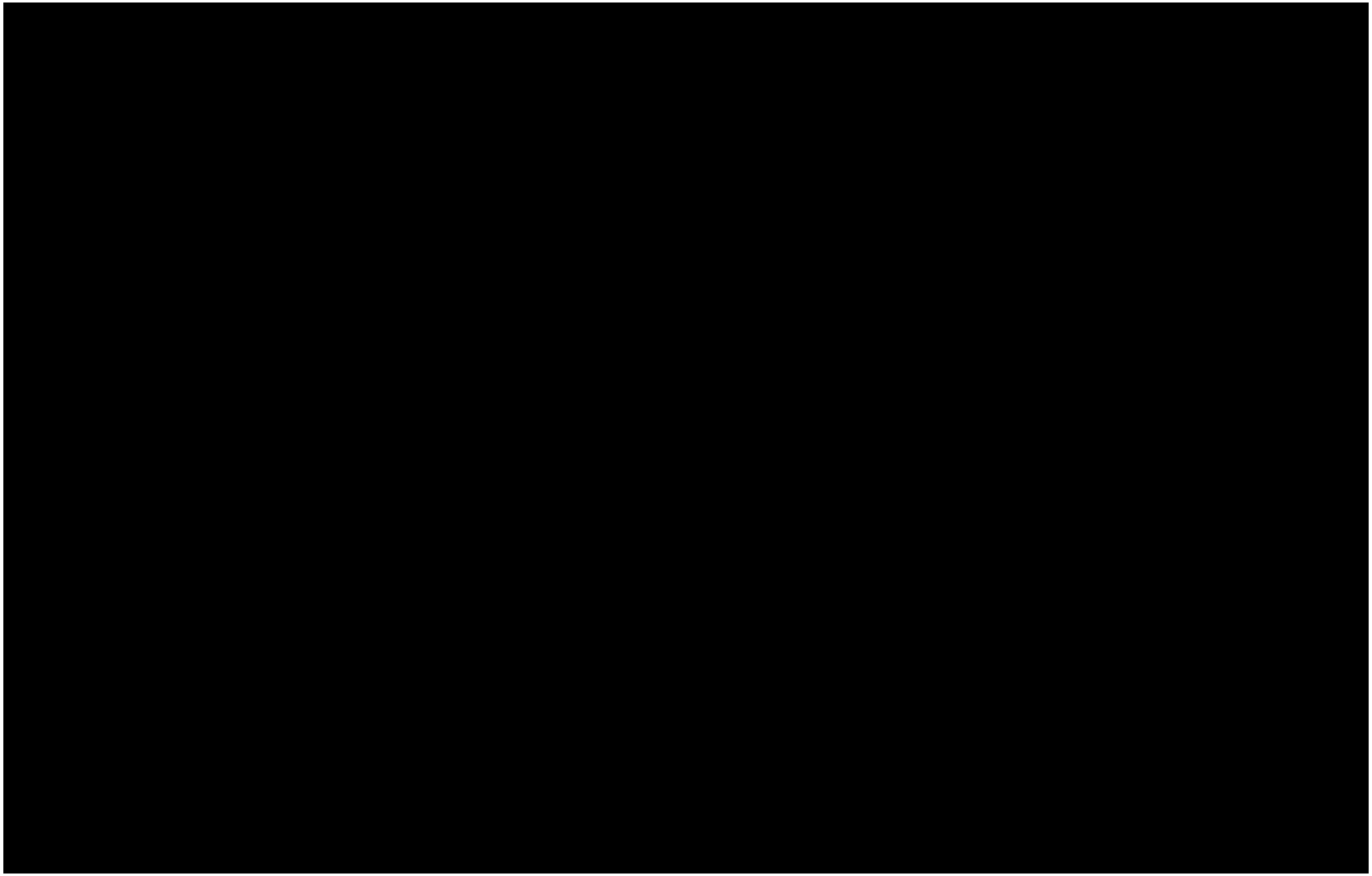
Not relevant for this submission.

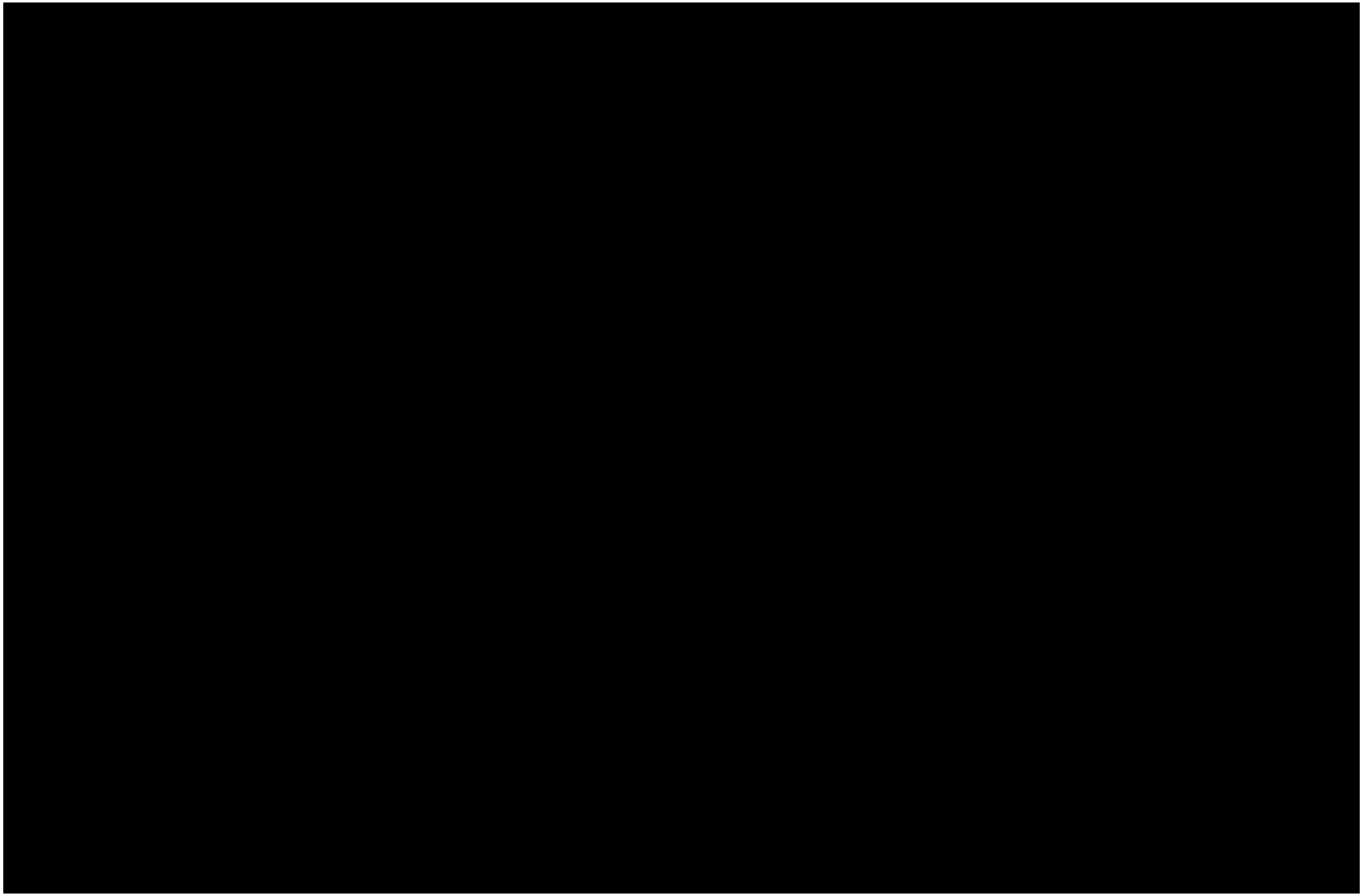
Appendix D. Extrapolation

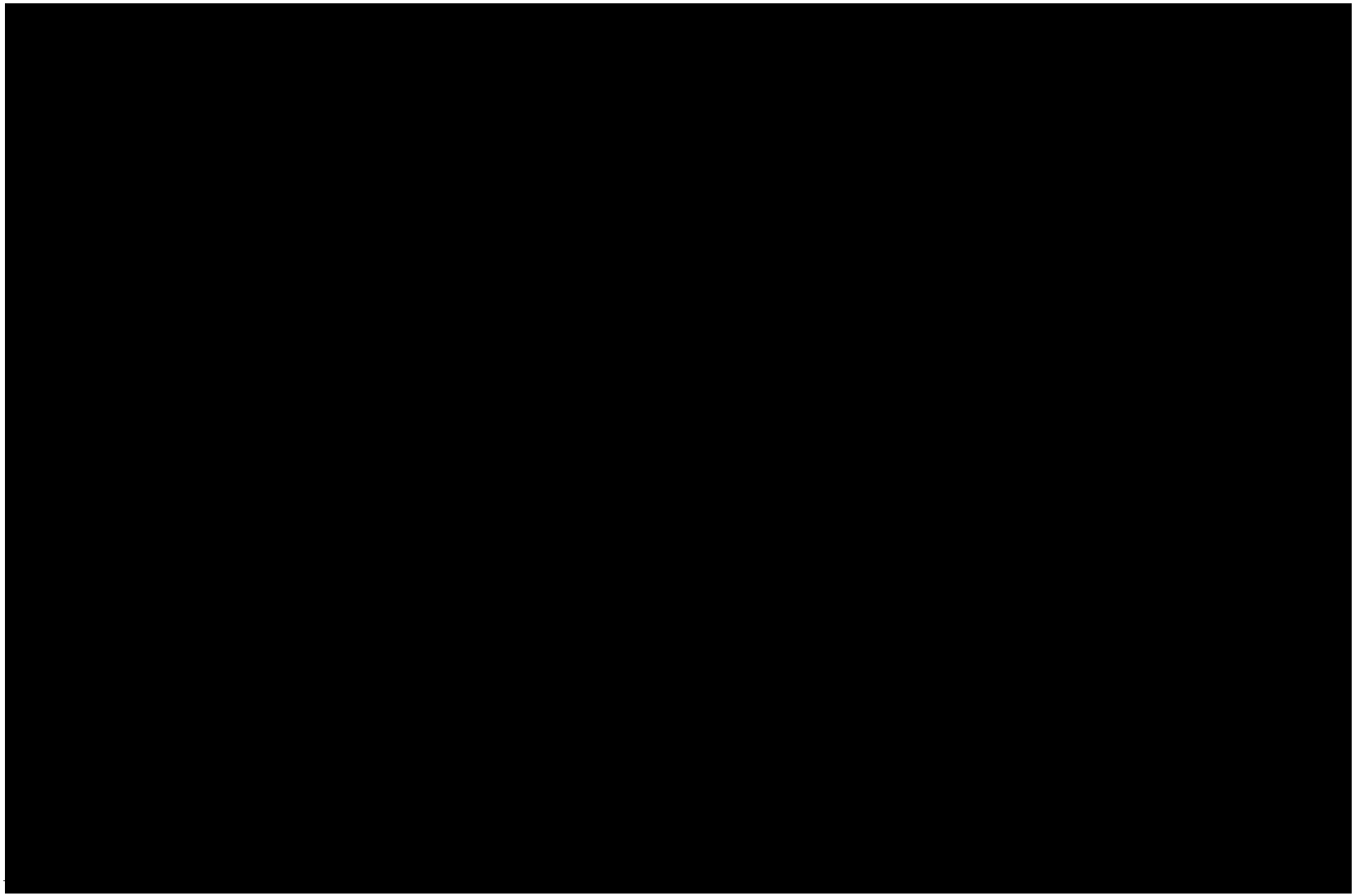
Not relevant for this submission

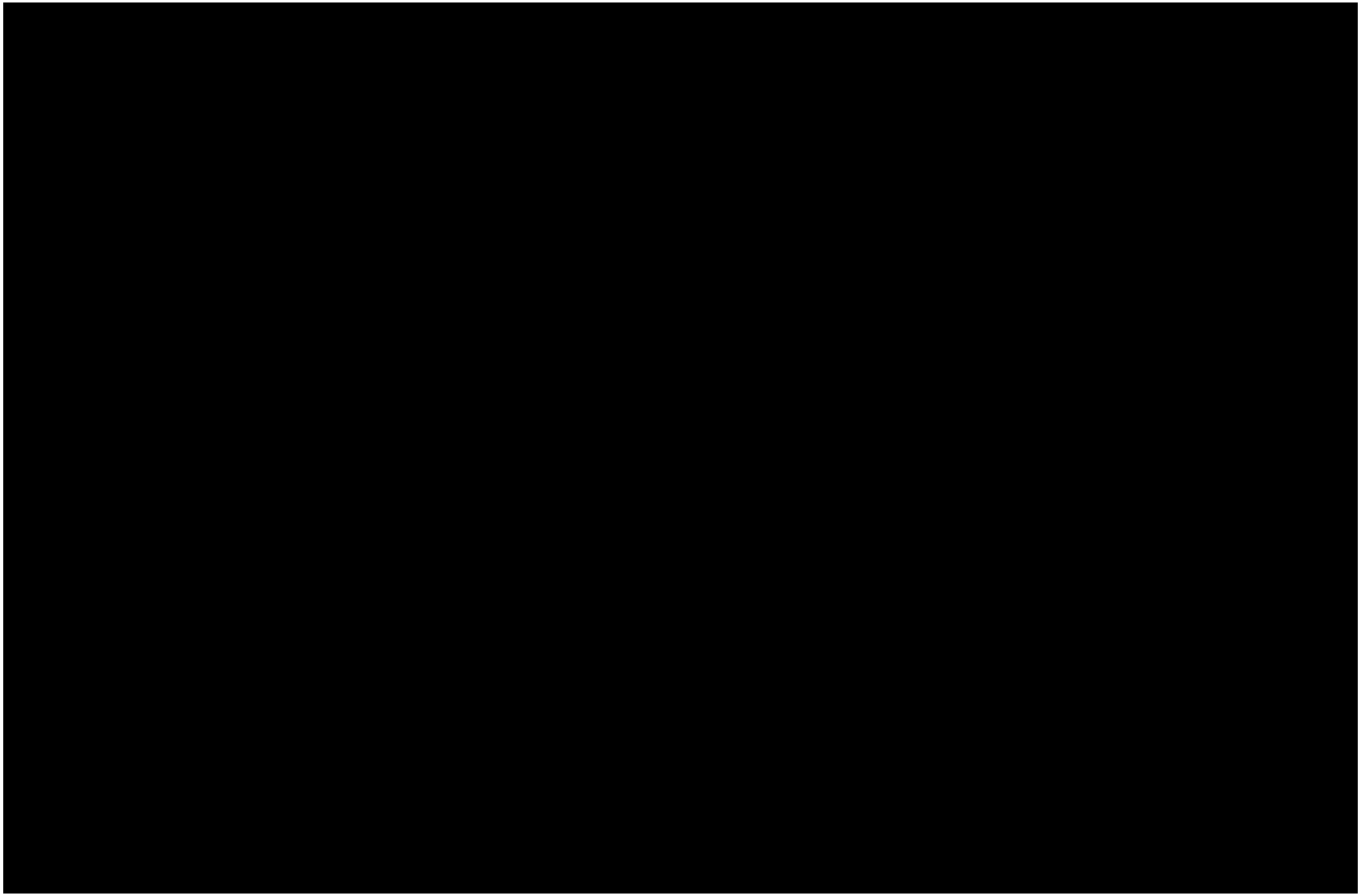
Appendix E. Serious adverse events

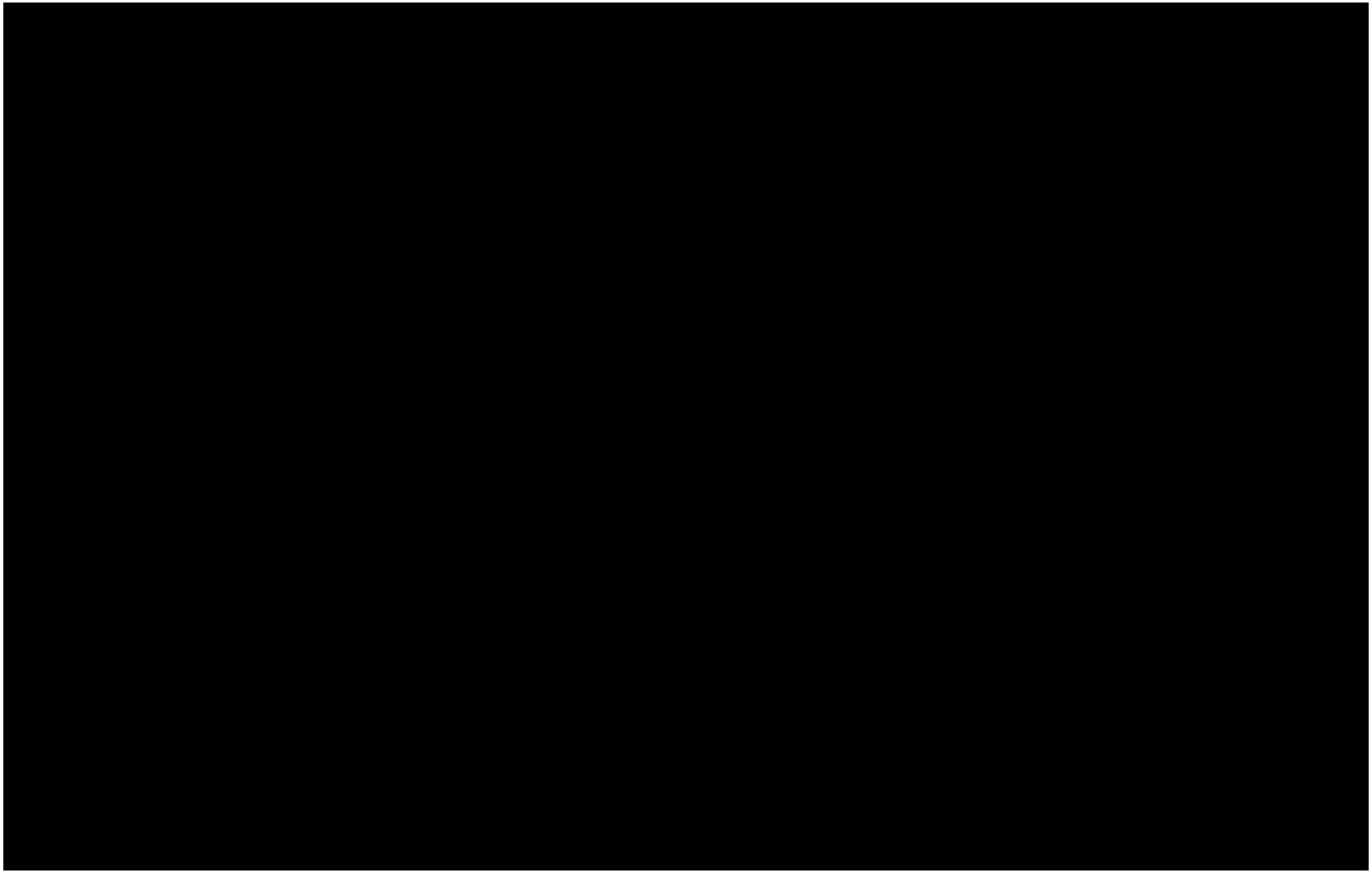


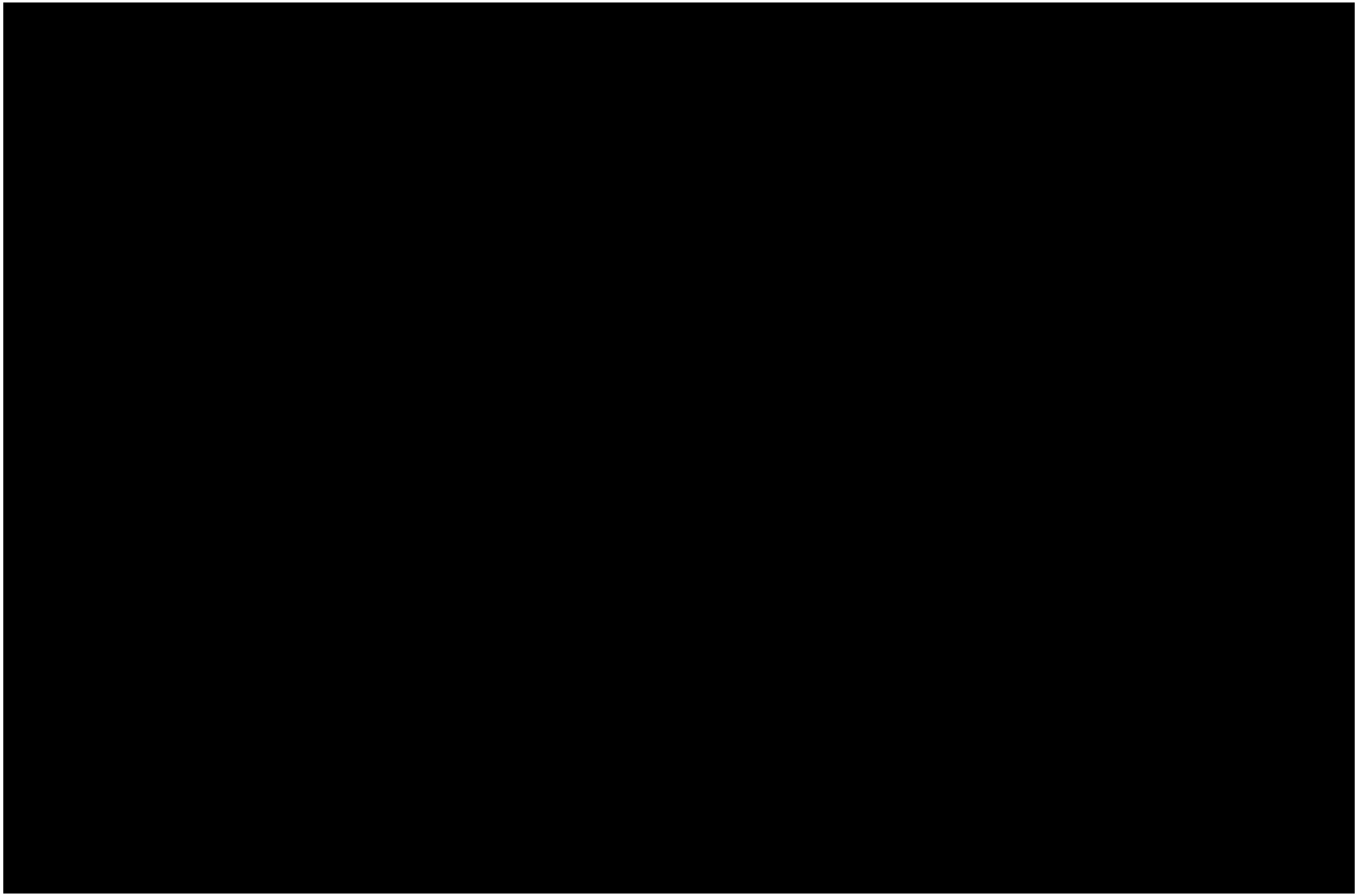


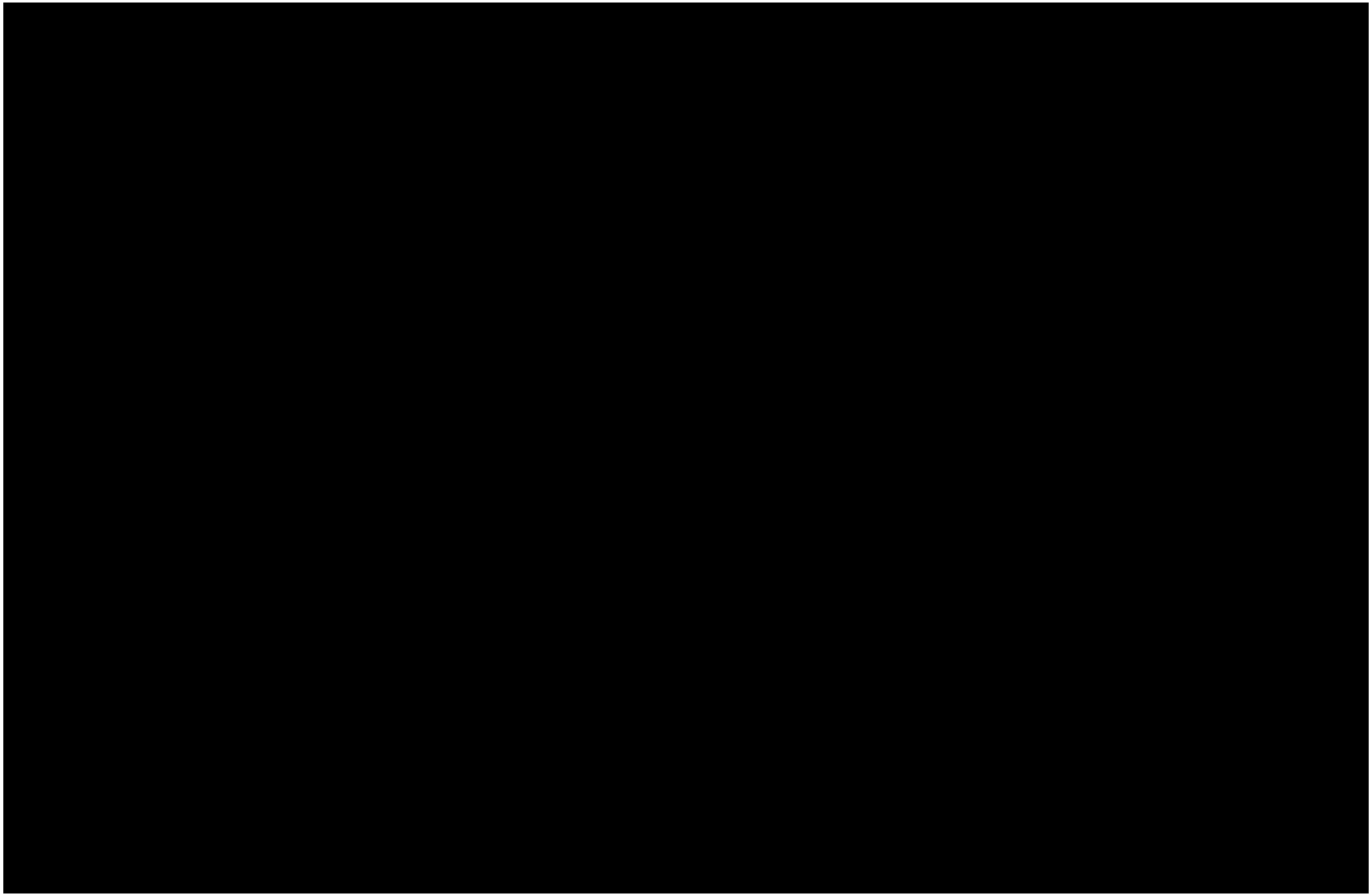


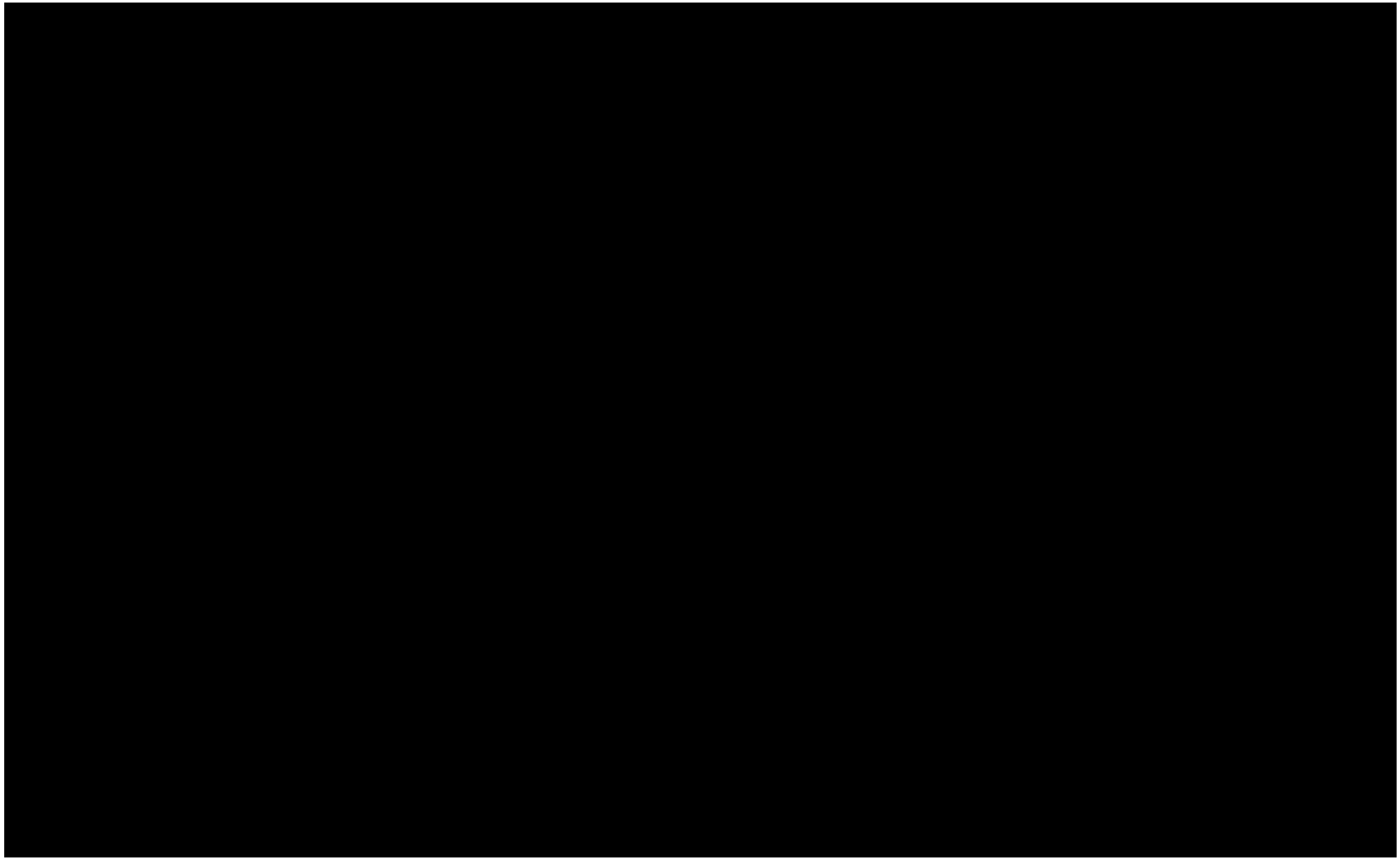


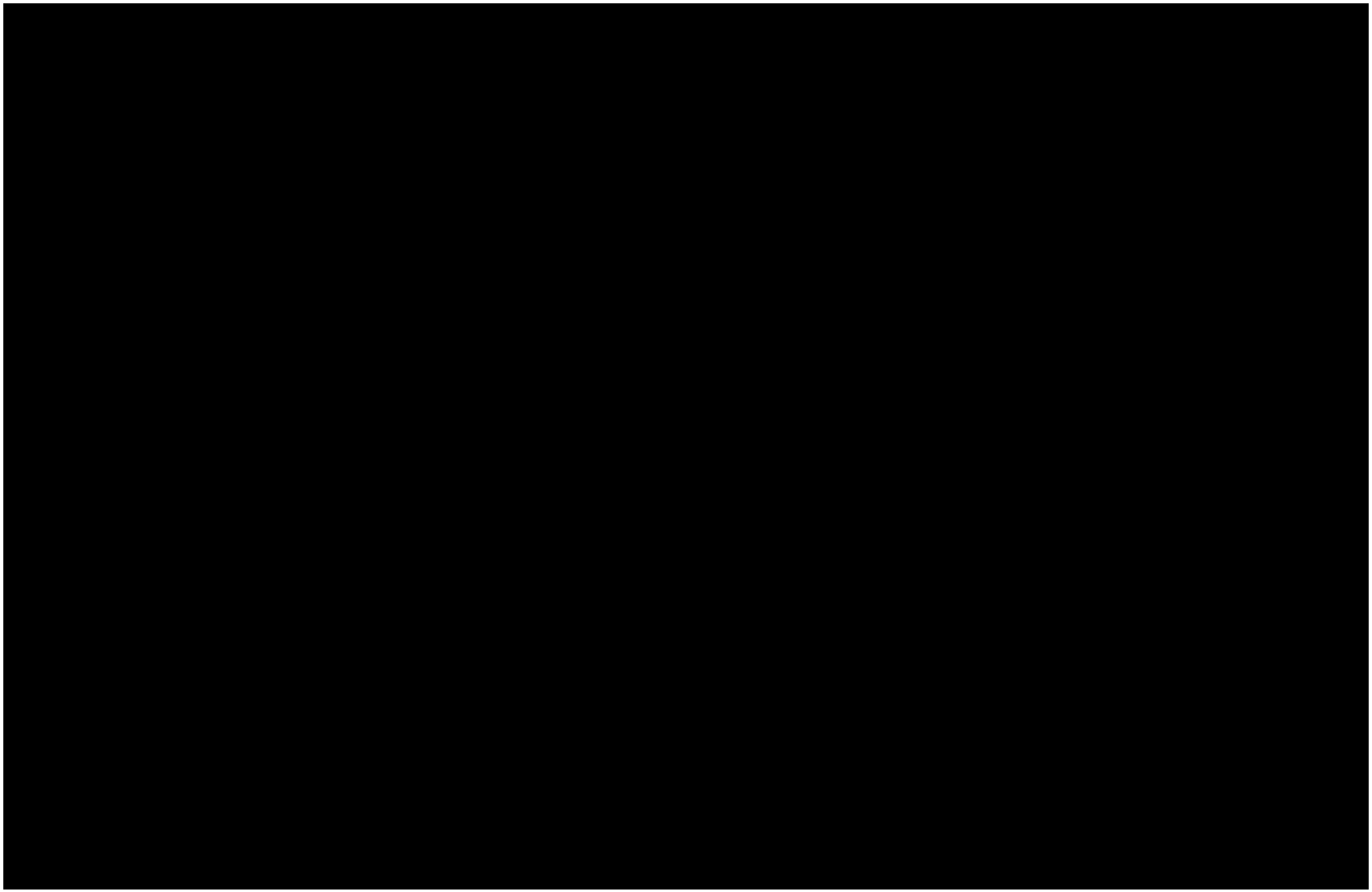


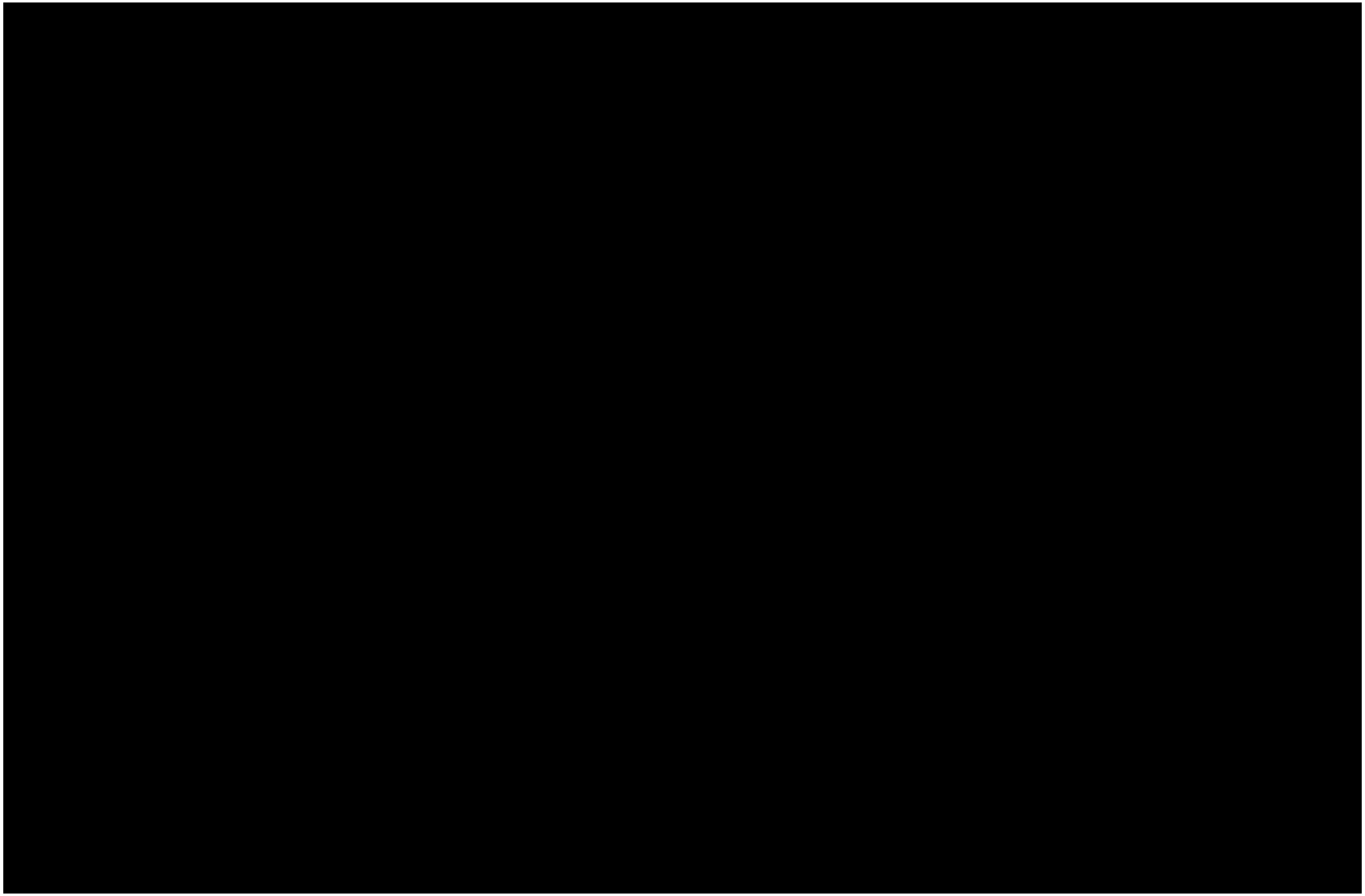


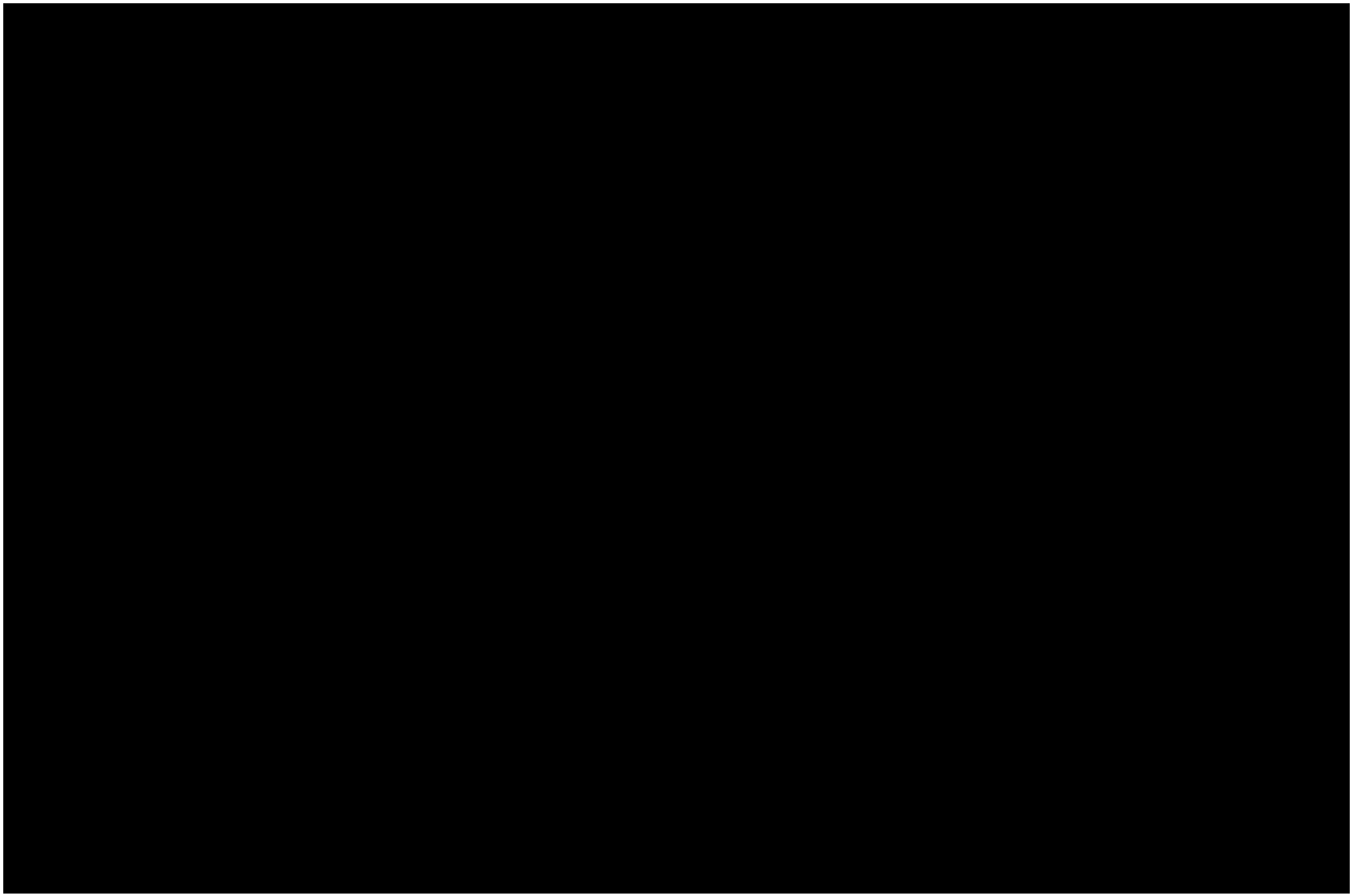


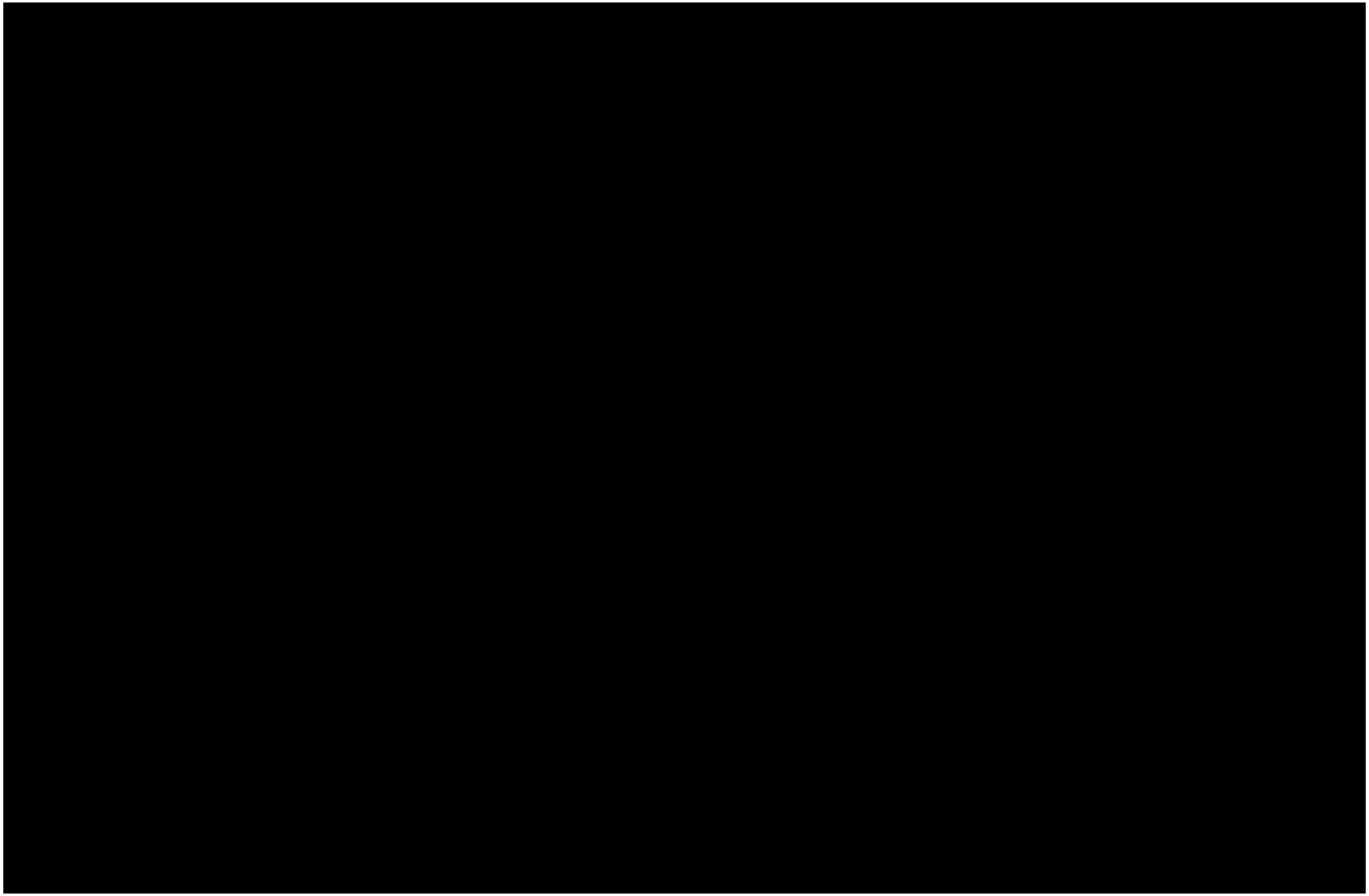


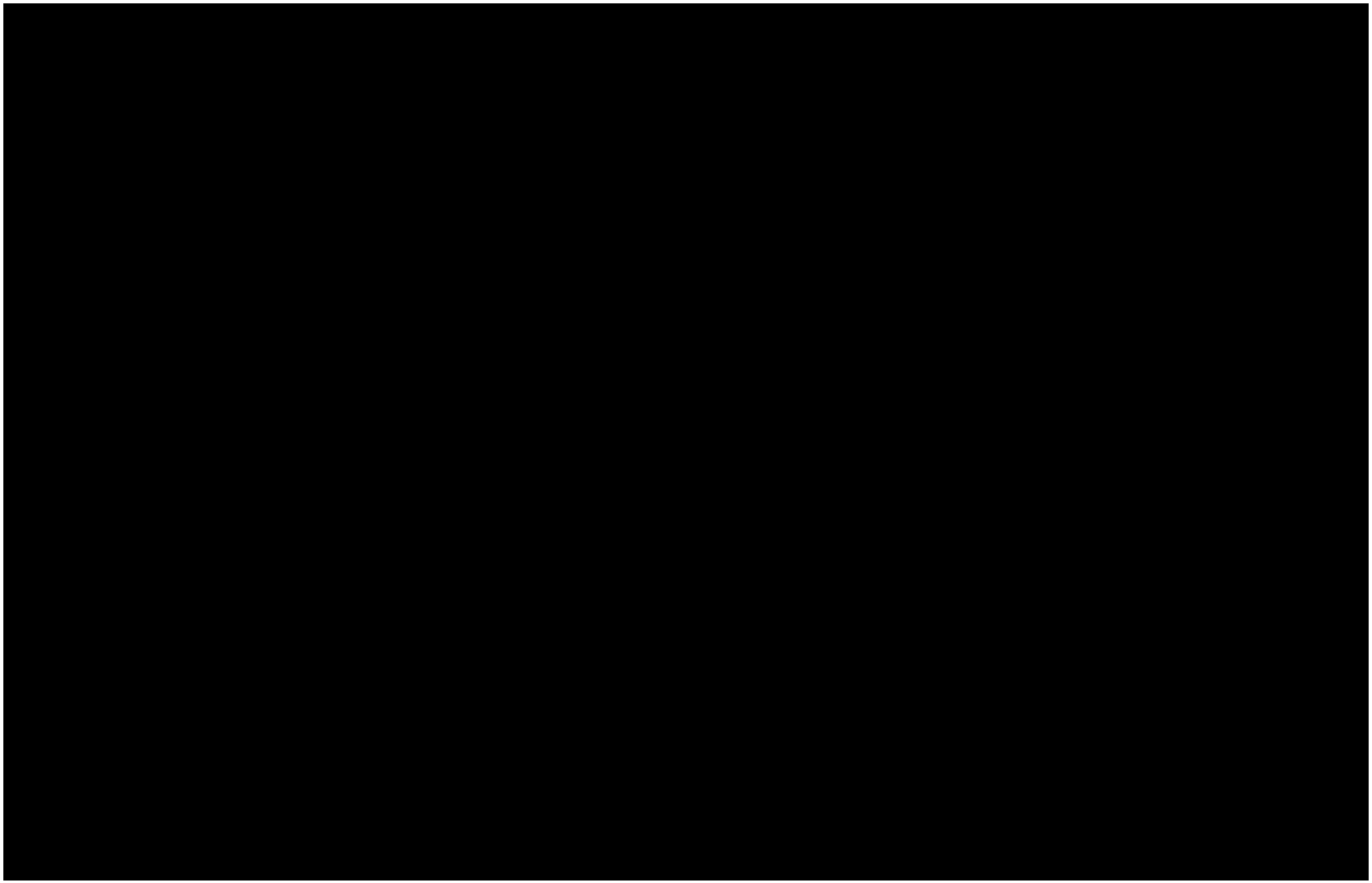


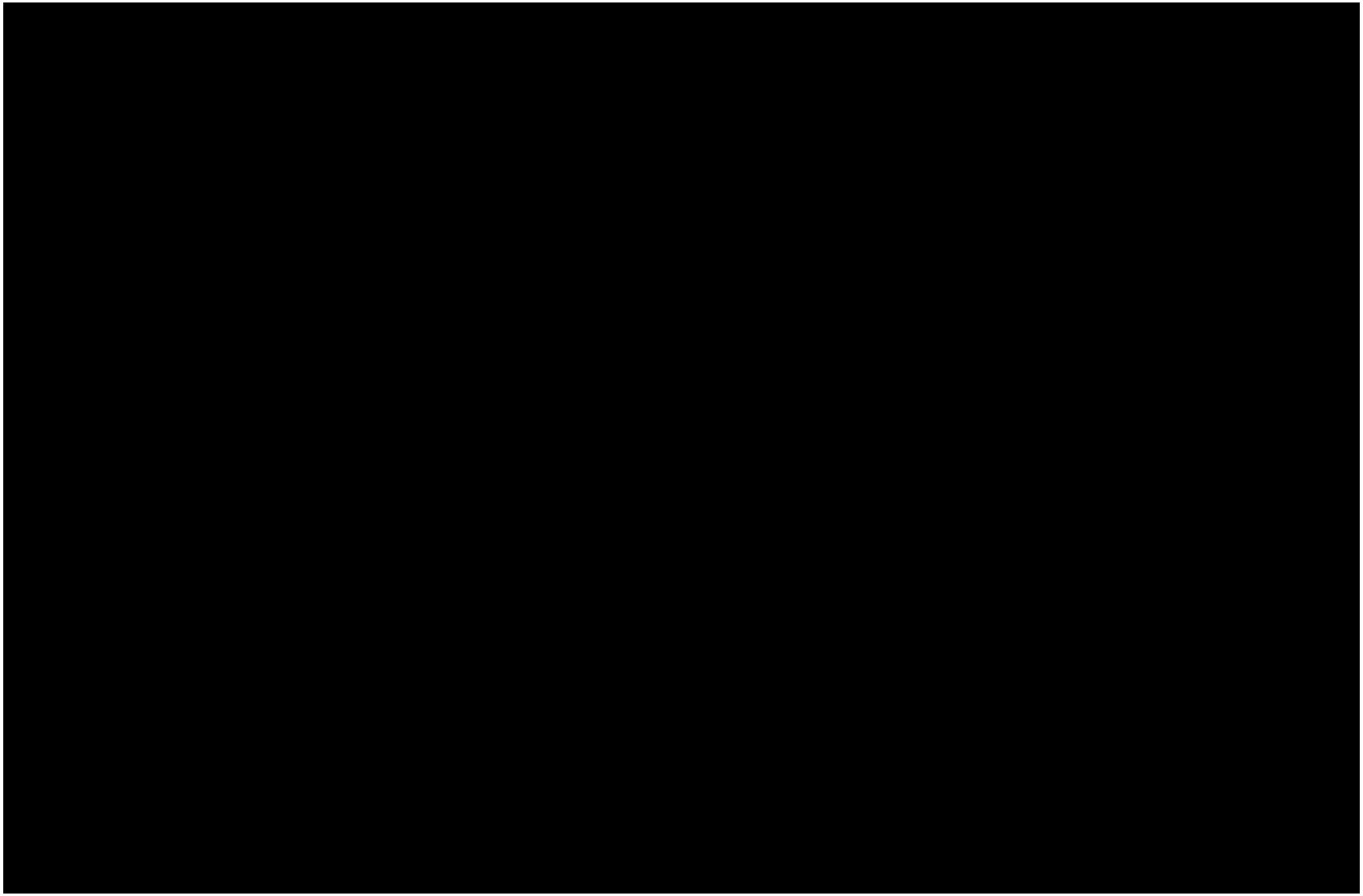


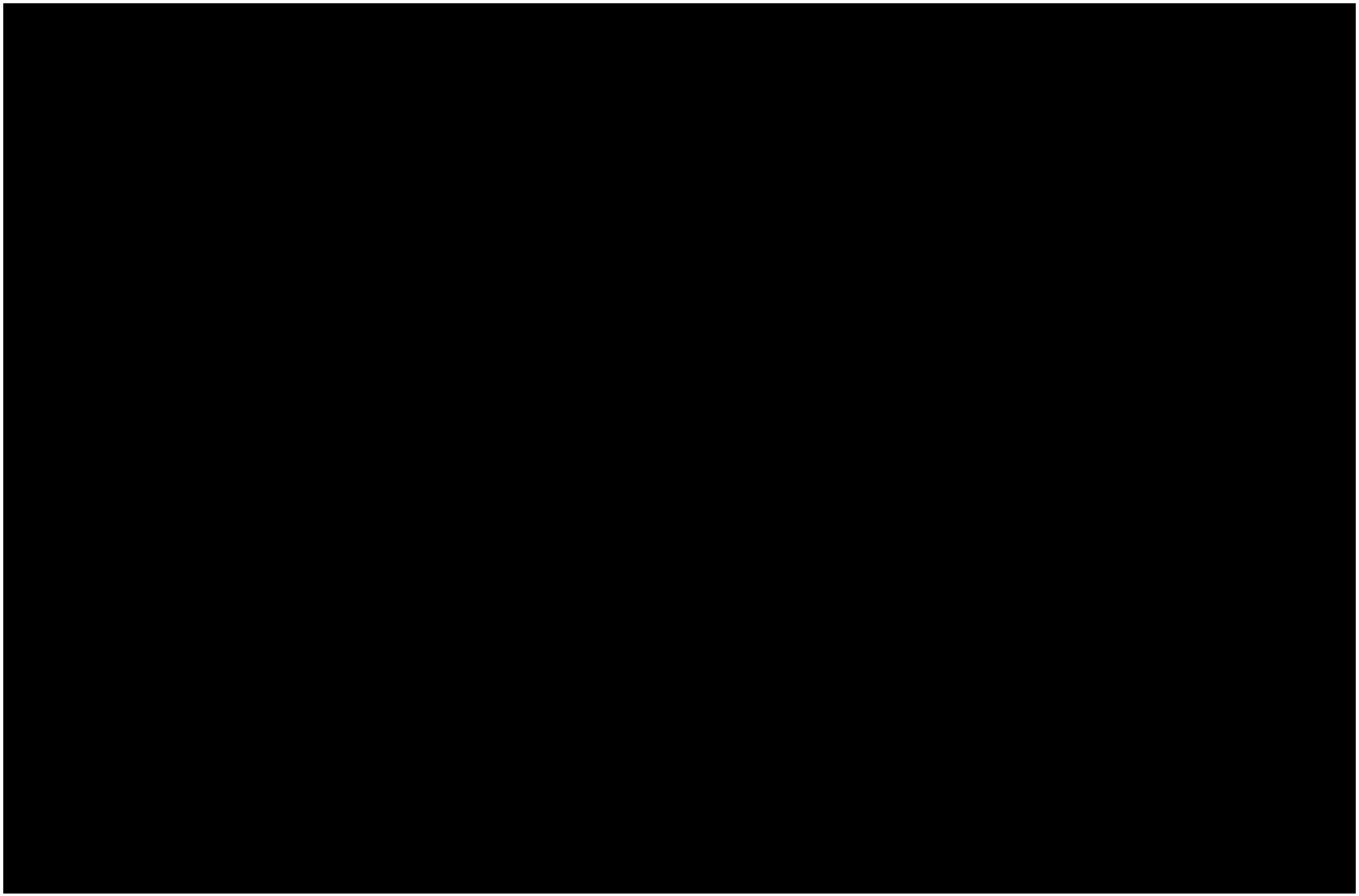


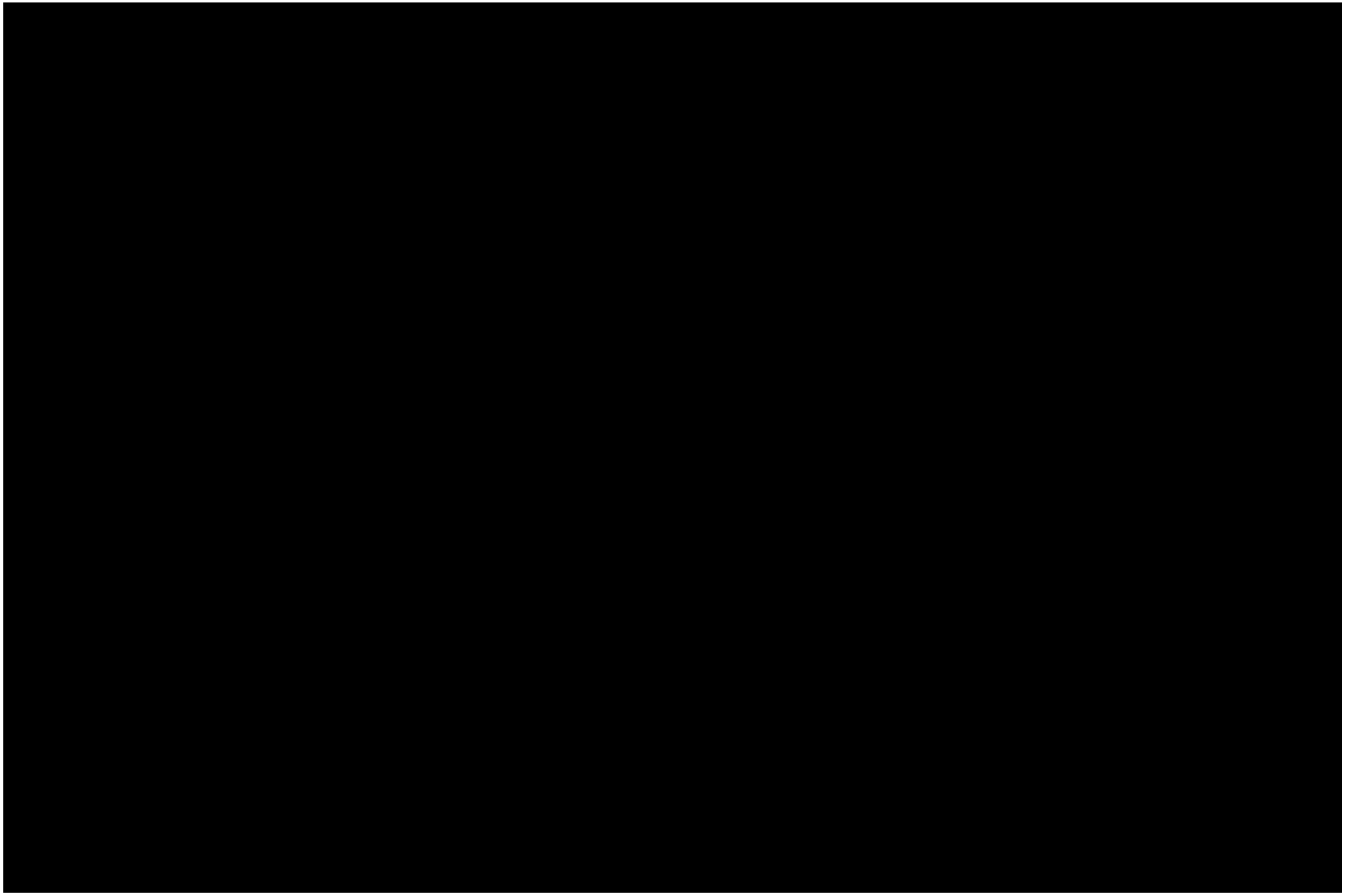


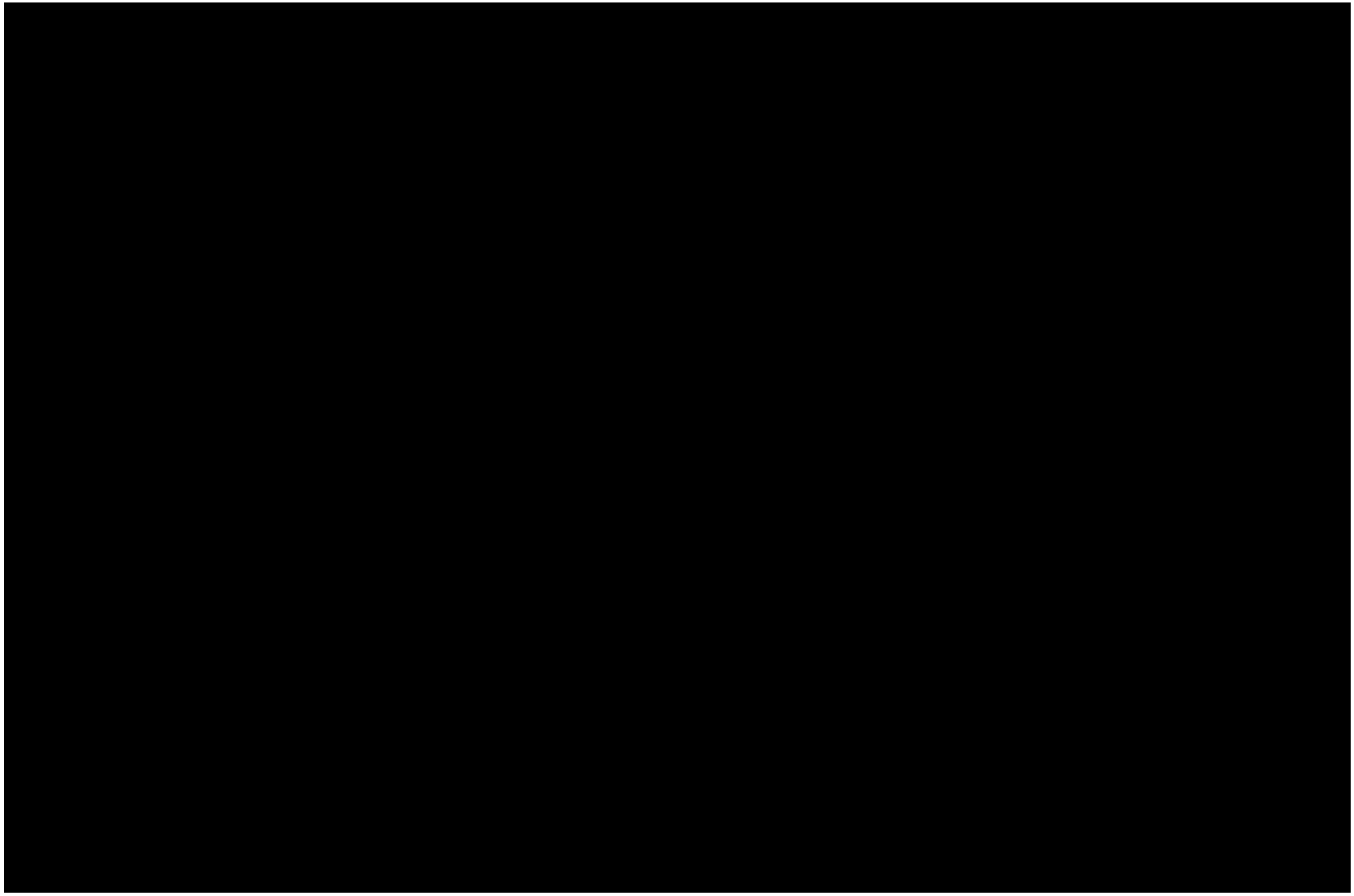


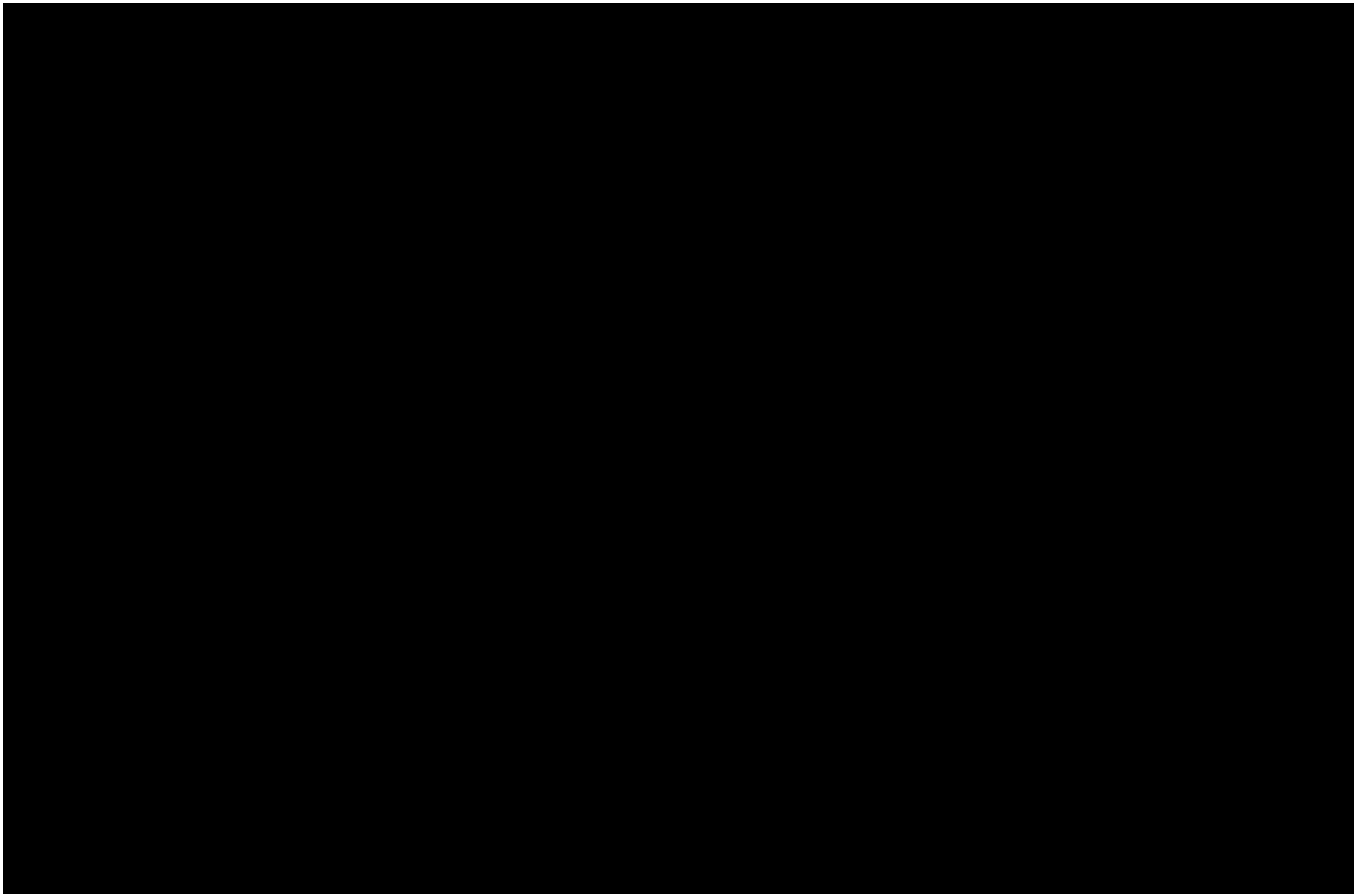


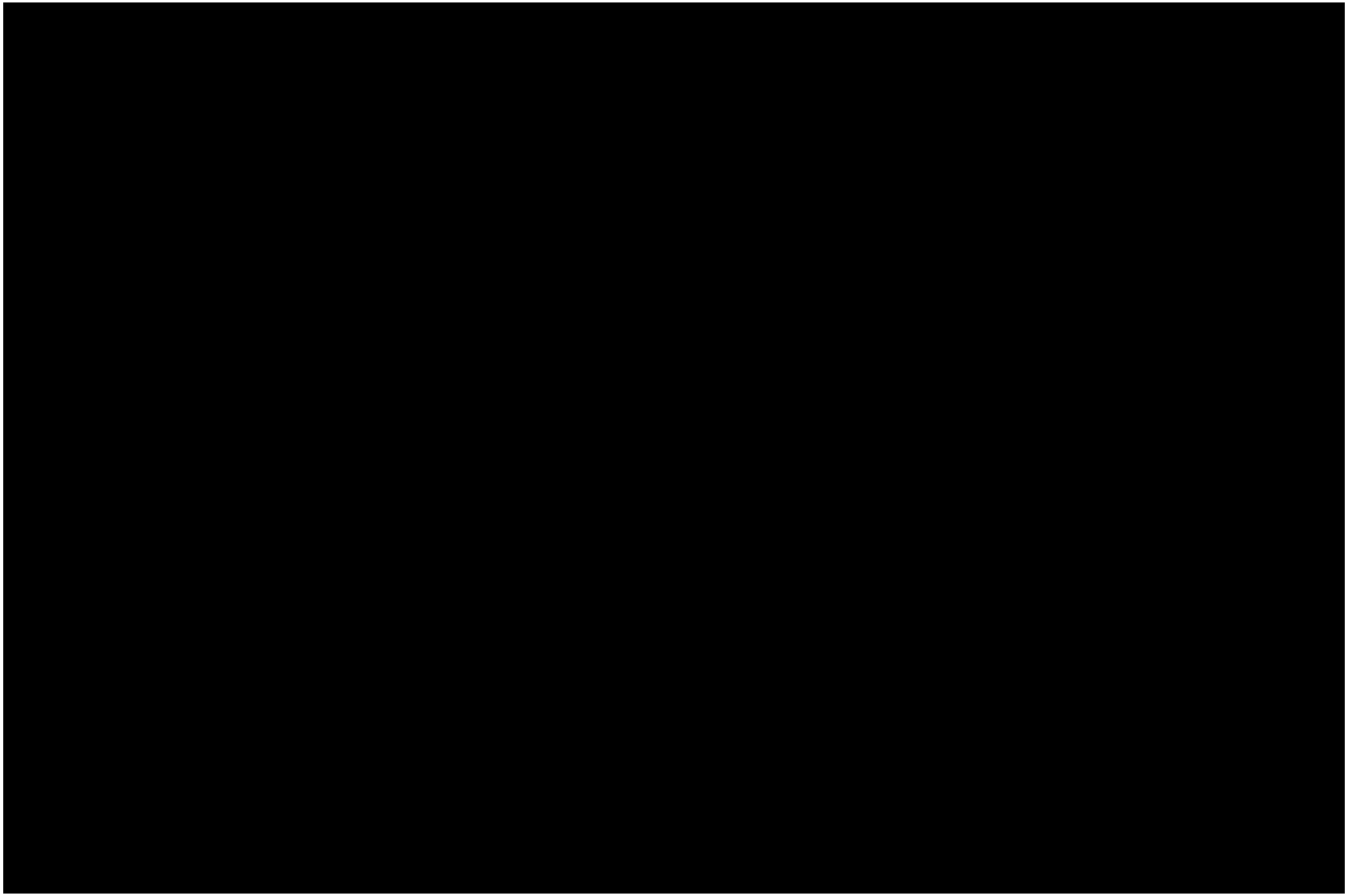


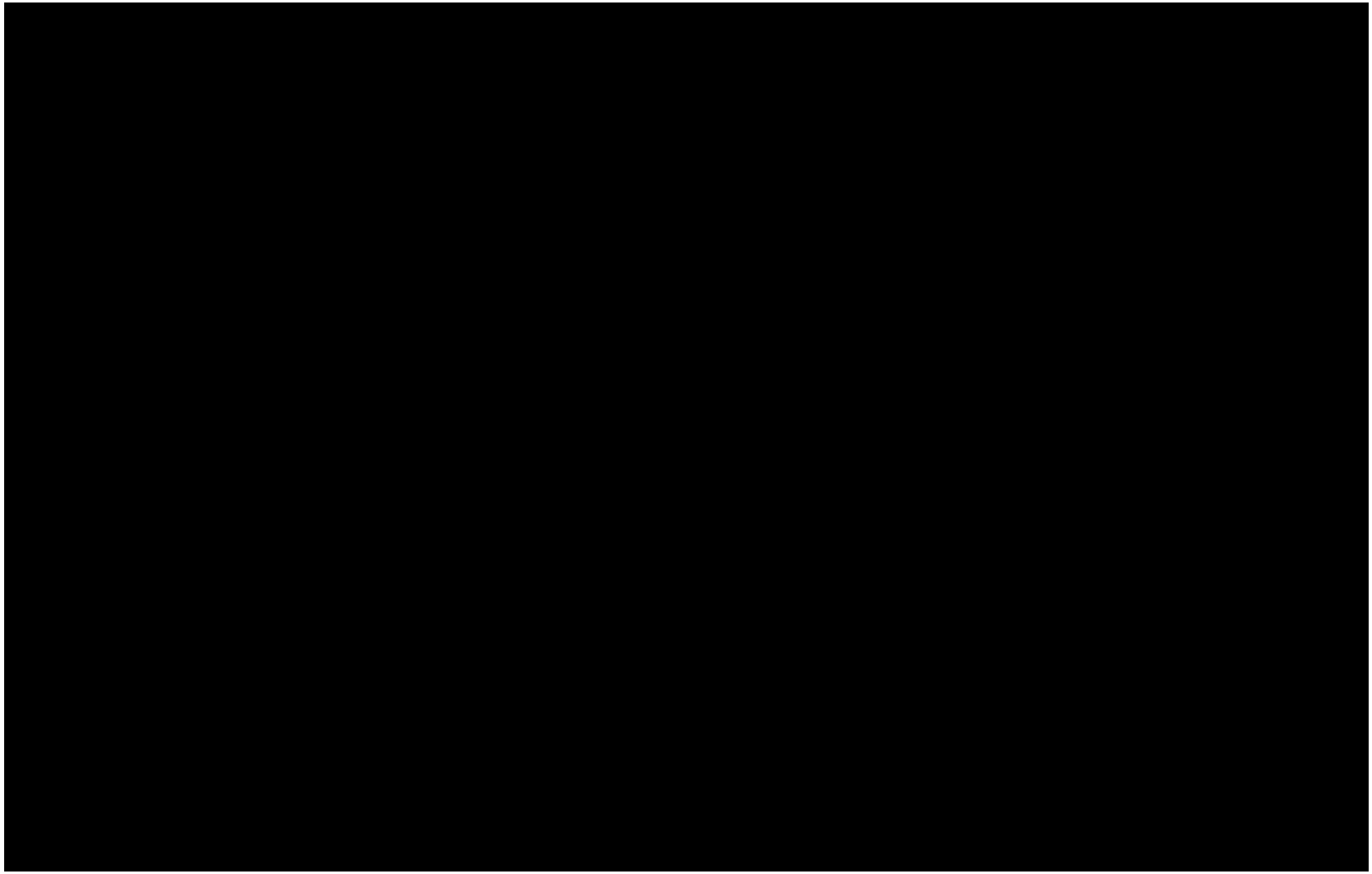


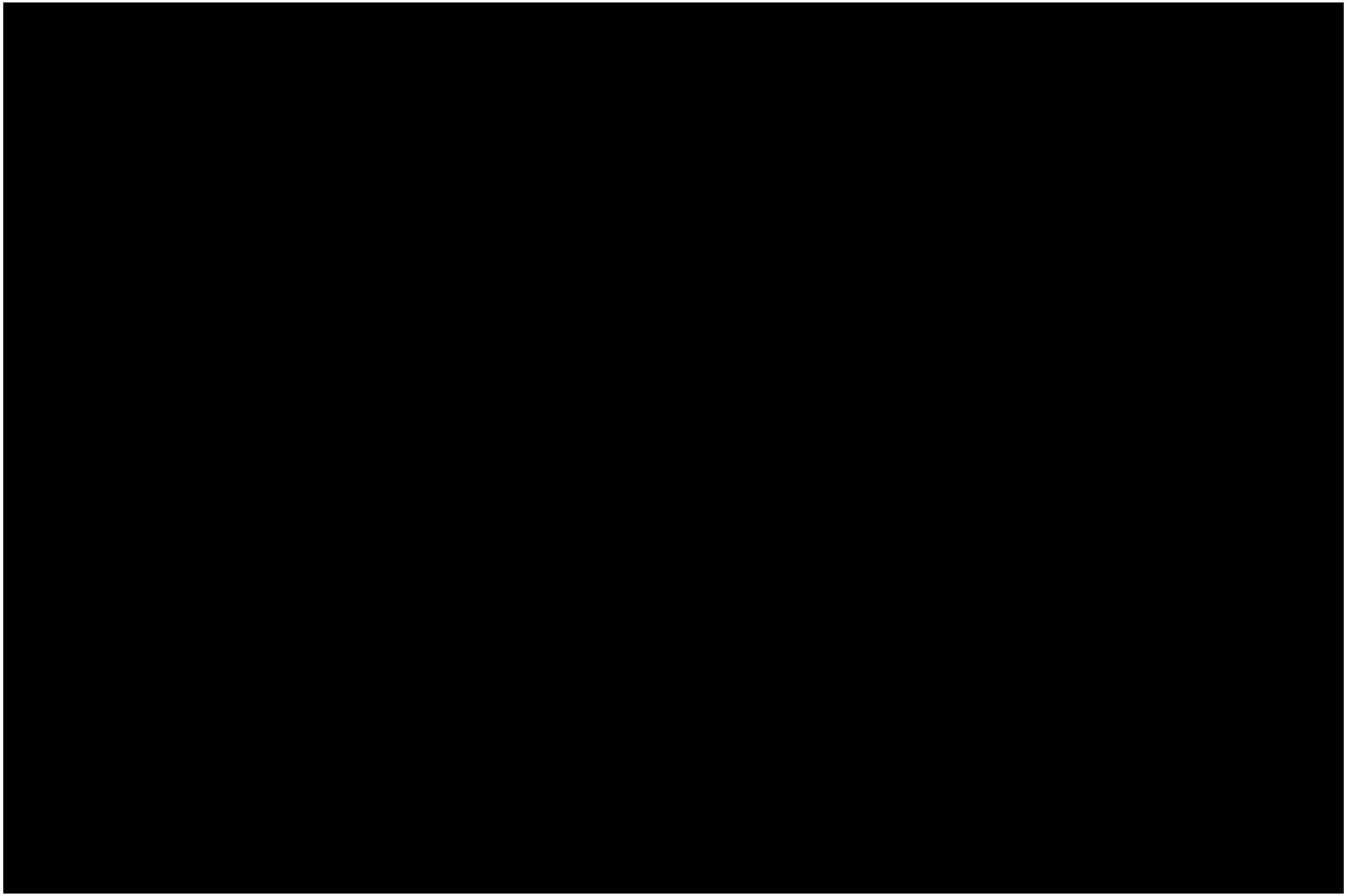


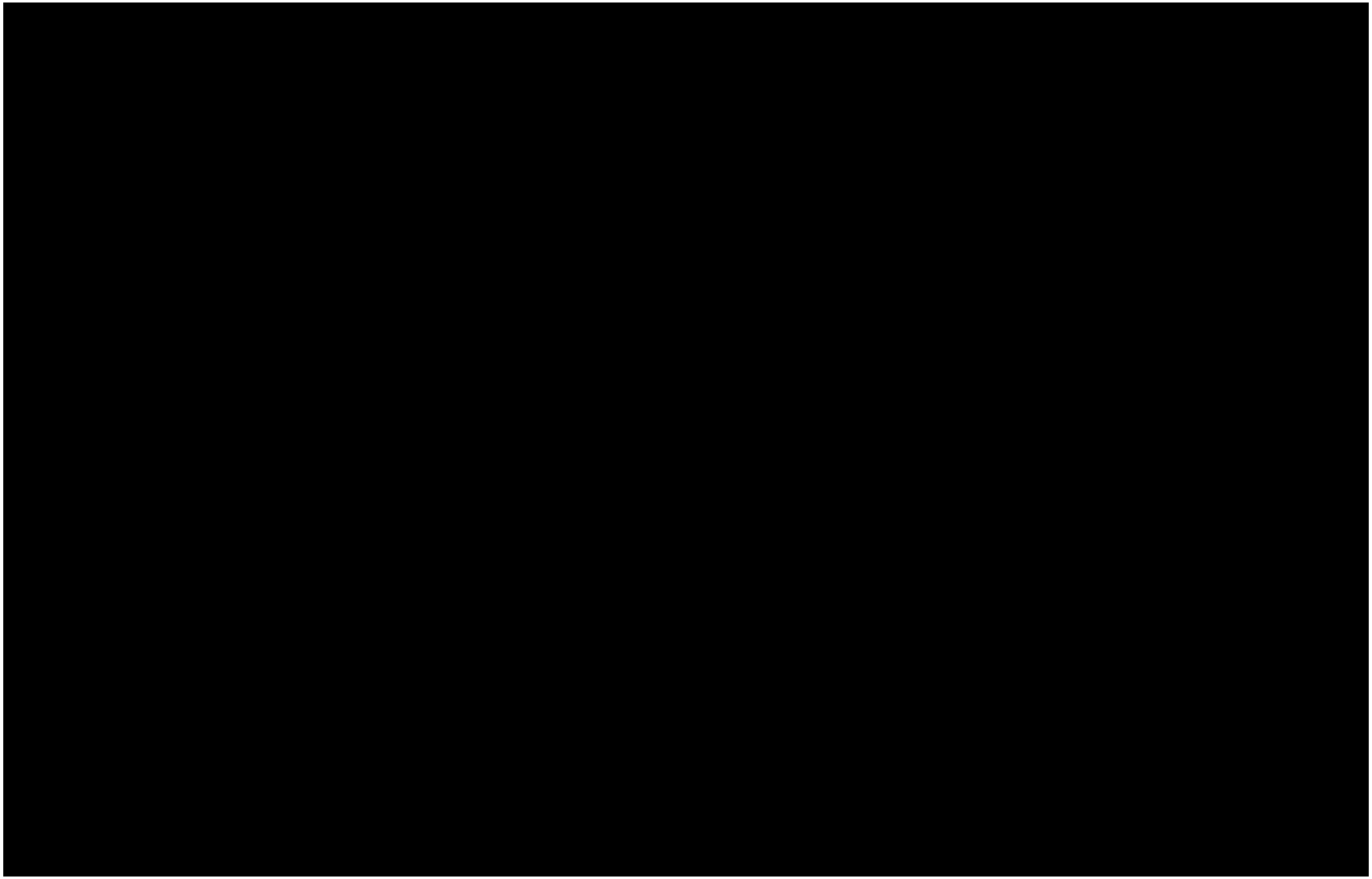


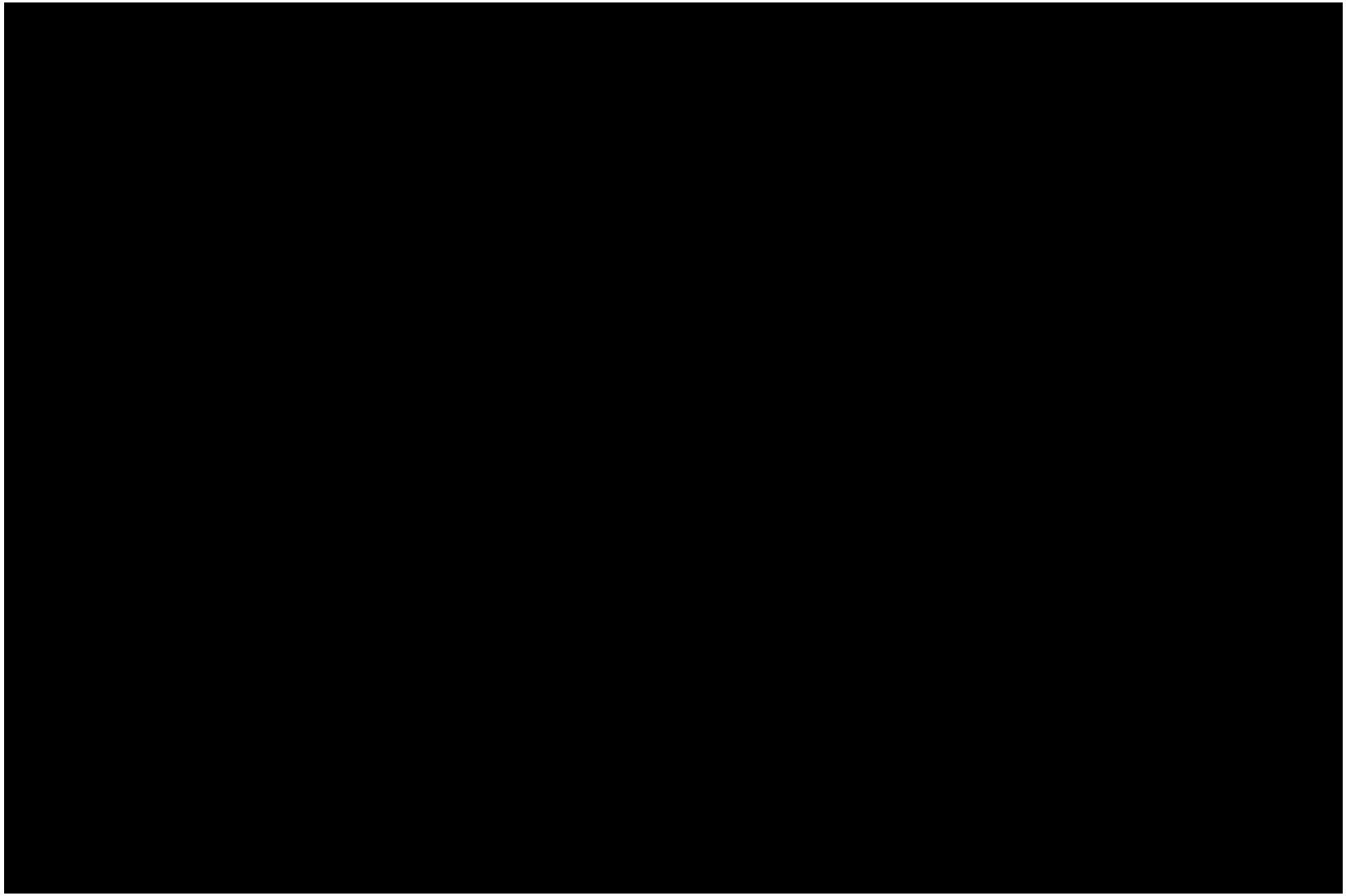


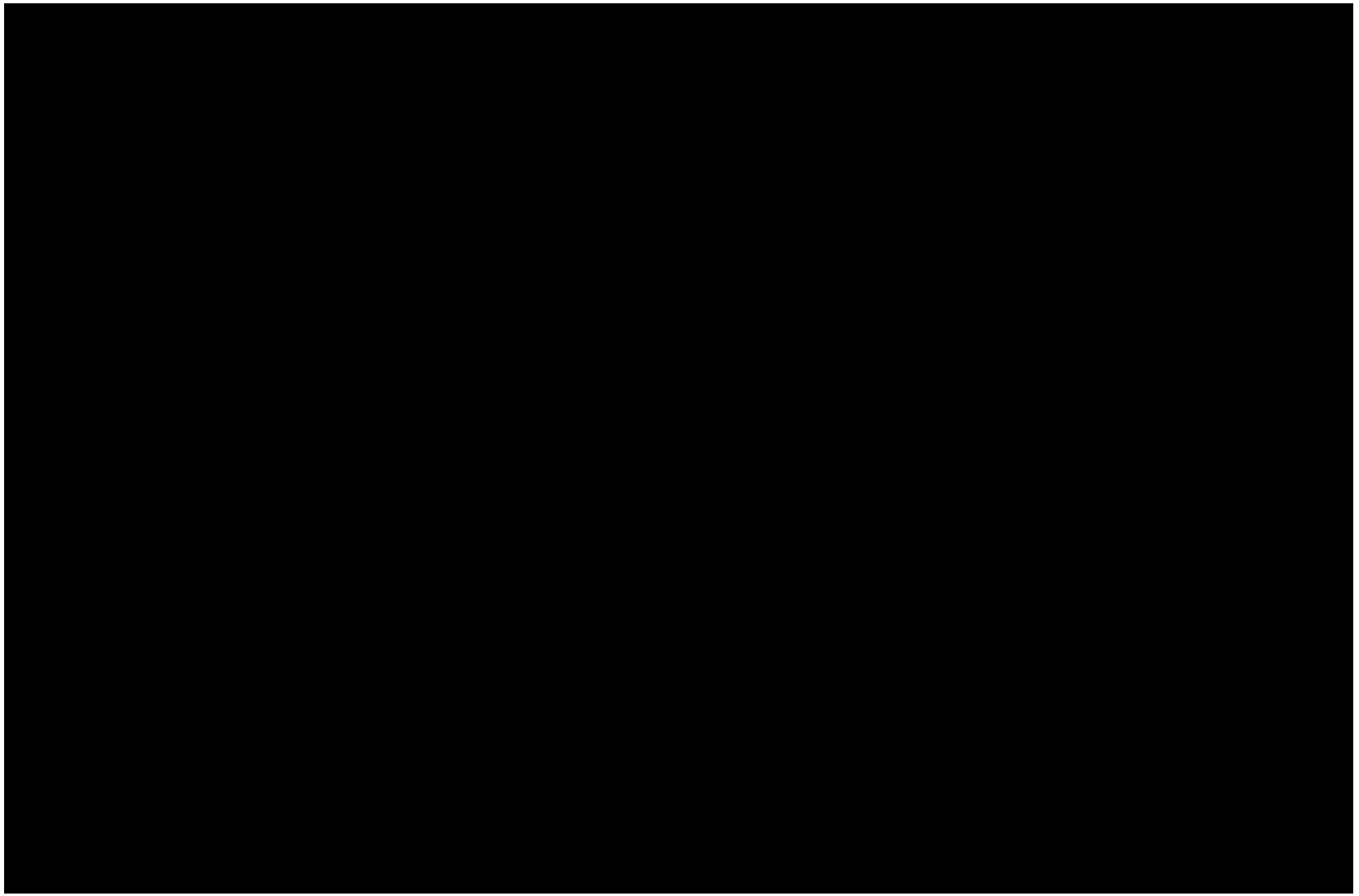


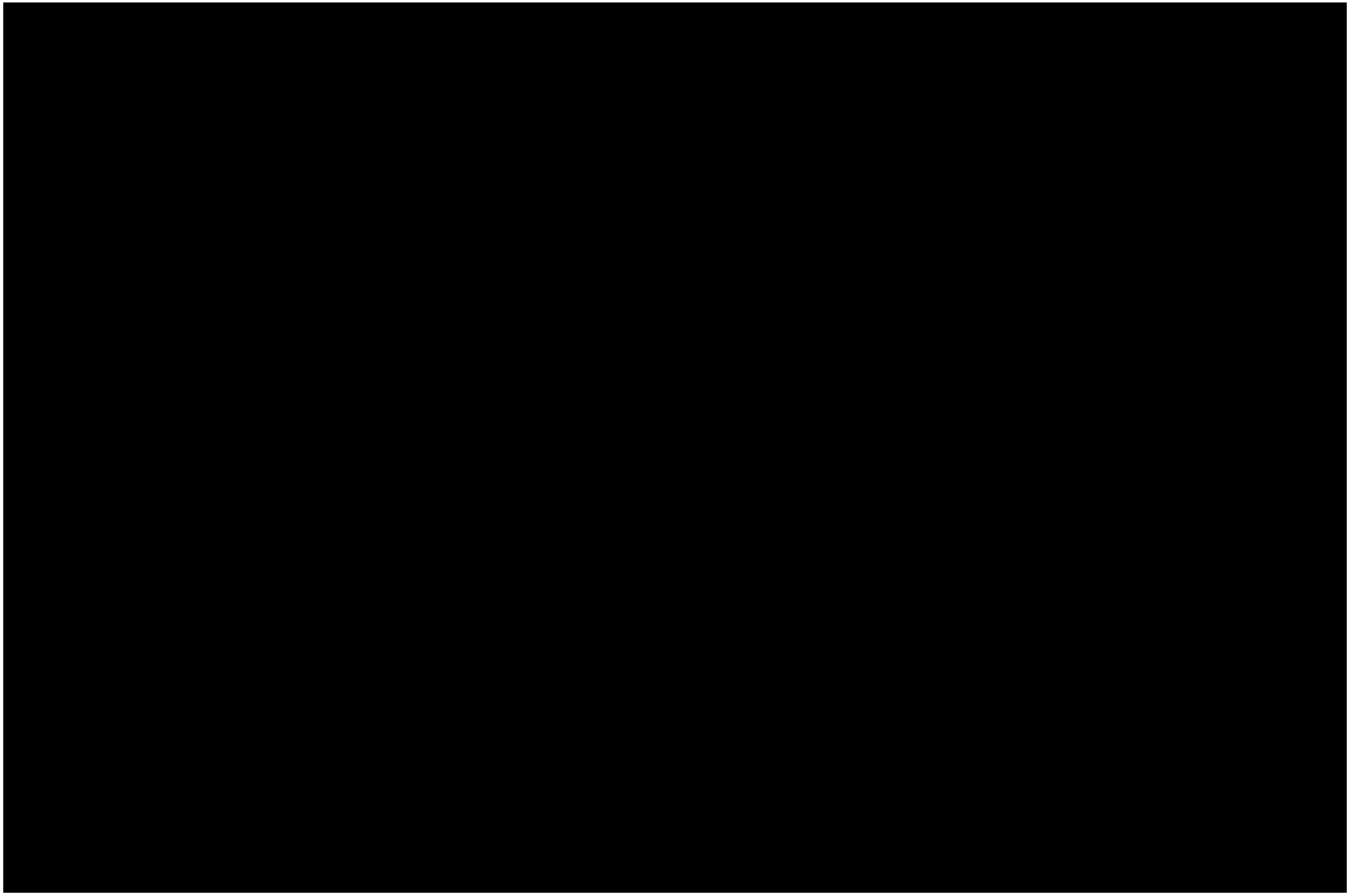


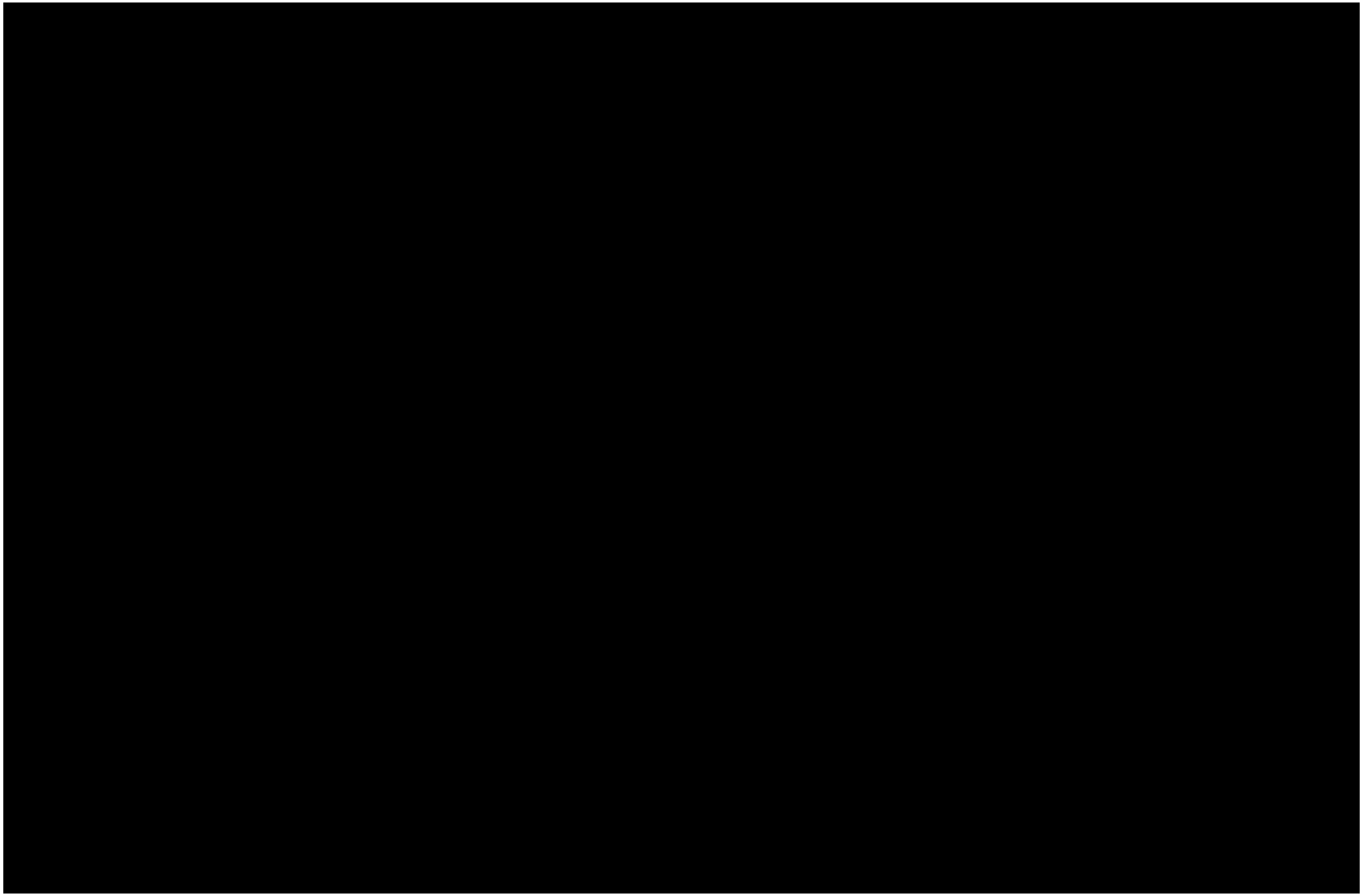


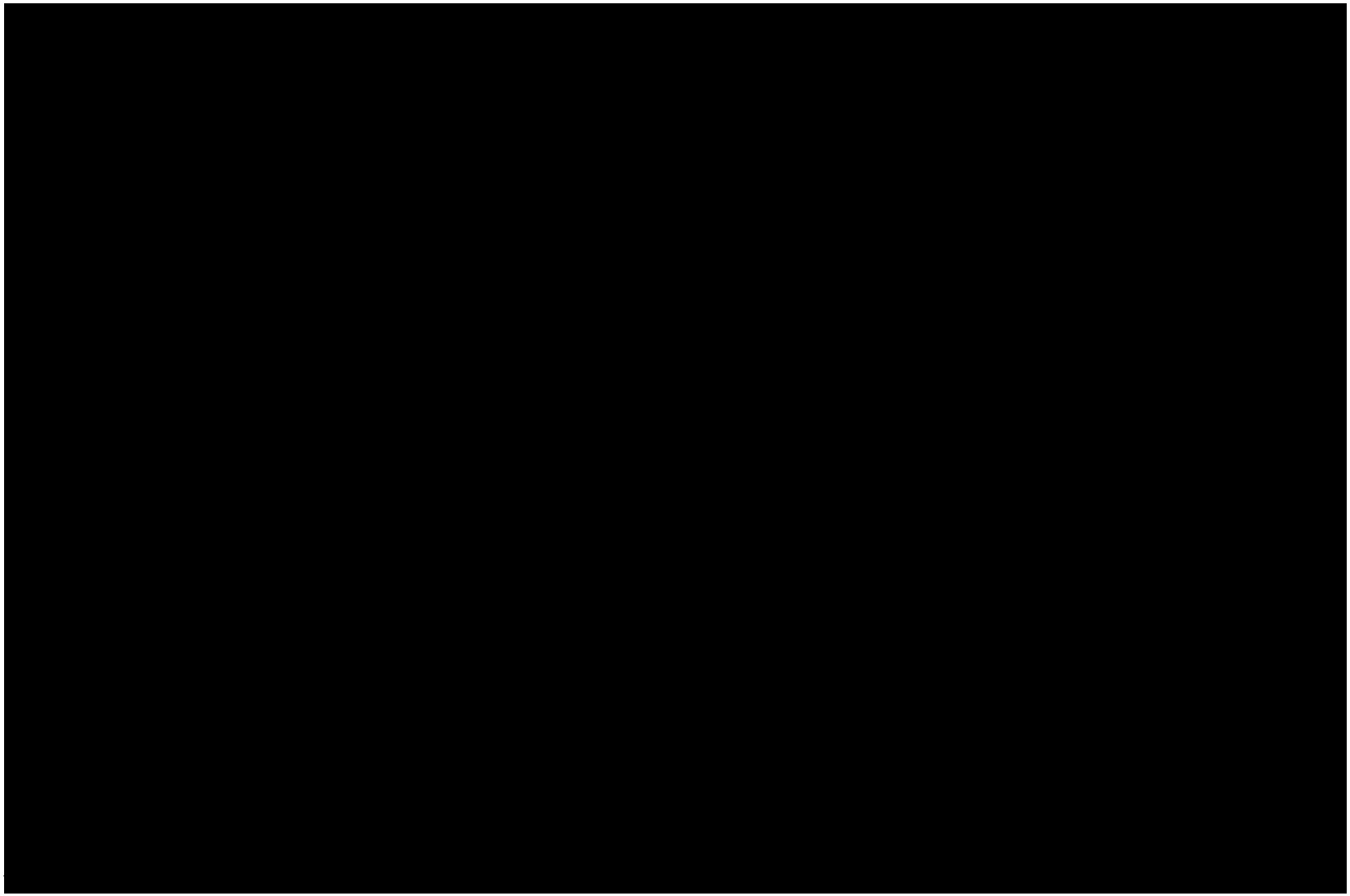


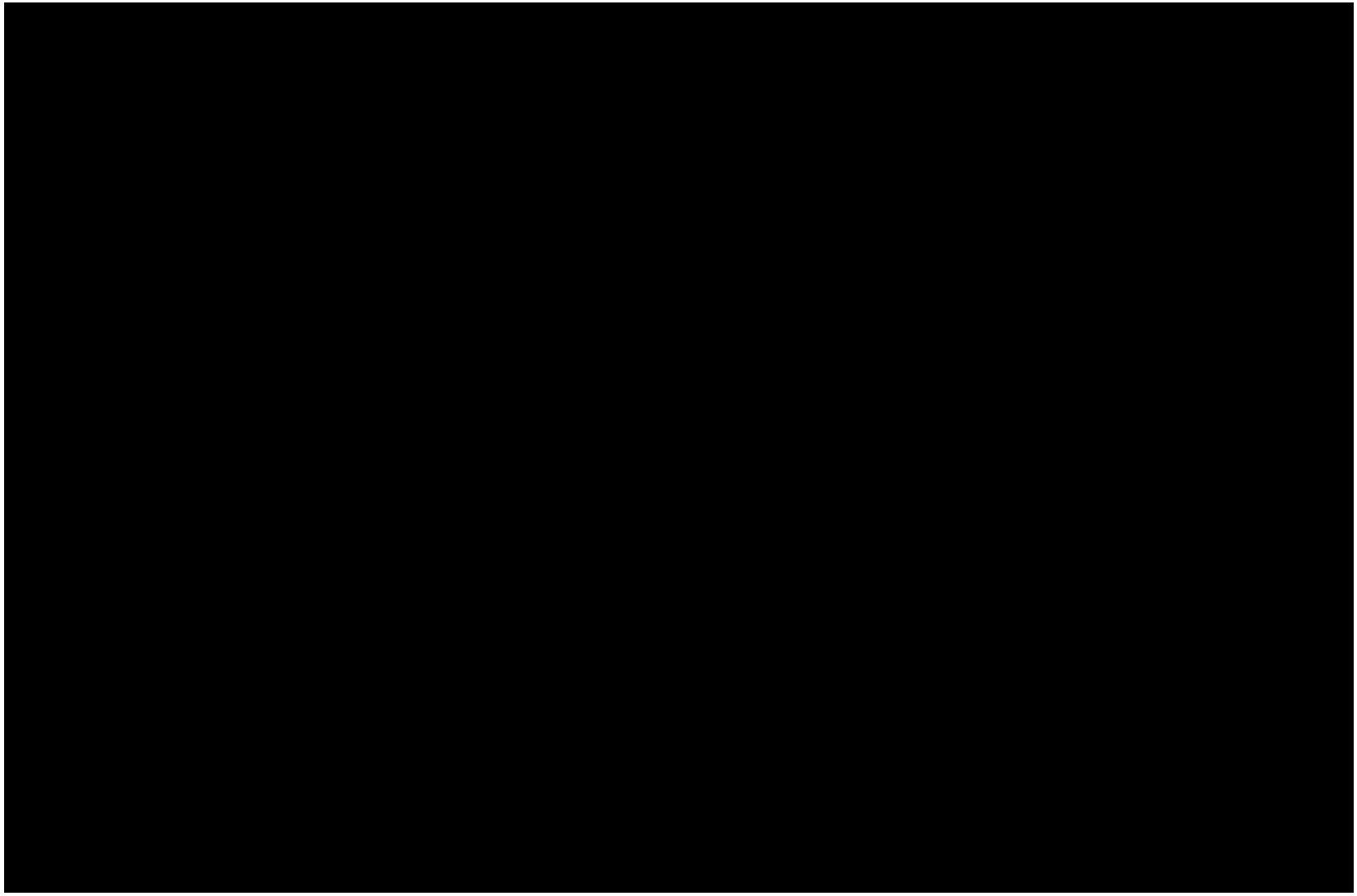


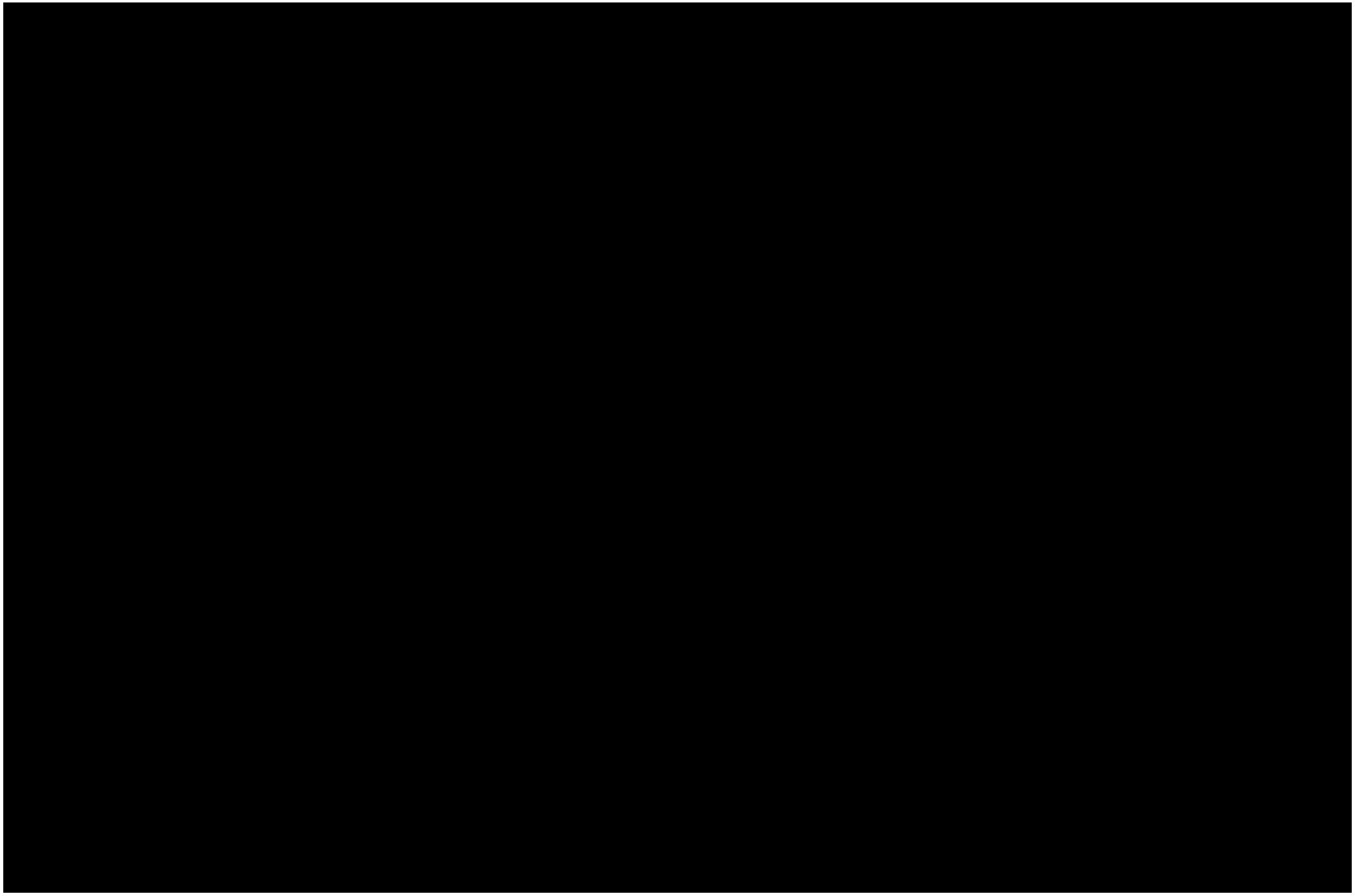


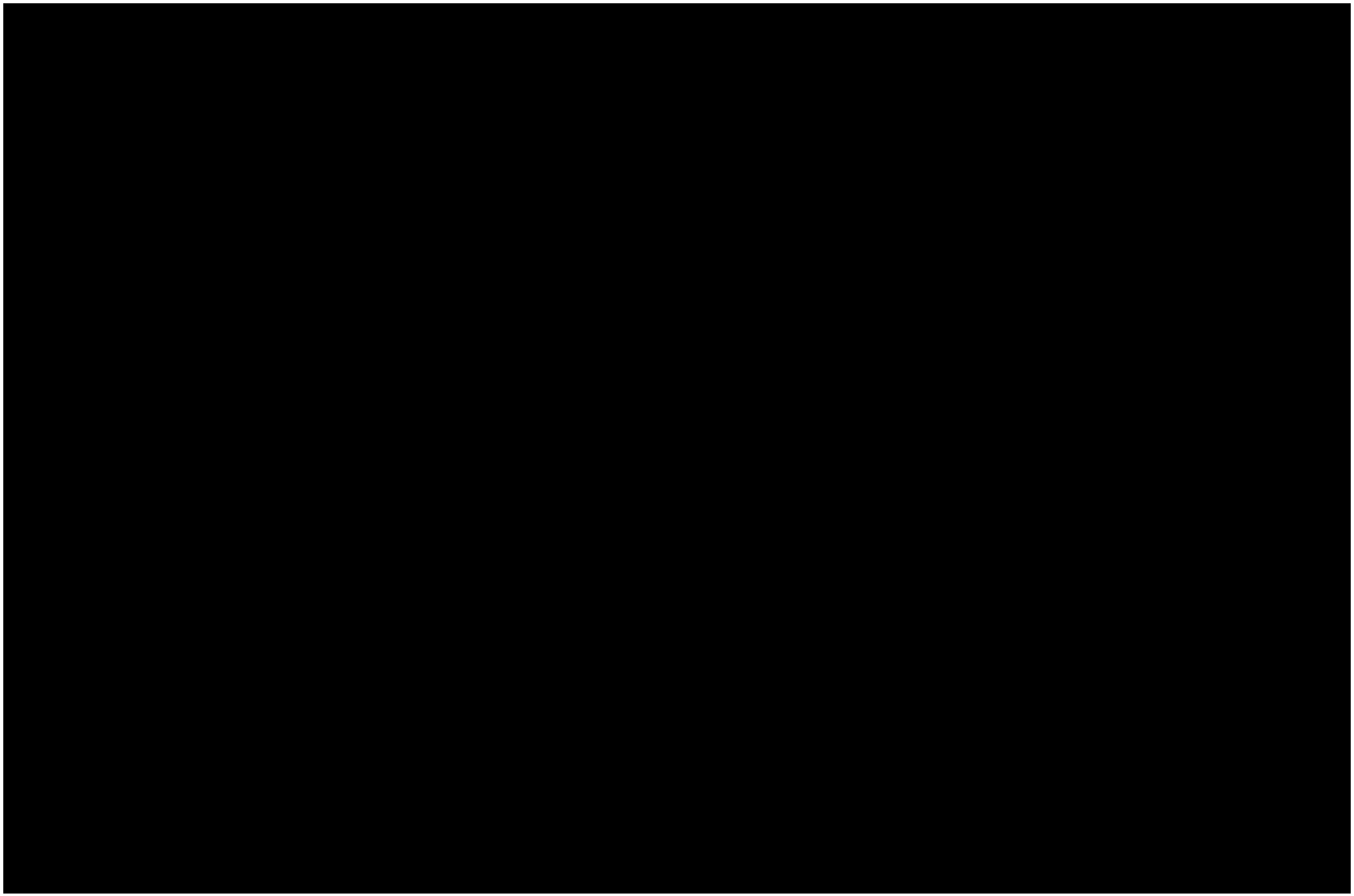


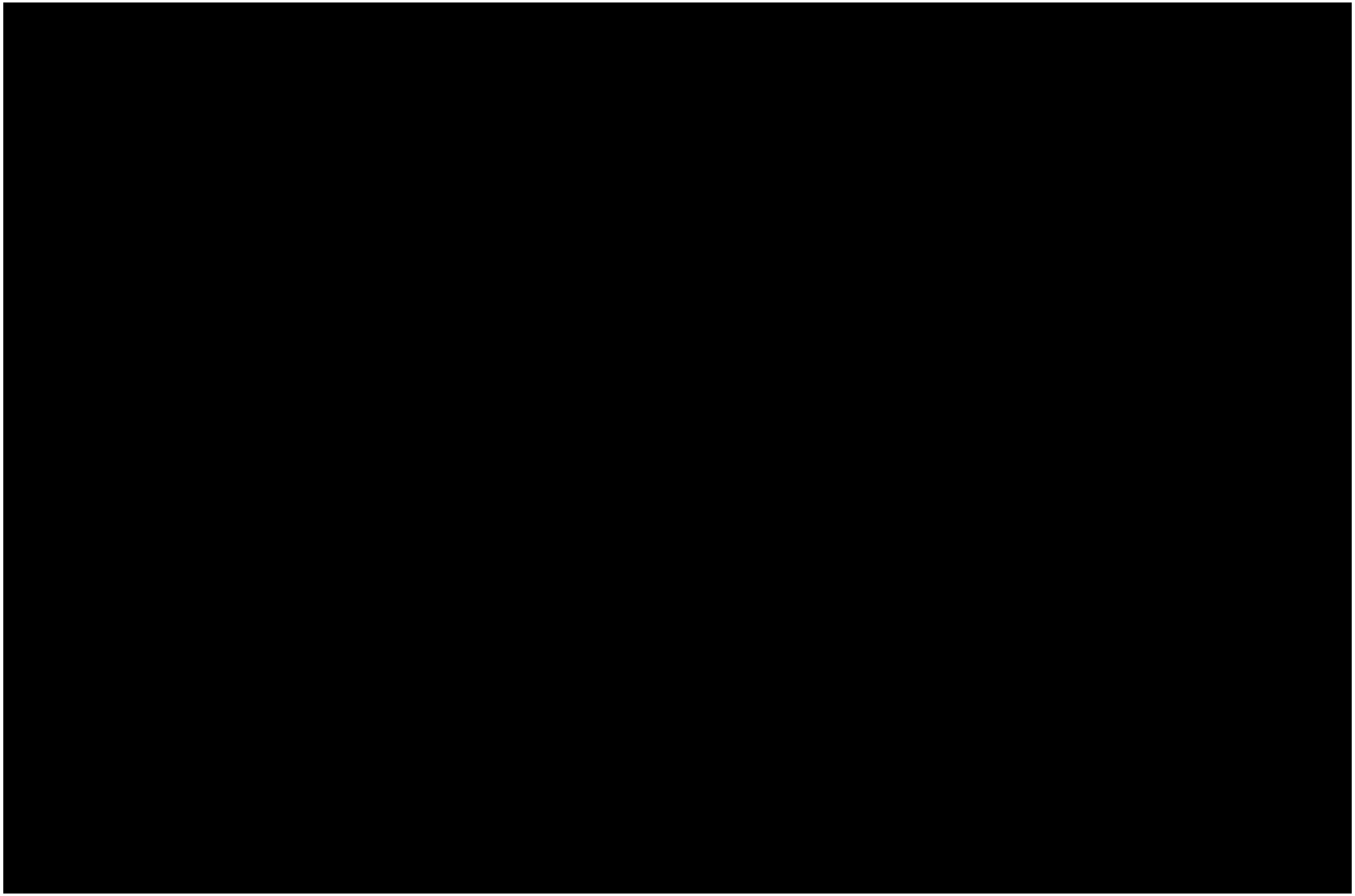


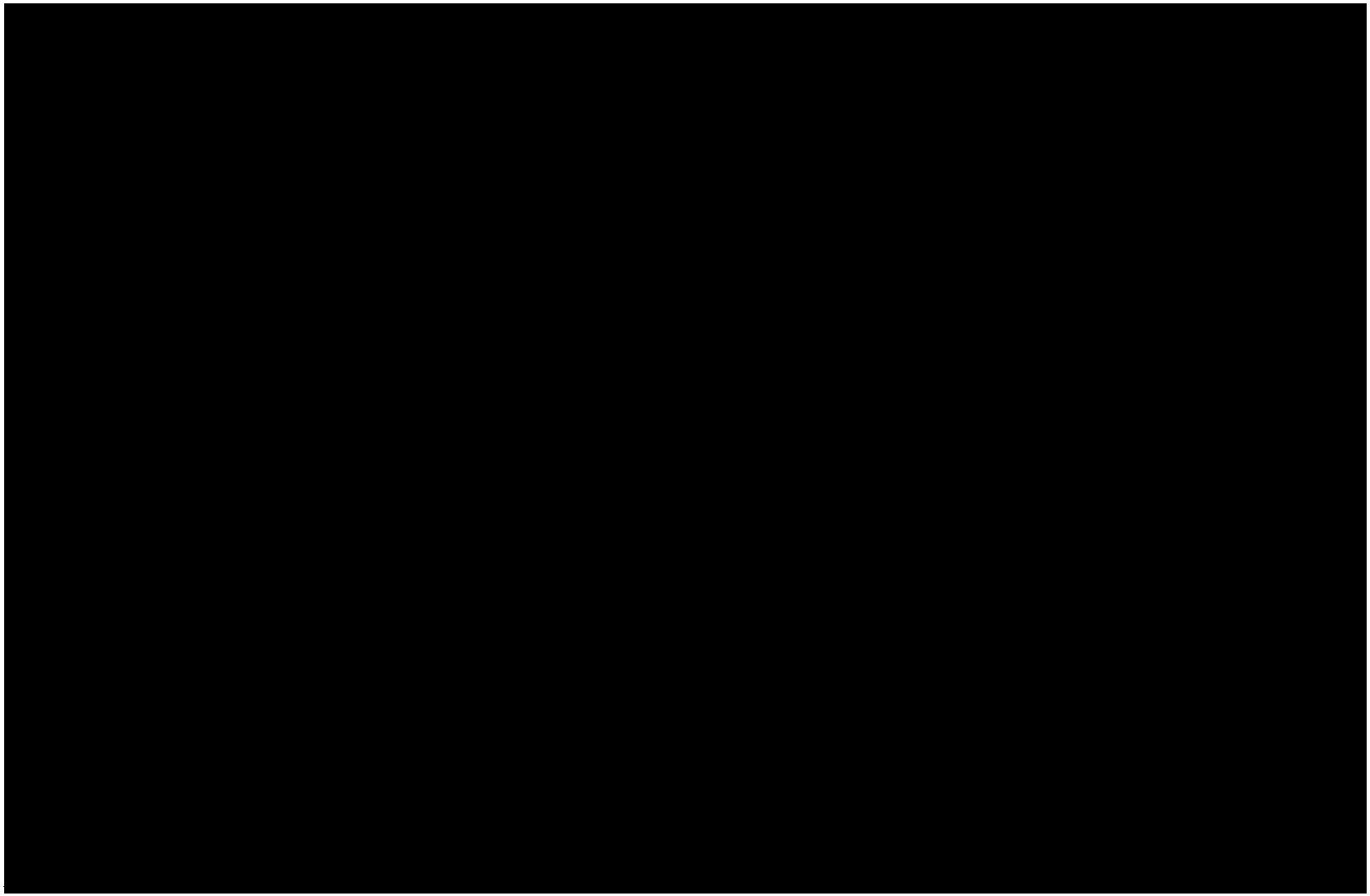


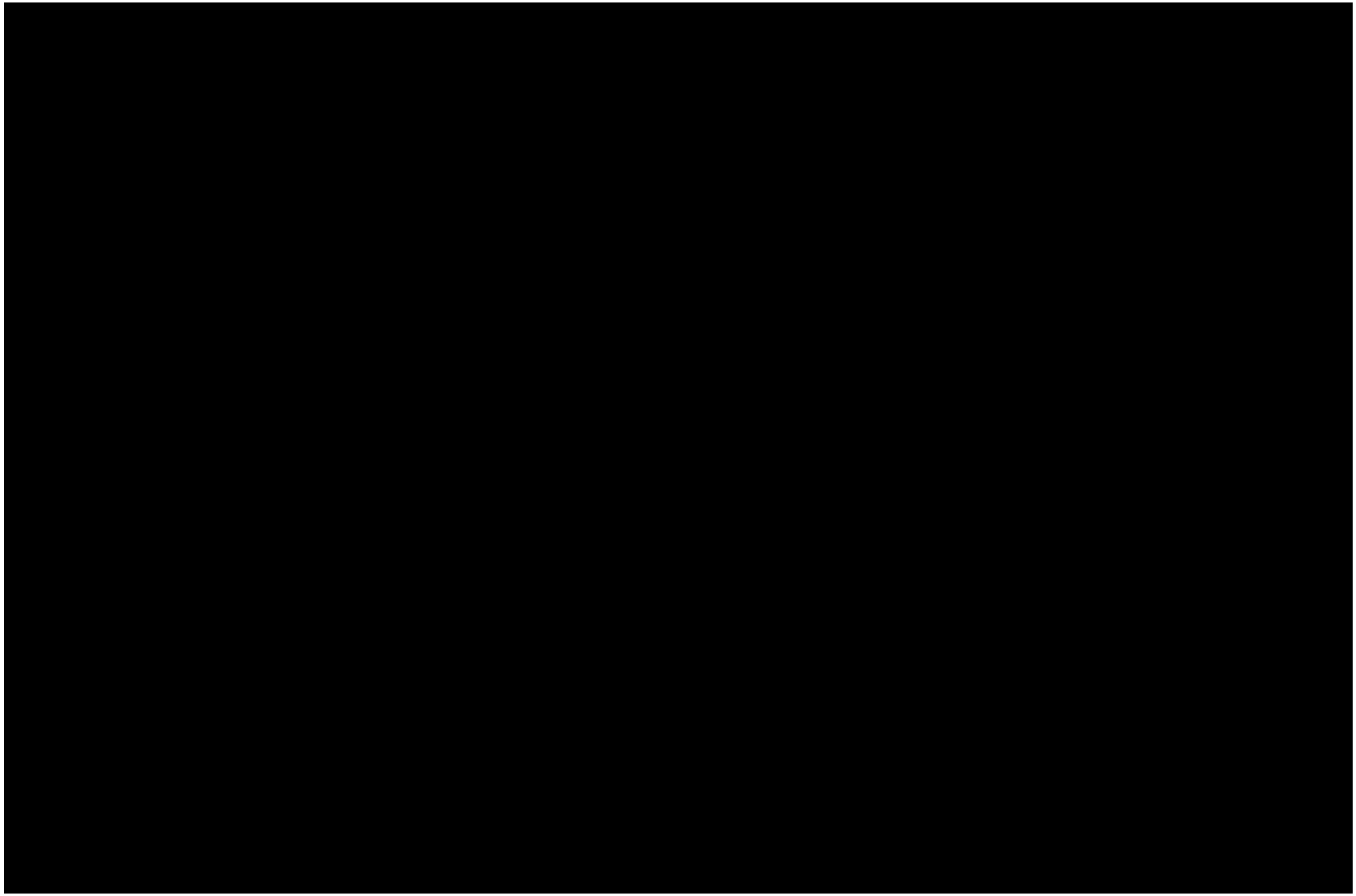


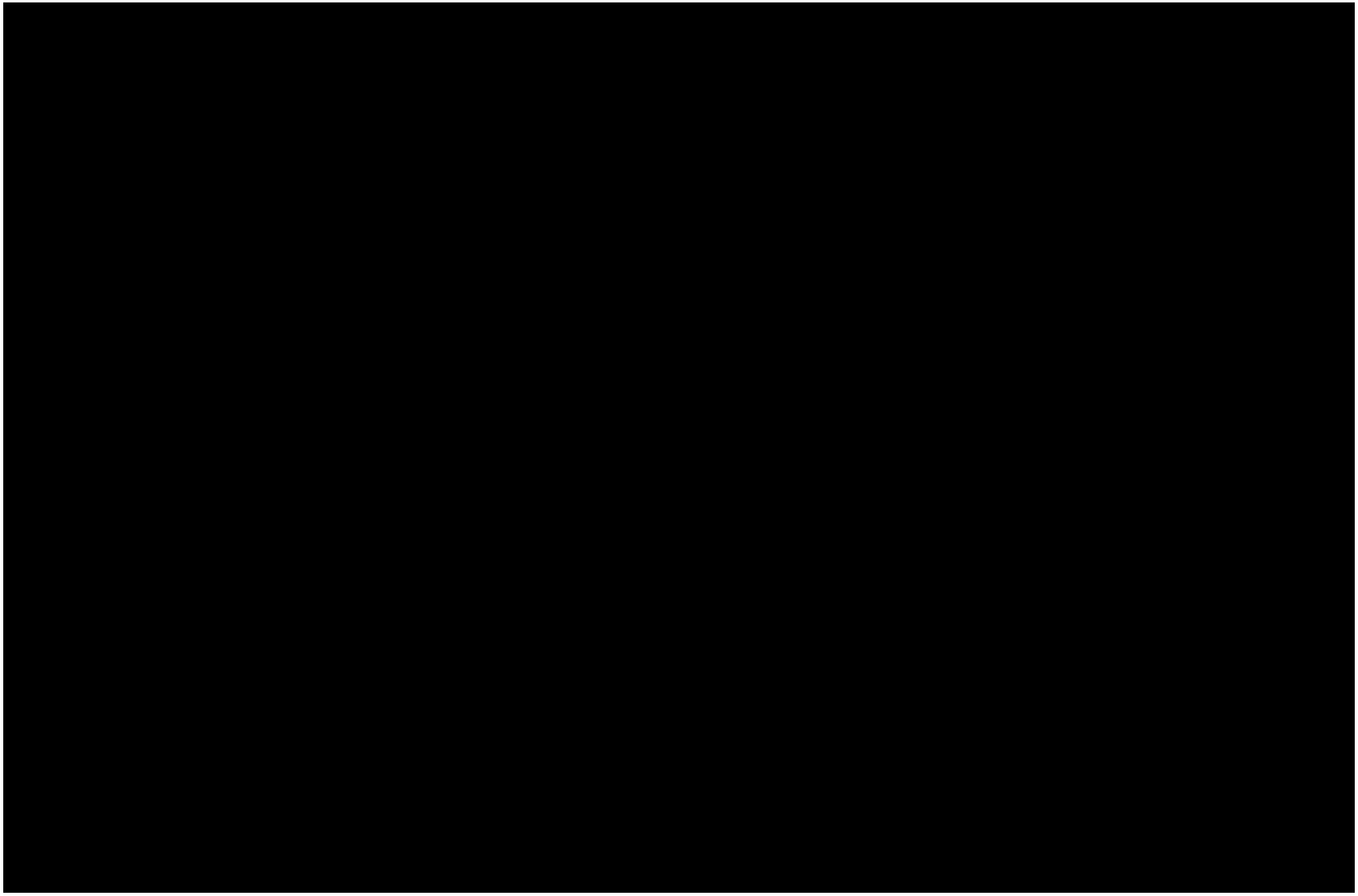


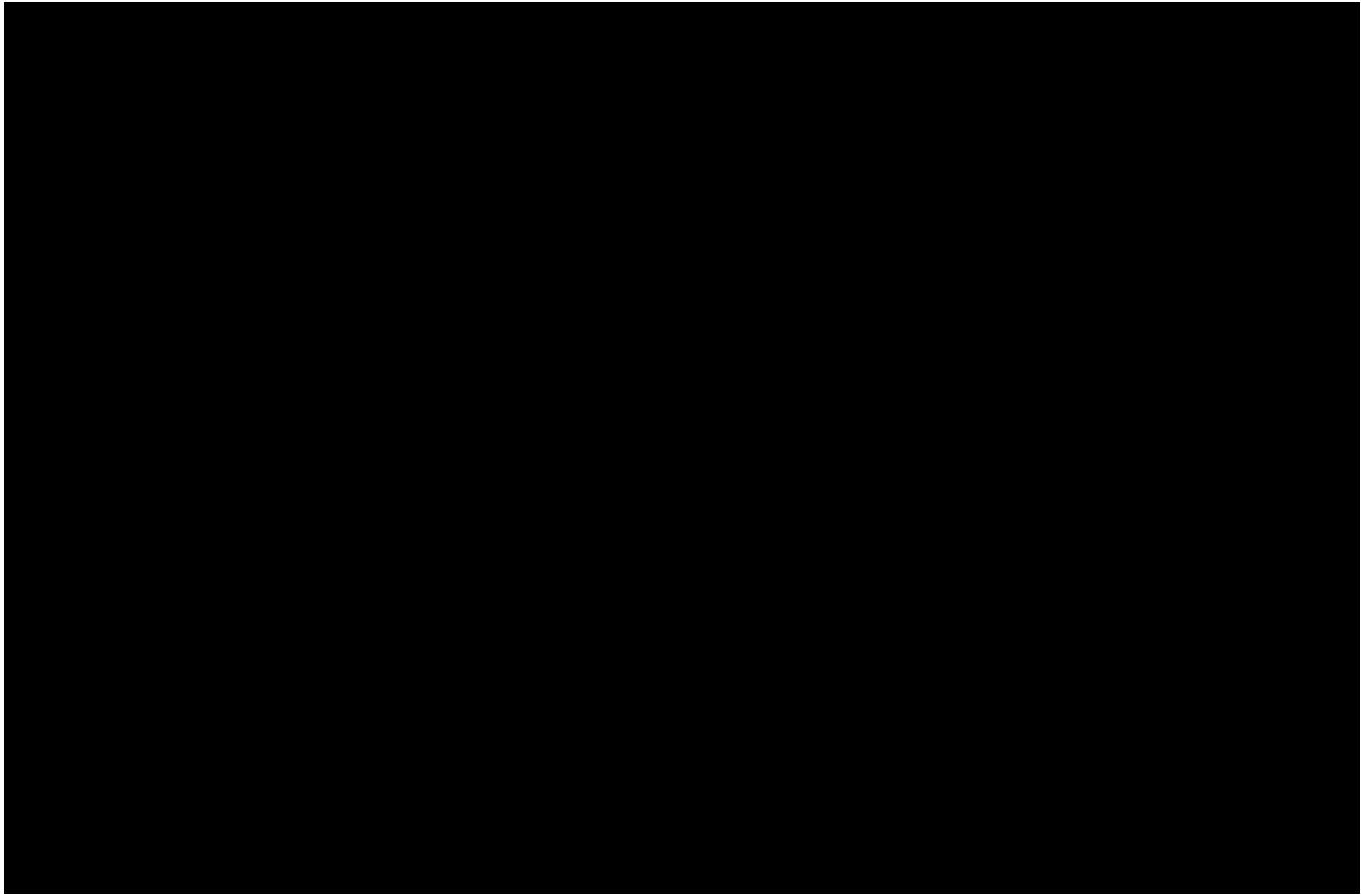


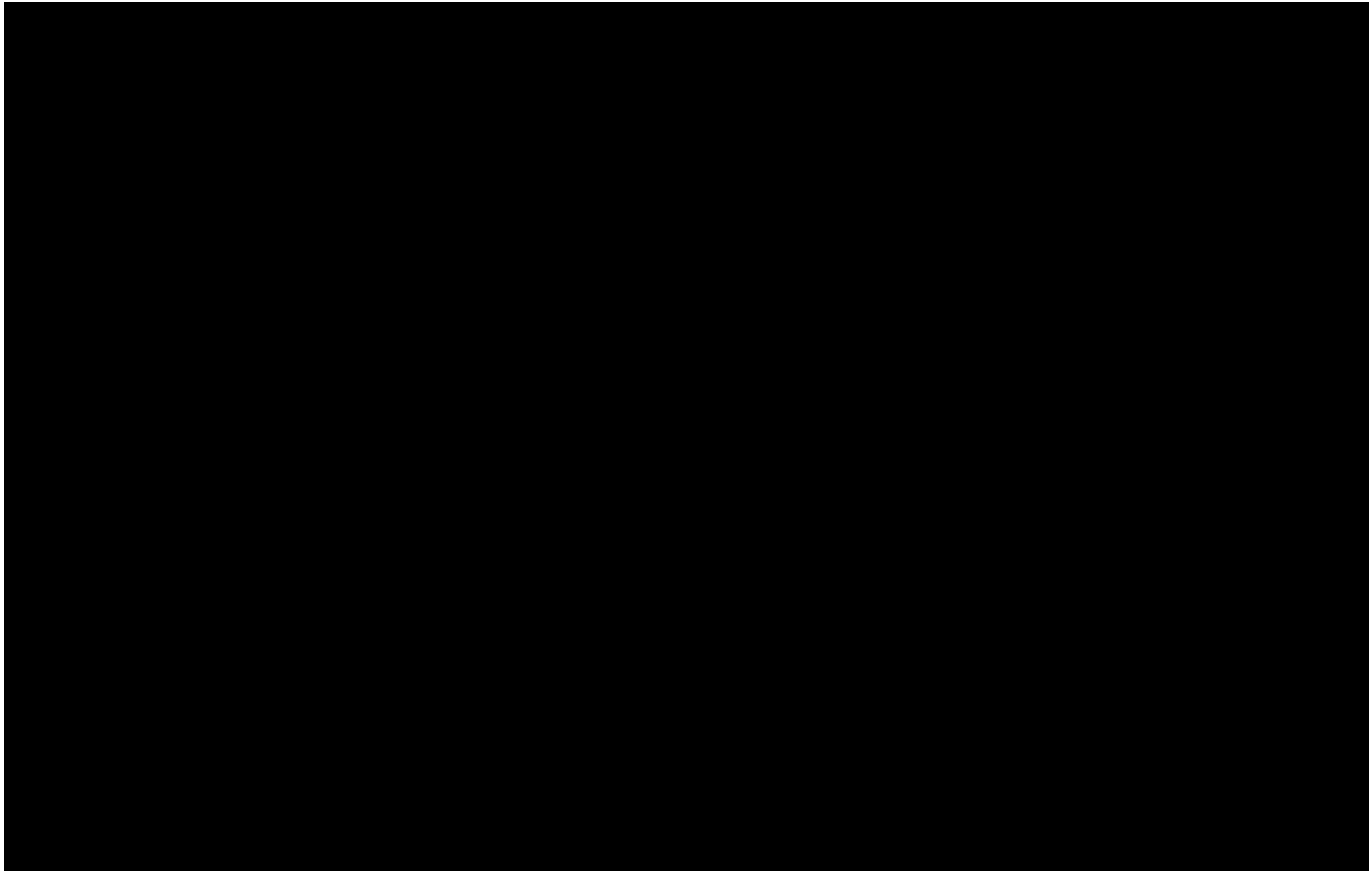


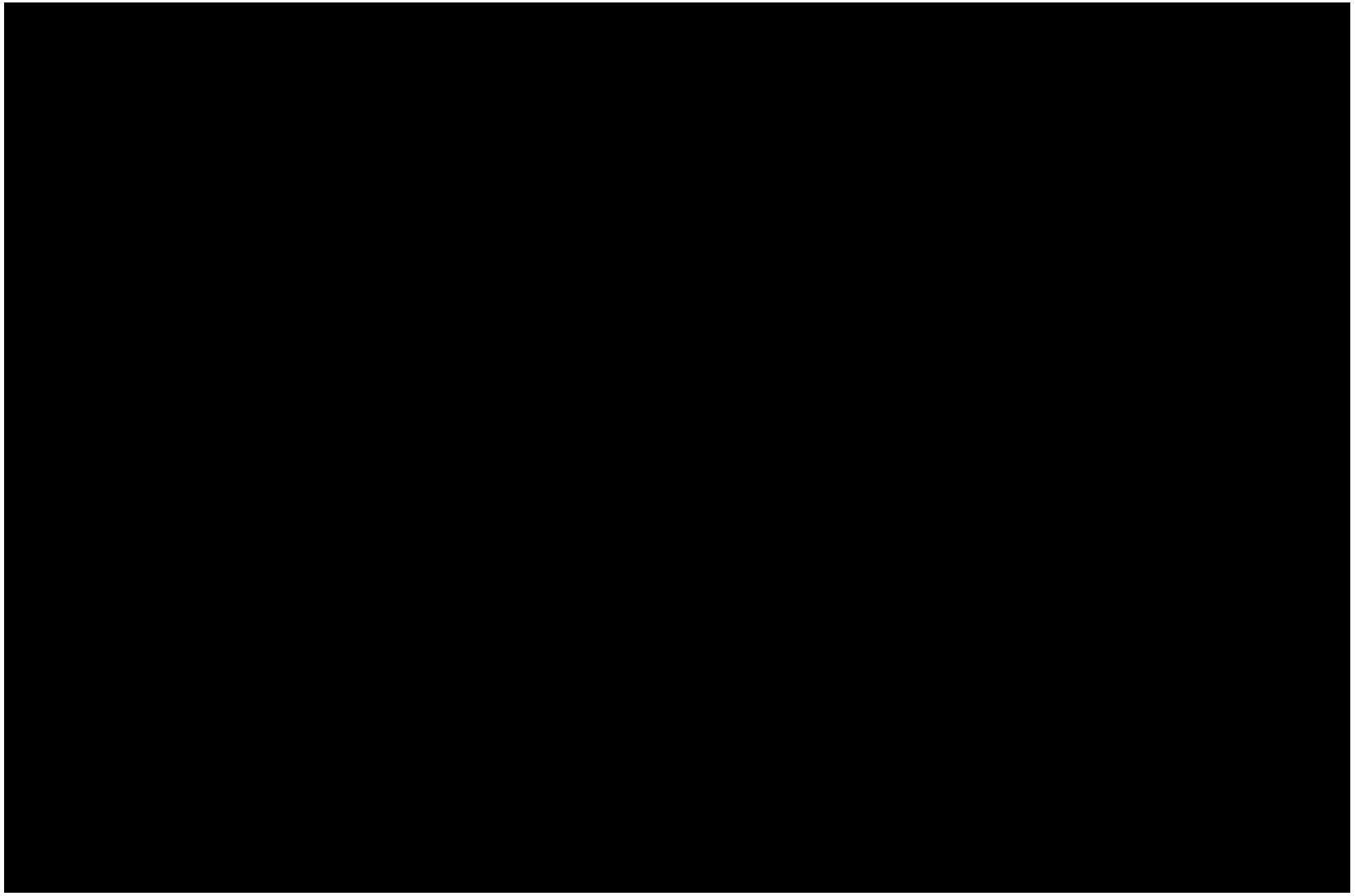


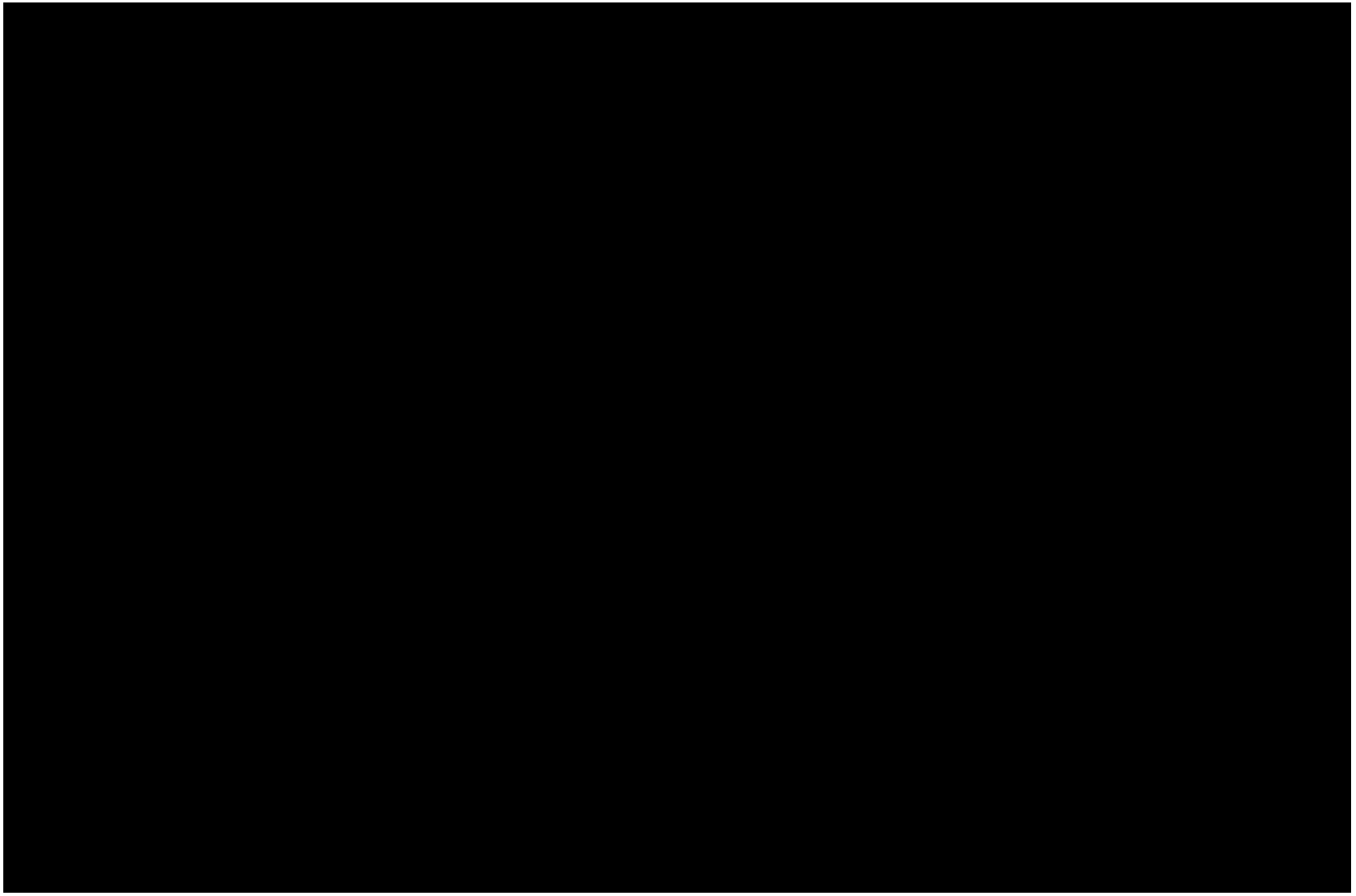












Appendix F. Health-related quality of life

Not relevant for this submission.

Appendix G. Probabilistic sensitivity analyses

Not relevant for this submission.

Appendix H. Literature searches for the clinical assessment

Not relevant for this submission.

Appendix I. Literature searches for health-related quality of life

Not relevant for this submission.

Appendix J. Literature searches for input to the health economic model

Not relevant for this submission.

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