Clinical development of medicinal products for the treatment of cancer – regulatory considerations

Markku Toivonen, LT
Scientific Director
NDA Group

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EU Regulatory Guidelines

- Guideline on the evaluation of anticancer medicinal products in man 2013 (EMA/CHMP/205/95/Rev.4)
  - Appendix 1: Methodological considerations for using progression-free survival or disease-free survival in confirmatory trials 2013 (EMA/CHMP/27994/2008/Rev.1)
  - Previous Appendix 2: Replaced by Appendix 4
  - Current Appendix 2: Use of patient reported outcome (PRO) measures and health-related quality of life in oncology studies, draft reflection paper 2014 (EMA/CHMP/292464/2014)
  - Appendix 3: Addendum on paediatric oncology 2004 (EMEA/CPMP/EWP/569/02), undergoing revision
  - Appendix 4: Condition specific guidance 2013 (EMA/CHMP/703715/2012

Endpoint definitions: Tumor response

- **ORR**: Objective response rate (the proportion of patients in whom a CR or PR was observed)
- **CR**: Complete response
- **PR**: Partial response
- **SD**: Stable disease
- **CBR:** Clinical benefit response rate. CR or PR or prolonged SD. “Prolonged SD” is defined condition specific, for breast cancer normally ≥24 weeks.

Endpoint definitions: Time-related

- **OS**: Overall survival (time from randomisation to death from any cause)
- **PFS**: Progression-free survival (time from randomisation to objective tumour progression or death from any cause)
- **DFS**: Disease-free survival (time from randomisation to recurrence or death from any cause)
- **TTP**: Time to tumour progression (time from randomisation to observed tumour progression, censoring for death not related to the underlying malignancy)
- **TTF**: Time to treatment failure (time from randomisation to discontinuation of therapy for any reason including death, progression, toxicity or add-on of new anti-cancer therapy)
- **EFS**: Event-free survival: lack of achievement of CR, relapse and death without relapse are counted as events in an EFS analysis. Those patients who did not reach CR during the pre-specified induction phase will be considered as having an event at time 0.

Regulatory philosophy (EU)

- Patient benefit may be demonstrated using several approaches, to be justified on the basis of the clinical setting, e.g.
  - Cure rate
  - Favourable effect on OS; OR
  - Prolonged PFS/DFS, if “large enough”
    - Supported by positive trend/absence of negative signal on OS
    - Supported by PRO/HRQoL endpoints
  - Symptom control, if related to anti-tumor effect
  - Biomarkers known to reflect tumor burden

Regulatory philosophy (EU)

- EU guidelines describe early (exploratory) development strategies primarily based on mode of action of treatment:
  - Cytotoxic compounds: single or combined
  - Non-cytotoxic compounds: single or combined
  - Combinations of cytotoxic and non-cytotoxic compounds

Regulatory philosophy EU vs US

- Compared to FDA, EMA more likely to view primary PFS endpoint positively
- Compared to FDA, EMA may have less issues in accepting non-inferiority studies
- Compared to EMA, FDA has more systematic interactions with Sponsors*
- Compared to EMA, FDA may be less “risk averse” in decision making*
- FDA Accelerated approvals furnish for early licensing based on reasonable assumption of benefit

* G Tafuri et al. Annals of Oncology 25:265-269, 2014

Regulatory philosophy (EU)

- EU guidelines describe Phase 3 confirmatory strategies mainly based on the aim of treatment
  - Curative
  - Long-term disease control
  - Palliation

General requirements to support MA

- Phase 2 studies are exploratory – only exceptionally sufficient for marketing authorisation (MA)
  - High unmet need, rare cancer, unprecedented antitumor activity
  - May result in conditional MA or MA under exceptional circumstances
- Standard development to support MA:
  - Phase 2 supportive evidence
  - Phase 3 single pivotal trial (SIC) or 2 trials

Phase 2 exploratory studies: Single agent

- Hypothesis generation, testing and confirmation may all be part of Phase 2 development
  - Heterogenous or homogenous population depending on primary study objectives
  - Look for signals of activity already in Phase 1: biomarkers, imaging
- Cytotoxic compounds
  - Consider RCT vs. control treatment instead of “last line” single arm trial, if alternatives available
  - ORR according to international standards, modifications to be justified – external review
  - Duration of response, TTP, PFS, OS to be reported
  - Symptom control

Phase 2 exploratory studies

- Non-cytotoxic compounds
  - Less clear distinction between Phase 1 and 2
  - If dose escalation to MTD not appropriate to guide dose/schedule selection, alternative data sources and analyses needed, including PK-PD modelling
  - ORR relevant marker of activity also in single arm trials
  - Reference arm recommended, particularly when assessing prognostic/predictive value of biomarker(s)
  - TTP, PFS in RCTs
  - CR + PR + no progression at 6 months (clinical benefit response, CBR) may be interpretable without control arm

Phase 2 exploratory studies

- Non-cytotoxic compounds
  - Exploratory trial designs with time related endpoints have challenges
    - ORR using conventional criteria or modified criteria
    - Independent response review
    - TTP, % progression-free at fixed time point
    - Pseudoprogression
    - RCT vs. Cytotoxic compound: higher tumor burden at progression in patients failing growth inhibitory treatment
    - Within-patient comparison of TTP/PFS vs prior treatment
    - RCT low vs. higher dose

Phase 2 combination therapy studies

- Cytotoxic compounds
  - MTD and recommended Phase 2 dose determination
  - ORR and PFS/TTP
  - Dose intensity priority given to component with highest activity
- Non-cytotoxic compounds
  - Study design according to activity of individual components and the combination
    - Uni-enhancement
    - Co-enhancement
    - Synthetic lethality

Phase 3 confirmatory studies

- Approach dictated by aim of therapy
- Study population selection: balance between homogeneity and external validity
- Importance of stratification for prognostic covariates cannot be over-emphasised!
- Choice of reference therapy
  - ”best available evidence-based option”
  - In add-on setting, may have select few reference therapies
  - In case of no established reference, BSC or a ”documented” reference or investigator’s best choice

Phase 3 confirmatory studies

- Superiority vs. Non-inferiority
  - Non-inferiority studies acceptable:
    - Substitution studies: B+C vs B+A
    - Long-term disease control (PFS) – reduced or similar toxicity expected
    - PFS endpoint in non-inferiority studies requires that NI margin determination accounts for effects on different types of progression events
- Interim analyses
  - Generally discouraged, particularly on PFS data other than for futility
  - Treatment effect in early events and late events may be different
  - If stopped early for efficacy, maturity of OS data?

Phase 3 endpoint selection

- Acceptable primary endpoints:
  - Cure rate
  - OS
  - PFS/DFS
  - (Symptom control)
- Rarely acceptable:
  - TTP
    - Deaths censored – hypothetical outcome
    - Insensitive to effects on OS that are not mediated by effects on tumor burden

PFS or OS?

- Cancer treatments must be shown to improve survival and/or quality of life
- If other endpoints are used, they must predict survival or QoL
- PFS is a potential surrogate, sometimes an established surrogate – generally the most complicated endpoint to assess
- Availability of treatments that prolong survival?
  - Yes: OS strongly preferred; PFS possible, but magnitude and consistency critical
  - No: OS preferred; PFS possible, magnitude, consistency
- In EU, conditional vs. full approval per se does not necessarily make clear distinction between endpoint requirements

PFS or OS?

- Primary endpoint, PFS or OS, should be chosen based on reasoned assumption that it will provide a valid and reliable measure of clinical benefit
  - In the clinical setting
  - In the clinical trial design setting (e.g. Open-label, DB)
  - Taking account of ethical issues: access to next line therapies
  - Whatever the hierarchy, primary should be supported by secondary variables

Pro PFS

- Points to consider
  - Large effect expected
  - Long median survival, long interval from progression to death
  - Historical evidence of certain HR translating to OS benefit
  - Next-line therapies available
  - Non-inferiority studies of new mono- or combination therapies, if supported by historical data (NI margin)

Pro OS

- Points to consider
  - Major difference in toxicity favoring control regimen
  - No evidence-based next-line therapies
  - Period from progression to death short
  - Tumor-shrinking control vs. Growth-inhibiting test treatment – PFS may favour the latter
  - Discordant ORR and PFS data in exploratory studies
  - High risk of detection/ascertainment bias
    - Open-label study
    - If symptoms, signs, biomarkers, intervals can lead to unscheduled assessments (asymmetry)
  - Meeting primary PFS endpoint in interim analysis followed by regulatory submission could lead to cross-over, reducing possibility to show OS benefit

PFS – Points to consider for study design

- Studies must be randomised and should be adequately blinded
- Frequency of assessments should be optimised: precision of assessment for progression vs. burden to patient
- Types of bias to be considered
  - Investigator bias
    - Particularly if not properly blinded
    - Usually not a major issue in DB studies, unless risk of unblinding
    - Independent assessment is generally required
  - Ascertainment/detection bias
  - Attrition bias

PFS – Points to consider for study design

- Adherence to protocol-defined schedules essential
  - Deviations must be reported
  - Primary analysis according to documented time of progression
  - Sensitivity analyses to explore effect of unscheduled assessments, e.g.
    - Progression imputed at the closest assessment time
    - Progression imputed at the next scheduled time
  - If unexpected asymmetry observed, various approaches have been proposed to minimise bias while preserving accuracy
    - Even if prospectively defined, may not establish absence of important bias

PFS – Points to consider for study design

- Missing data handling and rules of censoring must be pre-defined
  - Follow ITT principle for primary analysis: all patients randomised who started allocated treatment
  - Patients withdrawn prior to progression should be followed until progression, regardless of next-line therapy, allows informative PFS analyses:
    - Withdrawal prior to scheduled assessment or change of therapy prior to adjudicated progression = event
    - Censoring at time of withdrawal
  - Analysis of deaths in patients lost to follow-up – imbalance could overestimate PFS in treatment arm with less follow-up

Example: Oblimersen CHMP review

- Antisense-DNA to inactivate antiapoptotic bcl-2 mRNA
- Centralised MAA in 2006
  - Negative Opinion
  - Negative Opinion following re-examination & SAG-O consultation
  - No CHMP Scientific Advice sought
- Main study GM301, open-label, RCT of DTIC + oblimersen vs. DTIC in locally advanced/metastatic melanoma, no prior cytotox. treatment
  - OS primary; PFS, ORR, symptoms secondary

Oblimersen

- 24-mo analysis:
  - Median OS 9 vs. 7.8 mo (p=0.077)
  - PFS 2.6 mo vs. 1.6 mo (p=0.0007)
  - ORR 13.5% vs. 7.5%
- Normal LDH population (60%):
  - Median OS 11.4 vs 9.7 mo (p=0.018)
  - PFS 3.1 mo vs. 1.6 mo (0.0007)

Oblimersen – CHMP conclusions

- No survival benefit shown (primary)
- PFS, ORR results challenged, as no independent blinded review (open-label study), possibility of investigator bias, unscheduled assessments
  - Small effect on PFS
- Multiplicity issues
- LDH analysis post hoc
- ”Extensively higher” toxicity
- ”No clinical benefit established in terms of OS or other clinical benefit endpoint”

Subgroup analyses

- Draft guideline on the investigation of subgroups in confirmatory clinical trials 2014 (EMA/CHMP/539146/2013)
  - Subgroup analyses are an integral part of trial planning
  - Proportional to study population heterogeneity
  - Subgroup results must be interpreted in the context of all available results
  - Maximise a priori identification of important subgroups – minimise post hoc identification
  - Guideline addresses key considerations for switching from all randomised population to a subgroup for benefit-risk decision
  - Subgroup analyses will not usually rescue failed studies

Assessment of subgroups

- Consistency/inconsistency in subgroup effects
  - Both the subgroup of interest and its complement
  - Was randomisation stratified?
  - Baseline imbalances?
  - Absence of significant treatment-by-covariate interaction does not imply consistency
- Credibility (plausibility) – weight of evidence approach
  - Biological
  - Replication (independent sources)

Subgroup outcome scenarios

- #1: Statistically persuasive and clinically relevant results in overall study population - subgroup analyses to verify that efficacy and safety can be concluded across subgroups
- #2: Statistically persuasive, but clinically borderline results - subgroup analyses to identify a subgroup that has not been pre-specified as part of the confirmatory testing, where results would be convincing
  - External evidence, stratified/not stratified, biological plausibility?
  - Panitumumab (Vectibix) in mCRC
    - Small effect on PFS vs BSC in overall study population: median 8.0 vs 7.3 weeks ($p<0.0001$)
    - Larger effect on PFS in KRAS wild type subgroup
    - Conditional MA

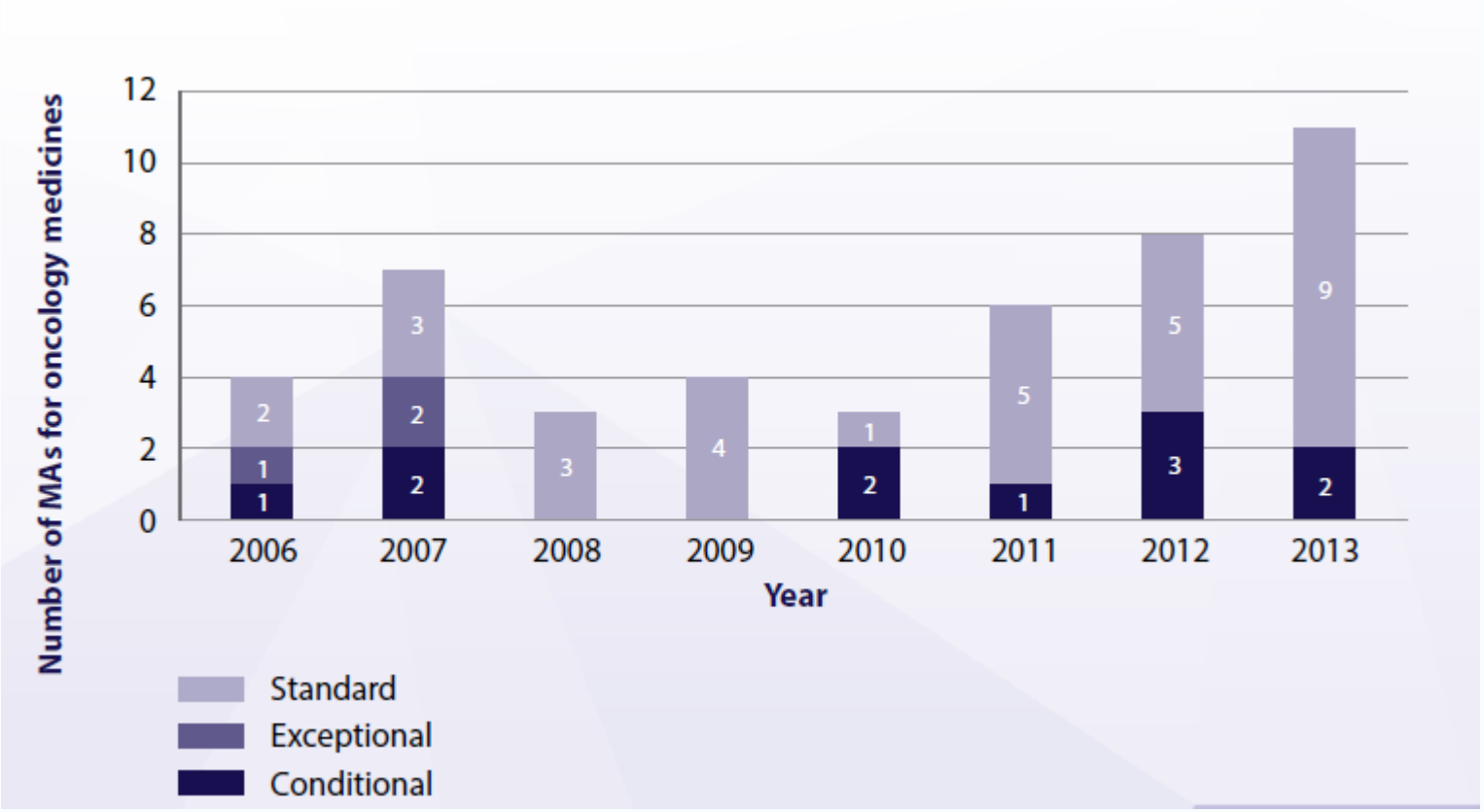
Subgroup outcome scenarios

- #3: No statistically persuasive evidence – interest in identifying a subgroup where relevant treatment effect is compelling
  - = rescuing a failed trial
  - In principle no further confirmatory conclusions are possible, as null hypothesis cannot be rejected
  - Presence of high unmet needs – prohibitive challenges in conducting further trials?
  - Inadequate in most cases to support MA
  - FDA will not accept NDA – EMA/NCA may take up for review

Conditional MA

- In order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally required.
- In such cases, it is possible for the CHMP to recommend the granting of a marketing authorisation subject to certain specific obligations to be reviewed annually ('conditional marketing authorisation').
- A conditional marketing authorisation may be requested by the applicant or proposed by the CHMP
- 75% of conditional approvals are for medicinal products to treat cancer

EU MAs for oncology indications 2006-2013



Improving the EU system for the marketing authorisation of medicines, ESCHER report, September 2014

EU MAs for oncology indications 2006-2013

	Standard MA (n=32)	Conditional MA (n=11)	P-value
Data			
Number of patients in pivotal study	662 (347)	265 (177)	<0.001
Pivotal study is RCT	29 (91%)	5 (46%)	0.004
Primary endpoint in pivotal study			
Overall survival	19 (59%)	0 (0%)	<0.001
Progression-free survival	7 (22%)	3 (27%)	
Time to progression	1 (3%)	1 (9%)	
Response rate	5 (16%)	7 (64%)	
Number of patients in safety population	980 (978)	453 (220)	0.006
Timelines			
Total assessment time in days	315 (77)	393 (84)	0.005
Active assessment time in days	197 (17)	201 (10)	0.809
Clock stop time in days	118 (68)	192 (76)	0.004
Accelerated assessment, n (%)	6 (19%)	0 (0%)	0.312
Procedures			
Scientific advice, n (%)	25 (78%)	8 (73%)	0.698
SAG-O meeting, n (%)	9 (28%)	8 (73%)	0.014
Consensus vote, n (%)	28 (88%)	6 (55%)	0.034
Appeal procedure, n (%)	0 (0%)	1 (9%)	0.256

Means (standard deviations) are reported unless specified otherwise. Comparison testing with Wilcoxon rank-sum tests for continuous variables and Fisher exact test for categorical variables.

Conditional MAs granted – end 2012

Tradename	Reasons for positive view of CHMP	Pivotal Clinical Studies (at the time of MA)		N in PIII (or PII if no PIII)	Study Design: Blinded?	Control Treatment?
		Ph II	Ph III			
panitumumab	Initial negative opinion (design of pivotal study, small effect on PFS and design flaw not allowing OS assessment) and significant skin reactions. Positive on appeal concluding marginal benefit by majority vote. Restricted indication.	√ 3	√ 1	463	X	√ Best supportive care
lapatinib	Trial stopped early for TTP benefit which inhibited OS assessment. Supportive sub analyses, modest side effects. few treatment options available.	√1	X	408	X	√ capecitabine
ofatumumab	Based on high RR in interim analysis. Indication restricted to double refractory patients. Unmet medical need, side effects not of special concern, on-going phase III study.	√1	X	154	X	X
pazopanib	Significant effect on PFS supported by OS trend, safety profile not of concern, lack of active comparator of concern but PIII trial vs sunitinib on-going.	√ 1	√ 1	435	√	√ placebo
everolimus	Good effect on tumour shrinkage, durable response, unmet medical need, safety well established in other indications, on-going phase III study.	√1	X	28	X	X

Conditional MAs granted – end 2012

Tradename	Reasons for positive view of CHMP	Pivotal Clinical Studies (at the time of MA)		N in PIII (or PII if no PIII)	Study Design: Blinded?	Control Treatment?
		Ph II	Ph III			
vandetanib	Significant PFS benefit, consistent across subgroups, QT prolongation needs managing, indication restricted, PIII study planned, unmet medical need.	√ 2	√ 1	331	√	√ placebo
pixantrone dimaleate	20% CR in relapsed/refractory patients, consistent PFS across all analyses and trend for OS, side effect profile not of concern, indication restricted, unmet medical need, PIII study planned	X	√ 1	140	√	√ chemotherapy
crizotinib	>50% RR in interim analysis of 2 studies, PFS supportive, Second study supportive, and preliminary results of on-going PIII study supportive, 2nd PIII also on-going	PI/II √ 1	X	125	X	X
brentuximab	High RR supported by PFS and other clinical endpoints, acceptable safety profile, OS to be followed up, PASS agreed, 2 single arm studies agreed, unmet medical need	√1	X	200	X	X

Conditional MA: Sought vs approved indications

Tradename	Indication submitted	Indication approved
panitumumab	treatment of metastatic carcinoma of the colon or rectum after failure of oxaliplatin- and/or irinotecan-containing chemotherapy regimens	Vectibix is indicated for the treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC): - in first-line in combination with FOLFOX; - in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan); - as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.
lapatinib	Not clear from EPAR	Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2); • in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1). • in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor (See section 5.1).

Conditional MA: Sought vs approved indications

Tradename	Indication submitted	Indication approved
ofatumumab	treatment of patients with chronic lymphocytic leukaemia (CLL) who have failed therapy with a fludarabine containing regimen and have failed therapy with, or are inappropriate for, an alemtuzumab containing regimen.	treatment of Chronic Lymphocytic Leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab
pazopanib	Votrient is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC).	Votrient is indicated for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease
everolimus	Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).	treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.
vandetanib	Vandetanib is indicated for the treatment of adult patients with unresectable locally advanced or metastatic medullary thyroid cancer.	Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. For patients in whom Rearranged during Transfection(RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1).

MA Under exceptional circumstances

The applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information,

A marketing authorisation may be granted subject to certain specific obligations. These obligations may include:

- a programme of studies within a time period with reassessment of the benefit/risk profile,
- prescription only and in certain cases only under strict medical supervision

MAs granted under Ex. circumstances

Tradename	Reasons for positive view of CHMP	Pivotal Clinical Studies (at the time of MA)		N in PIII (or PII if no PIII)	Study Design: Blinded?	Control Treatment?
		Ph II	Ph III			
nelarabine	Lack of randomized trial justified in view of the small size of the population of patients in second relapse, clinically meaningful response rate and duration of response in a significant proportion of adult and pediatric patients, allowing some patients to undergo a stem cell transplantation, acceptable safety profile.	√2	X	109	X	X
histamine dihydrochloride	statistically significant (but not compelling) increase of leukaemia-free survival (LFS) - only in the population in first remission. Commitment to further studies.	√1	√1	320	X	√ Standard of care
clofarabine	Lack of a randomized trial justified in view of the small size of the population of patients in second relapse, meaningful remission rate and facilitated HSCT in a significant proportion of patients, meaningful clinical effect that may have an impact on duration of survival, specific safety measure required.	√2	X	128	X	X
trabectedin	failed primary endpoint but a difference between the two treatment arms favoring the proposed posology of q3wk 24-h. Secondary endpoints consistent. Safety significant but manageable.	√ 3	√1	266	X	Randomised to two dosing regimens

UEC MA: Sought vs approved indications

Tradename	Indication submitted	Indication approved
nelarabine	treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.	treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens
histamine dihydrochloride	treatment of acute myeloid leukaemia	maintenance therapy for adult patients with acute myeloid leukaemia in first remission concomitantly treated with IL-2
clofarabine	treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Treatment of paediatric patients (≤ 21 years old) with acute myeloid leukaemia (AML) who are in first or subsequent relapse or are refractory	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis.
trabectedin	treatment of patients with advanced STS, who had failed anthracyclines and ifosfamide, or had failed ifosfamide and were unsuitable to receive anthracyclines/ifosfamide.	treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents; efficacy data are based mainly on liposarcoma and leiomyosarcoma patients

MA refusals, oncology

Product Number	Active Substance	ATC code	Applicant	Indication	Date
EMEA/H/C/002096	pralatrexate	L01BA05	Allos Therapeutics	peripheral T-cell lymphoma	19/04/2012
EMEA/H/C/000711	oblimersen		Genta	melanoma	31/10/2007
EMEA/H/C/000705	gemtuzumab ozogamicin	L01XC05	Wyeth	AML	24/01/2008
EMEA/H/C/000464	Trabectedin [1]	L01CX01	Pharma Mar	soft tissue sarcoma	20/11/2003

MA with Orphan Drug Status

Source: http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125

[1] Authorised subsequently with new data EMEA/H/C/000773; 17/09/2007

MA refusals, oncology

Tradename	Reasons for negative view of CHMP	Pivotal Clinical Studies		n	Study Design: Blinded?	Control Treatment ?
		Ph II	Ph III			
Praltrexate	Lack of randomised controlled study, modest efficacy (responder analysis), not possible to assess PFS or OS, significant AE's	√1	X	115	X	X
Oblimersen	No survival benefit, although effect on PFS, open label, single study, significant AEs	√ 1	√ 1	771	X	√ dacarbazine
gemtuzumab ozogamicin	Modest CR, not randomised, not controlled, significant AEs	√ 3	X	277	X	X
trabectidin	Discrepancy between PFS and OS, post hoc subgroup, baseline bias with historical controls, randomised study needed, significant AEs	√ 5	X	189	X	X

Thank you!

Questions?