Lead team presentation
Ceritinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer [ID1117] – STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee D

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Key clinical issues

- How reliable are results from the matched adjusted indirect comparison (MAIC)?
  - Which is more relevant: MAIC1 (PROFILE-1014) or MAIC2 (ALEX)?
  - Is PROFILE-1014 generalisable to clinical practice in the UK?
- How does the tolerability profile of ceritinib compare with crizotinib?
- Does ceritinib improve response rate and duration compared with crizotinib?

Disease background

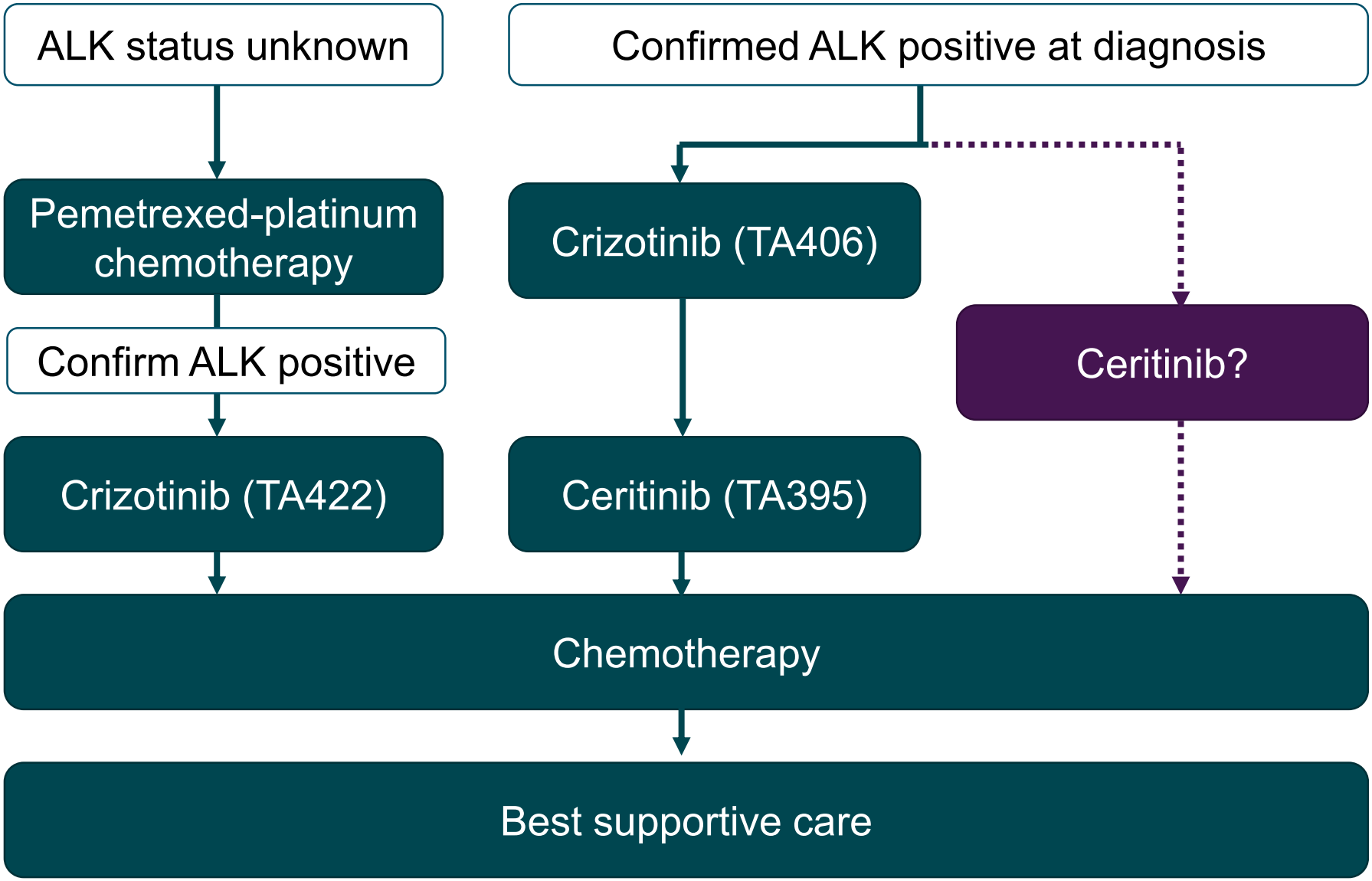
Lung cancer

- Presents in advanced stages III/IV (75%)
- Persistent cough, blood in sputum, breathlessness, weight loss
- 2 types: non-small-cell (85–90%) and small cell

ALK fusion gene mutation

- ~5% of stage III/IV NSCLC (1,170 patients in England)
  - estimates range from 1.6% to 11.7%
- Almost exclusively non-squamous
- ALK testing is routine practice at diagnosis (immunochemistry + FISH)
- Brain metastases are common
  - associated with poorer prognosis and increased symptom burden
  - present in 15–35% of people at diagnosis, >60% after treatment

Management of advanced NSCLC



Patient perspectives

- Treatment not curative, therefore patients value:
  - improved quality of life
  - symptom control
  - even small extensions in survival
- Advanced NSCLC has multiple debilitating and distressing symptoms
  - some are very difficult to manage clinically e.g. breathlessness
  - therapies with anti-tumour activity provide best option for symptom relief
- Ceritinib provides extra treatment option
  - oral drug
  - well tolerated, especially compared with chemotherapy
  - common side effects: diarrhoea, nausea, vomiting, tiredness, abdominal pain, cough and decreased appetite

Clinician perspectives

- Very poor prognosis; more effective treatments needed
  - median OS for ALK-positive NSCLC = 27 months
  - brain metastases are common and a poor prognostic factor
- Most important outcomes
  - survival, quality of life and symptom control
  - response rate is relevant because linked to symptom improvement
- Clinically significant response:
  - improvement in progression free survival of >3 months with an associated improvement in quality of life
  - objective response/stable disease important, but meaningful benefits can be seen even if RECIST definition of response is not achieved
- 2nd generation ALK inhibitors will replace crizotinib as standard of care
- Retrospective data shows survival benefit with ALK inhibitors

Decision problem

Population	People with untreated, anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer
Intervention	Ceritinib
Comparators	• Crizotinib • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) ○ with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only)
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.

The company did not include:

- Pemetrexed comparator because only relevant if ALK status unconfirmed
- Cost of testing for ALK mutations (routine practice)

	Intervention	Comparator
	Ceritinib	**Crizotinib**
Marketing authorisation	First-line treatment of adults with anaplastic lymphoma kinase-positive advanced NSCLC	
Mechanism of action	2nd generation ALK inhibitor	1st generation ALK inhibitor
Half maximal inhibitory concentration (IC50)	0.15 nM (lower IC50 = greater binding affinity)	3 nM
Administration & dosage	Oral, 750 mg once daily (without food)	Oral, 250 mg twice daily (with/without food)
Duration of treatment	"As long as clinical benefit is observed" (SmPC)	Not stated in SmPC
Cost	Both technologies have a confidential patient access scheme (PAS), agreed by the Department of Health, which provides a simple discount to the list price	
Phase III trial	ASCEND-4	PROFILE-1014 ALEX *(published after company submission; not included in base case)*

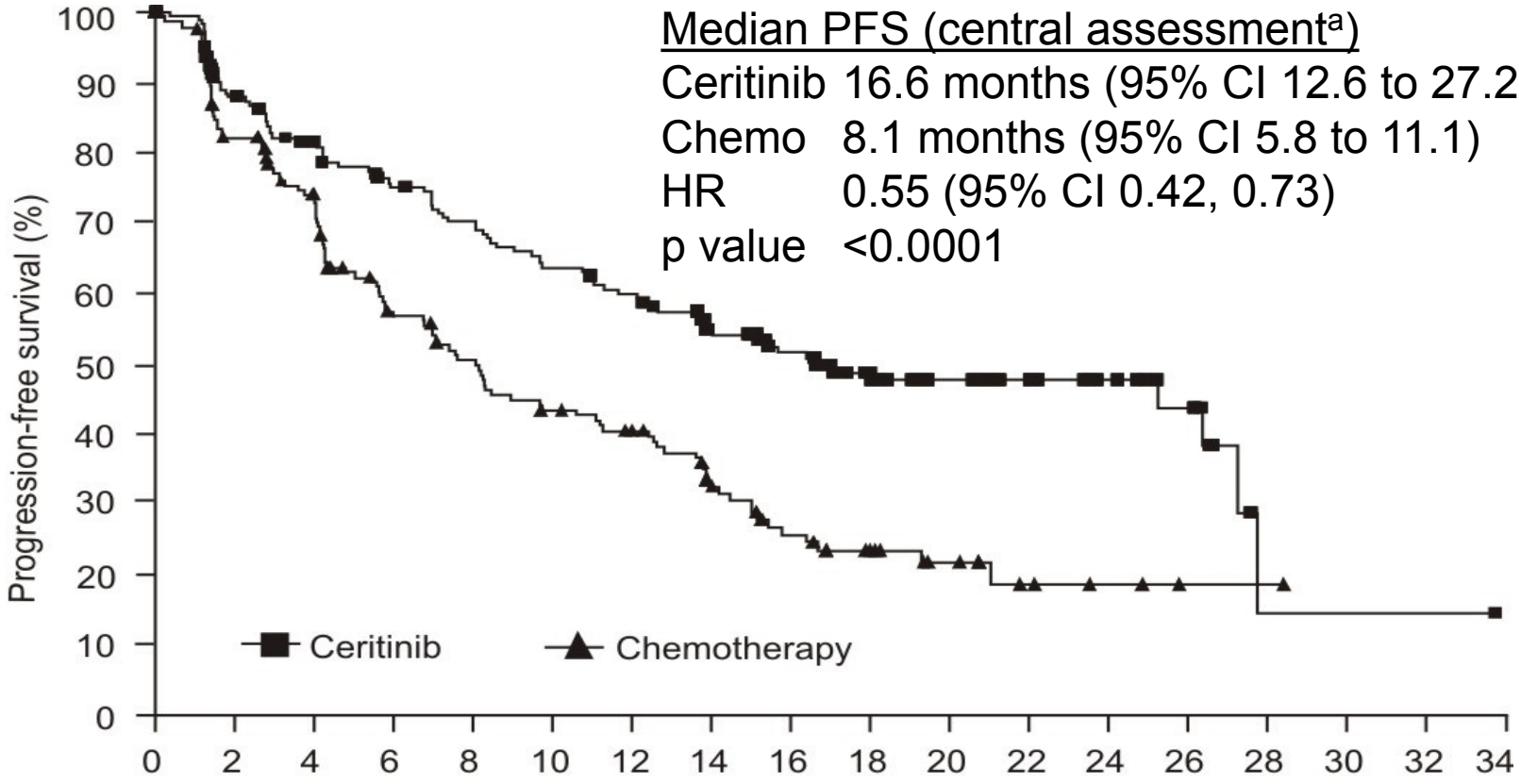
nM, nanomolar; SmPC, summary of product characteristics

Clinical effectiveness

ASCEND-4 (ongoing trial)

Study design	Multicentre (7 UK sites), randomised, open-label
Population	Adults with untreated stage IIIB/IV ALK-positive NSCLC Majority non-squamous, 96.5% adenocarcinoma Asymptomatic/neurologically stable brain metastases
Randomisation stratified by	• WHO performance status (0 versus 1–2) • Prior adjuvant therapy (yes versus no) • Brain metastases at screening (yes versus no)
Technologies	Intervention: ceritinib 750 mg/day (n=189), continued as long as clinical benefit observed (beyond progression)
	Comparator: platinum-based chemotherapy (n=187): cisplatin or carboplatin (investigator choice) with pemetrexed, followed by pemetrexed maintenance *cross over permitted (72% of pts had an ALK-inhibitor)*
Primary endpoint	Progression-free survival (RECIST), central assessment
Follow up	Median 19.7 months (data cut off June 2016)
HRQoL	EQ-5D-5L, EORTC QLQ-C30, LCSS, QLQ-LC13

ASCEND-4 primary endpoint: PFS



Median PFS (central assessment[a])

Ceritinib	16.6 months (95% CI 12.6 to 27.2)
Chemo	8.1 months (95% CI 5.8 to 11.1)
HR	0.55 (95% CI 0.42, 0.73)
p value	<0.0001

Number at risk

Ceritinib	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

[a]Concordance between central and local assessment: 88% (ceritinib), 87% (chemo)

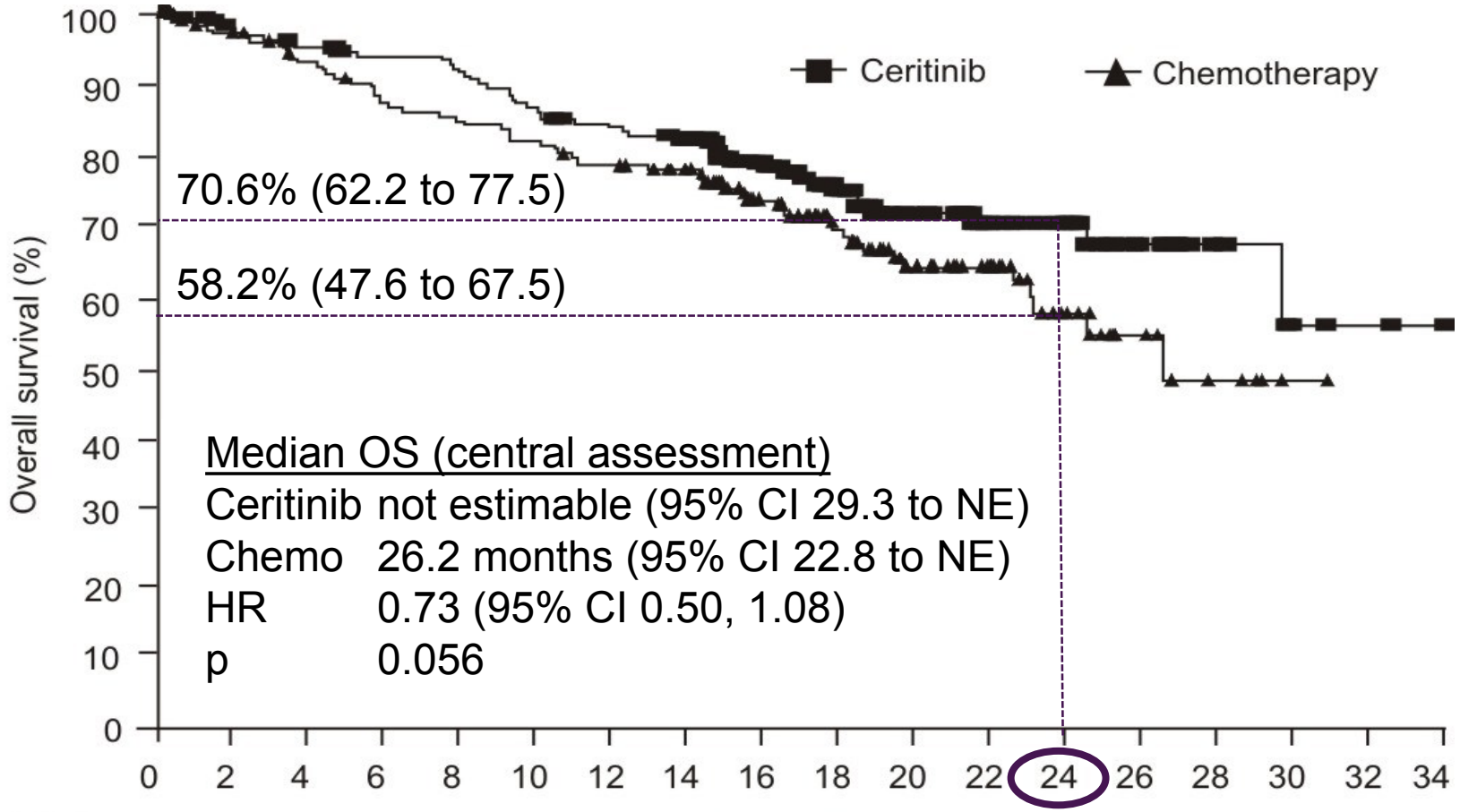
Source: Figure 6 company submission

Ceritinib did not have a statistically significant PFS benefit in people with brain metastases

Central assessment	Patients with brain metastases		Patients without brain metastases	
	Ceritinib (n=58)	Chemo (n=57)	Ceritinib (n=131)	Chemo (n=130)
Median PFS, months (95% CI)	10.7 (8.1 to 16.4)	7.0 (4.2 to 11.1)	26.3 (15.4 to 27.7)	8.2 (5.8 to 12.8)
HR (95% CI)	0.80 (0.50 to 1.28) p=NS		0.45 (0.32 to 0.64) p<0.05	
Source: table 12 company submission				

- Local assessment also showed no significant difference between treatment arms for people with brain metastases

ASCEND-4 overall survival



Number at risk

Ceritinib	189	180	175	171	165	155	150	138	103	77	56	39	26	18	6	3	2	0
Chemotherapy	187	172	161	150	146	141	134	124	97	69	49	35	19	10	5	1	0	0

After adjusting for crossover (chemo to ceritinib): HR 0.73 (95% CI 0.49 to 1.10)
Source: Figure 7 company submission

ASCEND-4 secondary endpoints (central assessment)

	Ceritinib (n=189)	Chemotherapy (n=187)
Overall response rate, % (95% CI)	72.5 (65.5 to 78.7)	26.7 (20.5 to 33.7)
Median time to response, weeks (range)	6.1 (5.1 to 61.7)	13.4 (5.1 to 90.1)
Median duration of response, months (95% CI)	23.9 (16.6 to not estimable)	11.1 (7.8 to 16.4)
EQ-5D utility (during treatment)	0.81	0.77

MAIC1 (PROFILE-1014): results used in company's base case model

	Before matching		After matching	
	Ceritinib (ASCEND-4) n=189	Crizotinib (PROFILE-1014) n=172	Ceritinib (ASCEND-4) n=189 (ESS=171)	Crizotinib (PROFILE-1014) n=172
Progression-free survival (PFS)				
Median, months (95% CI)	16.6 (12.6 to 27.2)	10.8 (8.5 to 13.8)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
HR (95% CI) p=	[redacted]		[redacted]	
1-year PFS rate	59.9%	47.8%	[redacted]	[redacted]
p value	[redacted]		[redacted]	
Overall survival (OS) *(median OS not reached)*				
HR (95% CI) p=	[redacted]		[redacted]	
1-year OS rate	83.6%	83.3%	[redacted]	[redacted]
p value	[redacted]		[redacted]	

CI, confidence interval; ESS, effective sample size; HR, hazard ratio; NR, not reached
Source: table 20 company submission

MAIC2 (ALEX): results used in scenario analyses

	Before matching		After matching	
	Ceritinib (ASCEND-4) n=189	Crizotinib (ALEX) n=151	Ceritinib (ASCEND-4) n=189 (ESS=174)	Crizotinib (ALEX) n=151
Progression-free survival (PFS)				
Median, months (95% CI)	16.6 (12.7 to 27.2)	10.4 (7.6 to 14.5)	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
HR (95% CI)	[redacted] p=[redacted]		[redacted] p=[redacted]	
Overall survival (OS) *(median OS not reached)*				
HR (95% CI)	[redacted] p=[redacted]		[redacted] p=[redacted]	
1-year OS rate	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; ESS, effective sample size; hazard ratio (HR); NR, not reached
Source: response to clarification question B2a

ERG critique of ASCEND-4

- Good quality trial, population generalisable to UK clinical practice
- 2nd line treatments do not reflect practice; face validity of OS results uncertain
- OS results confounded because patients:
  - remained on treatment beyond disease progression (not adjusted for)
  - switched to other active treatments after ceritinib (not adjusted for)
  - could switch from chemotherapy to ceritinib
- No evidence for a specific intracranial benefit with ceritinib
  - did not assess intracranial outcomes in people without baseline mets
  - median PFS in patients without brains mets at baseline was
    - with ceritinib: 15.6 months longer in than in patients with mets
    - with crizotinib (PROFILE): 2.1 months longer than in patients with mets
  - No clear difference between rate of AEs in ceritinib and crizotinib trials

ERG critique of the evidence synthesis

- Results of the MAIC are highly uncertain:
  - MAIC method not appropriate without a common comparator arm
  - Comparisons are still observational and subject to a high risk of bias
  - Matching process reduces precision by reducing the amount of data
  - OS results are more uncertain than PFS: highly simplistic comparison of highly uncertain immature data
  - Company's approach to matching for brain metastases inappropriate; the direction of the effect on the ICER of this (mis)matching is unclear
- MAIC1 matched whole population of ASCEND-4 to PROFILE-1014 population
  - Inappropriate; only the ceritinib and crizotinib arms should be matched
- Key baseline characteristics similar across trials, questioning the need to 'match'
- Unclear which MAIC is more accurate (MAIC1 or MAIC2)

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