Supplementary table 6: Details of included studies: temozolomide

Study (year) - Design	**Population (*n*)**	**Prior therapy**	**TMZ treatment regimen**	**MGMT**	**Mean duration of follow-up in months (range)**	**Outcome**			**Adverse events (*n*)**
						Radiological response (*n*)	**Biochemical response (*n*)**	**Survival**	
Aydogan (2017) - Retrospective case series	APT (3) - somatotroph (1) - lactotroph (1) - corticotroph (1)	Pituitary surgery 3/3 (100%) RT 3/3 (100%) Medical 3/3 (100%)	150 - 200 mg/m^2 in a 5/28 regimen until disease progression	n.a.	> 20 (3-45)	PD 100% (3) NB TMZ was discontinued after 6 cycles in the patient with lactotroph APT because of SD, but was reintroduced 36 months later because of PD	-	-	Nausea (1)
Bengtsson (2015)[§] - Cohort	APT (16) - somatotroph (2) - lactotroph (7) - lactotroph becoming somatotroph (1) - corticotroph (1) - NFPA (5) PC (8) - somatotroph (2) - lactotroph (2) - lactotroph becoming somatotroph (1) - corticotroph (3), of which 1 Nelson	Pituitary surgery 24/24 (100%) RT 20/24 (83%) Medical 19/24 (79%)	150 - 200 mg/m^2 in a 5/28 regimen for a median of 6 months (range 1-23) NB two persons received concurrent capecitabine because of non-responsiveness, two persons received concurrent radiotherapy	Responders: Median 9% (range 5-20) Non-responders: median 93% (range 50-100)	Median 32.5 (4-91)	APT: PR 46% (6) SD 15% (2) PD 38% (5) PC: CR 25% (2) PD 75% (6), of which 3 patients initially had PR NB treatment response data are based on 21/24 patients One patient with concurrent RT could be evaluated and had SD	-	-	Thrombocytopenia (4) Increase in liver enzymes, urinary tract infection and extreme fatigue (1) Hearing loss (3) Phlegmone (1)
Burman (2022) - Cohort	Whole cohort (171): APT (121) - somatotroph (12) - lactotroph (38)	n.s. for TMZ treatment	Mostly a 5/28 regimen NB 9 persons with clinically functioning tumours received	n.a.	n.a.	Treatment response in 146 patients, similar in APT and PC (p = 0.94): CR$^{\circ}$ 9.6% (14) PR$^{\circ}$ 30.1% (44)	≥50% decrease in hormone production in 33.6% of patients with functioning adenomas	-	TMZ dose reduction in 15 patients, TMZ discontinuation in 11 patients because of side-effects: Low granulocyte count (1) Pancytopenia (1)

	- corticotroph (32) - NFPA (33) - thyrotroph (3) - gonadotroph (1) - unknown (2) PC (50) - somatotroph (3) - lactotroph (16) - corticotroph (19) - nonfunctioning (12) TMZ was given to 156/171 patients (91%), outcome was reported in 146		concurrent RT, according to the Stupp protocol or ≤ 6 weeks prior to cessation of TMZ			SD◊ 28.1% (41) PD◊ 32.2% (47) Treatment response in 9 persons with concurrent RT: CR/PR◊ 77.8% (7) Effect of 2nd TMZ course in 31 patients: CR◊ 0 PR◊ 18.8% (6) SD◊ 31.3% (10) PD◊ 50% (16) Data of 64 unique patients, not already reported in the 1st ESE survey and for which there were evaluable endpoints, were used in the meta-analysis: CR◊ 6.3% (4) PR◊ 37.5% (24) SD◊ 23.4% (15) PD◊ 32.8% (21)			Severe depression (1) Not specified (8)
Cooper (2021) - Case series	APT (7)^ - corticotroph (3, all were initially silent) - lactotroph (3) - null cell (1)	Pituitary surgery 7/7 (100%) RT 7/7 (100%) Medical 3/7 (43%)	n.r. Mean 6 cycles (range 2-9) NB 3 persons received concurrent RT, 1 person concurrent pasireotide	Not possible to stratify for the 7 persons included	n.s.	CR* 0 PR* 3 (43%), of which 3 eventually PD SD* 2 (29%), of which one PD after 4 cycles PD* 2 (29%)	"Biochemical response" in 5 of 6 functioning tumours	-	n.r.
Du Four (2022) - Case series	PC (4) - corticotroph (of which 1 silent) (2) - lactotroph (1)	Pituitary surgery 4/4 (100%) RT 3/4 (75%) Medical 3/4 (75%)	Dose reported in 1 patient: 150 mg/m^2 in a 5/28 regimen	n.r.	n.r.	'Slight tumour decrease' 25% (1) (1 year after last TMZ dose PD) SD 25% (1)	Normalization of hormone production (1) n.r. (2)	-	In one patient, TMZ was discontinued due to persistent side-effects

	- lactotroph + somatotroph (1)		Mean 9 cycles (range 3-12)			PD 25% (1) n.a. 25% (1)			
Elbelt (2020) [§§] - Cohort	APT (34) PC (13) - corticotroph (20, of which 14 clinically functioning) - lactotroph (18) - nonfunctioning (9)	Pituitary surgery 47/47 (100%) RT 39/47 (83%) Medical 31/47 (66%) Bilateral adrenalectomy 9/47 (19%)	Median 150 mg/m^2 in a 5/28 regimen n = 39 NB 7 persons received concurrent RT according to Stupp protocol, 3 persons repeat pituitary surgery, 1 person PRRT, 1 person radiosurgery for metastatic disease	MGMT IHC (*n* = 9): ≤10% MGMT positive cells *n* = 7 25-50% *n* = 1 >50% *n* = 1 MGMT promotor methylation (*n* = 21): Positive *n* = 9 Negative *n* = 12	Median 32 (2-137)	After end of treatment or at last radiological assessment: 'tumour regression' 33% (15) SD 37% (17) PD 30% (14) After long-term follow-up: 'tumour regression' 20% (9) SD 17% (8) PD 63% (29)	Biochemical response in corticotroph tumours: ACTH decreased from 42 pmol/L (range 9-794) at baseline to minimum 23 pmol/L (range 10-276) and then reincreased to 183 pmol/L (range 12-671) In prolactinomas: serum prolactin from 1116 µg/L (range 40-19.129) at baseline to minimum 124 µg/L (range 0.4-6.335) and 553 µg/L (range 3-26.999)	PFS APT median 22 months (95% CI 11-33) PFS PC median 24 months (95% CI 20-28)	Thrombocytopenia (12) Leukocytopenia (7) Anemia (3) Unspecified cytopenia (2) Nausea (7) Vomiting (4) Severe fatigue (2) Vertigo (1)
Hirohata (2013) - Cohort	APT (3) - corticotroph (Crooke cell) (1) - lactotroph (2) PC (10) - corticotroph (3, of which 2 Crooke cell) - lactotroph (3) - nonfunctioning (4)	n.r.	n.r. NB 1 person with APT and 1 person with PC received concurrent RT	APT: MGMT positive *n* = 1 MGMT negative *n* = 2 PC: MGMT positive *n* = 6 MGMT negative *n* = 4	Length of treatment 10.5 (1.5-24)	APT: CR* 33% (1) PR* 33% (1) PD* 33% (1) PC: CR* 20% (2) PR* 50% (5) SD* 20% (2) PD* 10% (1)	-	-	n.a.
Jordan (2018) - Retrospective case series	APT (4) - corticotroph (1) - lactotroph (2) - somatotroph (1)	Pituitary surgery 7/7 (100%) RT 7/7 (100%) Medical 6/7 (86%)	Mostly 150 - 200 mg/m^2 in a 5/28 regimen	MGMT promotor methylation (*n* = 3): Negative *n* = 3	Length of treatment mean 21.1	PR 57% (4) SD 43% (3)	Decrease in hormone production 43% of patients (3)	PFS median 1.66 years OS 4 years	Grade 2 leukopenia (1) Grade 1 neutropenia (1) Grade 1 thrombocytopenia (2) Grade 2 thrombocytopenia (1)

	PC (3) - corticotroph (2) - lactotroph (1)								Grade 1 anemia (2)
Lamas (2023) §§§ - Cohort	APT (24) - somatotroph (3) - lactotroph (8) - corticotroph (11) - gonadotroph (1) - NFPA (1) PC (4) - lactotroph (2) - NF (2)	Pituitary surgery 28/28 (100%) RT 25/28 (89%) Medical 14/28 (50%)	Mean initial dose of 265 ± 73 mg in a 5/28 regimen median of 13 cycles (range 3-66) NB 5 persons received concurrent RT (Stupp)	MGMT analysis (*n* = 2): Negative IHC *n* = 1 Methylation of MGMT gene promotor *n* = 1	n.r. (≥ 6 months follow-up was inclusion criterium)	APT: CR* 0 PR* 29% (7) SD* 46% (11) PD* 21% (5) PC: CR* 0 PR* 25% (1) SD* 75% (3) PD* 0 NB After a median follow-up of 29 months, 8 out of the 22 patients with PR or SD progressed (median time from first TMZ dose to progression 16.5 months, IQR 7-27).	Normalization of hormone production 38% of hyperfunctioning tumours (3)	2 year PFS 64% 2 year OS 79%	Mild AE (14): Asthenia Anorexia Mucositis Nausea Vomiting Gastrointestinal discomfort Anemia Leukopenia Thrombopenia Dizziness Adrenal insufficiency (in patient with Cushing's disease) Severe AE (4): Moderate gastrointestinal symptoms/mucositis/anemia (2) Severe exanthema (1) – discontinued TMZ Leukemia (1) – discontinued TMZ
Lizzul (2020) §§§§ - Retrospective case series	APT (7) - corticotroph (5, of which 2 silent) - lactotroph (1 – nonsecreting during TMZ) - NFPA (1) PC (1) - corticotroph (silent) (1)	Pituitary surgery 6/8 (75%) RT 6/8 (75%) Medical 1/8 (12.5%)	150 - 200 mg/m^2 in a 5/28 regimen Median 25.5 cycles (14-45) Patients with functioning tumours concomitantly took hormone-reducing drugs	MGMT promotor methylation (n = 2): Unmethylated n = 2	Median 224 (48-336)	APT+PC: CR° 0 PR° 50% (4) SD° 50% (4) PD° 0 After TMZ withdrawal: APT+PC: CR° 0 PR° 0 SD° 25% (2) PD° 37.5% (3) TMZ still ongoing 37.5% (3)	In 3 corticotroph secreting tumours: CR (1) PR (2, of which 1 delayed escape after 14th TMZ cycle)	-	Grade 1 anemia (3) Grade 1 thrombocytopenia (6) Grade 1 elevated transaminases (1) Grade 2 elevated transaminases (1)
Losa (2016) §§§§§	APT (25) + PC	Pituitary surgery	1st cycle 150	MGMT IHC (n =	Median 43 (IQR	APT+PC:	APT+PC:	2 year PFS	SAE:

- Cohort	(6): - corticotroph (13) - lactotroph (5) - somatotroph (2) - nonfunctioning (10) - thyrotroph (1)	31/31 (100%) RT 27/31 (87%)	mg/m^2, subsequent cycles 200 mg/m^2 in a 5/28 regimen NB 3 persons received RT concomitantly or one month thereafter	7) + MGMT promotor methylation (n = 9): "favorable MGMT status" n = 7 "absent favorable MGMT status" n = 9	24-72)	CR[□] 0 PR[□] 35.5% (11) SD[□] 45.2% (14) PD[□] 19.4% (6) Regrowth at the end of the follow-up period in 25 patients with initially PR or SD: 52% (13)	Normalization 28.6% (6) Improvement (≥50% reduction compared to baseline) 28.6% (6) No change 42.8% (9)	47.7% (95% CI 29.5-65.9) 2 year OS 83.9% (95% CI 70.7 – 97.1) 4 year OS 59.6% (95% CI 40.0 – 79.2)	Cerebral vascular event (1) Severe thrombocytopenia (2)
McCormack (2018) - Cohort	Whole cohort (166): APT (125) - somatotroph (14) - lactotroph (25) - corticotroph (56) - thyrotroph (4) - gonadotroph (5) - immunonegative (21) PC (40), - somatotroph (2) - lactotroph (15) - corticotroph (19) - thyrotroph (0) - gonadotroph (1) - immunonegative (3) unclassified (1) TMZ was given to 157/166 patients (95%)	n.s. for TMZ treatment	Mostly 150 - 200 mg/m^2 in a 5/28 regimen NB 6 persons received concurrent RT (Stupp), 6 persons an additional chemotherapeutic agent	Low (n = 41) Intermediate (n = 7) High (n = 17)	Median treatment duration 9 months (range 1–36) in 136 patients	CR[◊] 5.7% (9) PR[◊] 31.2% (49) SD[◊] 33.1% (52) PD[◊] 29.9% (47)	In 113 tumours: CR 19% (21) PR 34% (38) SD 27% (30) PD 21% (24)	-	Clinically relevant side effects in ; TMZ was discontinued in 16 patients due to side effects n.s. Cytopaenias (14): thrombocytopaenia (7), leukopenia (2), combination (5) Fatigue (11) Nausea/vomiting (10) Sensorineural hearing loss (1)
Minniti (2020) -	APT (17) + PC (4):	Pituitary surgery 21/21 (100%)	TMZ + 2nd course fractionated	MGMT IHC (*n* = 19):	Median 27 (12-58)	APT+PC: CR* 9.5% (2)	-	2 year OS 82%	TMZ: Grade 3 thrombocytopenia

Cohort	- corticotroph (8, of which 3 silent) - lactotroph (6) - nonfunctioning (7)	RT 21/21 (100%) TMZ 14/21 (67%)	stereotactic radiotherapy (re-SRT) TMZ: 75 mg/m^2 concurrent with re-SRT, subsequent cycles 150-200 mg/m^2 in a 5/28 regimen or 50 mg/m^2/day for 12 months Re-SRT: 36 Gy/18 fractions (*n* = 13) 37.5 Gy/15 fractions (*n* = 8)	<10% MGMT positive cells *n* = 9 MGMT promotor methylation (*n* = 15): Methylated *n* = 6 Unmethylated *n* = 9		PR* 52.4% (11) SD/PD* 33% (8) Estimated 2 year local control 73% Estimated 4 year local control 65%		4 year OS 66%	(3) Grade 2 leukopenia (2) Grade 2 haematologic toxicity (5) Fatigue (2) Headache (1) Nausea/vomiting (1) Re-SRT: Grade 3 visual field defect (1) Deterioration 6th nerve palsy (2) Transient 5th and 6th nerve palsy (2)
Zacharia (2014) - Case series	APT (4) - corticotroph (4, of which 1 silent)	Pituitary surgery 4/4 (100%) RT 4/4 (100%) Medical 4/4 (100%)	Capecitabine 1500 mg/m^2 day 1-14 TMZ 150-200 mg/m^2 day 10-14 14 days off treatment Mean 28 cycles (4-45)	MGMT IHC (*n* = 3): <15% MGMT positive cells *n* = 3	34 (range 5.5-54)	CR* 50% (2) PR* 25% (1) SD* 25 (1)	In 3 corticotroph secreting tumours: Normalization (1) Decrease (2)	PFS mean 34 months (range 5.5-54)	Grade 3 thrombocytopenia (1) Grade 3 lymphopenia (1)
Zheng (2020) - Case series	APT (3)^^ - corticotroph (all were initially silent)	Pituitary surgery 3/3 (100%) RT 3/3 (100%) Medical n.r.	150 mg/m^2 in a 5/28 regimen (1) n.r. (2)	n.r.	102 (range 81-141)	CR 0 PR 1 (33%) SD 0 PD 1 (33%) Not evaluated because of early discontinuation (1)	Normalization (1) Decrease (1) Not evaluated because of early discontinuation (1)	-	In one patient, TMZ was discontinued due to rash

TMZ = temozolomide
MGMT = O6-Methylguanine-DNA Methyltransferase
IHC = immunohistochemistry
APT = aggressive pituitary tumour
PC = pituitary carcinoma
NFPA = nonfunctioning pituitary adenoma
RT = radiotherapy
PRRT = peptide receptor radionuclide therapy
PFS = progression-free survival

OS = overall survival
(S)AE = (serious) adverse event

n.a. = not assessed
n.r. = not reported

§ 5 patients were also reported in Burman (2022)
§§ 13 patients were also reported in Burman (2022)
§§§ 1 PC patient was also reported in Burman (2022), 4 APT patients were possibly also reported in Burman (2022)
§§§§ 1 patient was also reported in Losa (2016) and in Burman (2022)
§§§§§ 15 patients were also reported in Burman (2022)

^The original article described 9 cases, however 1 did not receive TMZ treatment and 1 did not meet our criteria of aggressive pituitary tumour.
^^ Only original cases treated with TMZ included.

◊ According to the following criteria:
CR = complete response: disappearance of all lesions
PR = partial response: ≥ 30% reduction in tumour volume
SD = stable disease: change in tumour volume between ≤ 30% decrease and ≤ 10% increase from baseline
PD = progressive disease: ≥ 10% increase in tumour volume

* According to RECIST criteria:
CR = complete response: disappearance of all lesions
PR = partial response: ≥ 30% reduction in tumour volume
SD = stable disease: neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD
PD = progressive disease: ≥ 20% increase in tumour volume

° According to the Modified RECIST criteria:
CR = complete response: disappearance of any intra-tumoral arterial enhancement in all target lesions
PR = partial response: ≥ 30% decrease in target lesions
SD = stable disease: insufficient shrinkage to qualify for PR, nor a sufficient increase to qualify for PD
PD = progressive disease: ≥ 20% increase of the longest diameter, or ≥ 1 new lesion

□ According to the following criteria:
CR = complete response: disappearance of all lesions
PR = partial response: ≥ 50% reduction in tumour volume
SD = stable disease: change in tumour volume between ≤ 50% decrease and ≤ 25% increase from baseline
PD = progressive disease: > 25% increase in tumour volume