Alogliptin, Alogliptin/ pioglitazone, Alogliptin/ metformin **oral** Takeda	***Indication:*** Type 2 diabetes mellitus.	***Current status:*** Filed in EU May 2012.	***Predicted UK launch:*** 2013	***National guidance:*** As for dapagliflozin above. ***Reviews:*** No recent reviews.
Target population: As for dapagliflozin above. ***Sector:*** Primary and secondary care.		***Implications:*** Additional therapy for uncontrolled type 2 diabetes in a crowded market although fixed-dose combination tablets could be attractive. Cardiovascular outcome studies are awaited. ***Financial:*** Alogliptin is likely to be competitively priced to other gliptins. ***PbR:*** Likely in tariff.		

Pharmacology: Dipeptidyl peptidase IV (DPP IV) inhibitor.

Efficacy: All outcomes relate to 26-week data unless otherwise specified.

Monotherapy. The efficacy of alogliptin 12.5mg or 25mg was compared with placebo in treatment-naïve patients (n=329). Mean change in HbA1c was -0.56%, -0.59% and -0.02%, respectively (p<0.001).

Combination therapy. In a dual therapy study (n=493), alogliptin 12.5mg, 25mg or placebo were added to pioglitazone therapy. Mean changes in HbA1c were -0.66%, -0.8% and -0.19%, respectively (p<0.001). A PIII study assessed alogliptin 12.5mg or 25mg alone or combined with pioglitazone 15mg, 30mg or 45mg in 1,554 patients on stable metformin doses (≥1,500mg). Both alogliptin doses resulted in greater reductions in HbA1c vs. pioglitazone (-1.4 vs. -0.9, p<0.001). A PIII study (n=654) assessed alogliptin 12.5mg or 25mg plus pioglitazone with alogliptin or pioglitazone monotherapy, in treatment-naïve patients. Mean HbA1c changes were -1.56%, -1.71%, -0.96% and -1.15%, respectively. The addition of alogliptin 12.5mg or 25mg in patients uncontrolled with metformin (n=527) resulted in changes in HbA1c of -0.6% (both doses) vs. -0.1% with placebo (p<0.001). Alogliptin 12.5mg, 25mg or placebo was added to glyburide therapy (n=500). Mean HbA1c changes were -0.38%,-0.52% vs. +0.1%, respectively (p<0.001). HbA1c ≤7% was seen in 34.8% of patients on alogliptin vs. 18.2% on placebo (p=0.002). In a study (n=390) alogliptin 12.5mg or 25mg (added to insulin therapy ± metformin) was compared with placebo. HbA1c reductions were -0.63%, -0.71% and -0.13%, respectively (p<0.001). In a 52-week study (n=803) alogliptin 25mg or pioglitazone 15mg were added to current metformin (≥1500mg) plus pioglitazone 30mg therapy. Change from baseline for HbA1c was -0.7% vs. 0.29%, respectively (p<0.001). The EXAMINE study (n=5,400) will assess long-term cardiovascular safety.

Safety: Adverse events and hypoglycaemia with alogliptin were similar to those in placebo and active therapy groups.

Lixisenatide **injection** *Lyxumia* Sanofi	***Indication:*** Type 2 diabetes mellitus.	***Current status:*** Filed in EU Oct 2011.	***Predicted UK launch:*** 2013	***National guidance:*** As for dapagliflozin above. ***Reviews:*** No recent reviews.
Target population: As for dapagliflozin above. ***Sector:*** Primary and secondary care.		***Implications:*** Lixisenatide will have to compete with other GLP-1 agonists, including those administered once weekly, but it may have the advantage of a reduced potential for nausea. ***Financial:*** As for dapagliflozin above. Lixisenatide will have to compete in a relatively crowded market. ***PbR:*** Likely in tariff.		

Pharmacology: A once daily s.c. formulation of an exendin-4 analogue glucagon-like peptide-1 (GLP-1) receptor agonist.

Efficacy: All outcomes relate to 24-week data unless specified otherwise. In GETGOAL-S, lixisenatide 20mcg or placebo was added to sulfonylurea ± metformin therapy (n=859). HbA1c reductions from baseline were -0.85% and -0.10%, respectively (p<0.0001). In GETGOAL-F1, lixisenatide (1-step [10mcg for 2 weeks then 20mcg] and 2-step [10mcg for 1 week, 15mcg for 1 week then 20mcg] dose increases) was compared with placebo in patients treated with metformin (n=482). HbA1c reduction was -0.92% with 1-step lixisenatide, -0.83% with 2-step lixisenatide vs. -0.42% with placebo, (p<0.0001). More patients treated with lixisenatide reached HbA1c ≤6.5% (25.6% and 20.4% with 1- and 2-step, respectively) vs. placebo (7.6%). In GETGOAL-X (n=634) lixisenatide 20mcg daily was compared with exenatide 10mcg twice daily as add-on therapy to metformin. The primary outcome of non-inferiority in HbA1c reduction was achieved with a -0.79% reduction with lixisenatide vs. -0.96% with exenatide. In GETGOAL-P lixisenatide was compared with placebo in patients inadequately controlled on pioglitazone ± metformin (n=479). Mean change in HbA1c was -0.9% vs. -0.34%, respectively (p<0.0001). HbA1c ≤6.5% achieved by 28.9% (lixisenatide) vs. 10.1% (placebo), p<0.0001. In GETGOAL-MONO treatment-naïve patients (n=361) were treated with lixisenatide or placebo 1-step or 2-step treatment regimens (see GETGOAL-F1). Mean changes in HbA1c at week 12 with lixisenatide vs. placebo were -0.66% (1-step) and -0.54% (2-step), p<0.0001. More patients treated with lixisenatide 1- and 2-step achieved HbA1c ≤6.5% (25.4% and 31.9%, respectively, vs. 12.5%, for placebo, p<0.01).

Safety: Nausea and vomiting occurred more frequently with lixisenatide than with placebo. Rates of hypoglycaemia were similar between lixisenatide and placebo but higher in patients treated with exenatide.

Insulin degludec injection *Tresiba* Novo Nordisk	***Indication:*** Type 1 (T1DM) and type 2 (T2DM) diabetes mellitus.	***Current status:*** Filed in EU Sept 2011.	***Predicted UK launch:*** 2012	***National guidance:*** As for dapagliflozin above. ***Reviews:*** NYRDTC Aug 2012, NPC/UKMi - T2DM Mar 2012, NHSC - T1DM and T2DM Jan 2011.
Target population: As for dapagliflozin above. About 10% of patients with diabetes have type 1 disease. ***Sector:*** Primary and secondary care.		***Implications:*** Insulin degludec may be associated with fewer episodes of nocturnal hypoglycaemia vs. other analogues. Flexible dosing regimens may be possible. ***Financial:*** The total cost of insulin rose from £156 million in 2000 to £359 million in 2009, a 130% increase. Spending on analogue insulin increased from 66% of total insulin cost in 2005, to 85% in 2009. Insulin degludec could be up to 30% more expensive than insulin glargine. Further licensed insulin analogues may introduce more competition but combination use of analogues is likely to increase. ***PbR:*** Likely in tariff.		
Pharmacology: Insulin degludec (IDeg) is a neutral, soluble, long-acting insulin analogue. ***Efficacy:*** *T1DM.* In the open-label, non-inferiority BEGIN BB T1 LONG 52-week study (n=629) once-daily IDeg was compared with once daily insulin glargine (IGlar). Insulin aspart (IAsp) was given prior to each meal. HbA1c changes were -0.40% vs. -0.39%, respectively ($p<0.0001$ for non-inferiority). Rates of overall hypoglycaemia were similar between the groups. BEGIN BB T1 (n=456) investigated IDeg vs. insulin detemir in T1DM also receiving IAsp. The primary outcome was HbA1c change from baseline at 26 weeks. Extensions of both studies are ongoing. *T2DM.* In the BEGIN-FLEX study (n=687), IDeg given as alternate morning and evening doses (flexible dose) was compared to IDeg given daily at the evening meal (fixed-dose) and daily IGlar. At 26 weeks, the mean HbA1c reduction was -1.28%, -1.10% and -1.26%, respectively. In the 52-week BEGIN-ONCE-LONG study (n=1,030), IDeg was compared with IGlar in combination with oral glucose lowering drugs. Mean change from baseline in HbA1c was -1.06% vs. -1.19%, respectively, demonstrating non-inferiority. Fasting plasma glucose was lower with IDeg than with IGlar ($p<0.05$). In the 26-week BEGIN-EARLY study (n=458) once-daily IDeg or sitagliptin was added to stable treatment with ≥1 oral anti-diabetes drugs. At 26 weeks the mean HbA1c was 7.2% (IDeg) vs. 7.7% (sitagliptin), $p<0.0001$. ***Safety:*** IDeg had similar rates of adverse events as IGlar in trials but hypoglycaemia episodes have been lower with IDeg.				
Insulin degludec/ insulin aspart injection *Ryzodeg* Novo Nordisk	***Indication:*** Type 1 (T1DM) and type 2 (T2DM) diabetes mellitus.	***Current status:*** Filed in EU Sept 2011.	***Predicted UK launch:*** 2013	***National guidance:*** As for dapagliflozin above. ***Reviews:*** NHSC - T1DM + aspart, Jan 2011, NHSC - T2DM + aspart, Jan 2011), NPC/UKMi (T2DM, Mar 2012)
Target population: As for insulin degludec above. ***Sector:*** Primary and secondary care.		***Implications:*** As for insulin degludec above. ***Financial:*** As for insulin degludec above. ***PbR:*** Likely in tariff.		
Pharmacology: A soluble co-formulation of 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp) designed to provide mealtime and basal insulin coverage. ***Efficacy:*** *T1DM.* In the BOOST-T1 study (n=548) IDegAsp given once-daily with any meal with IAsp at remaining meals was compared with once-daily insulin detemir with IAsp at all meals. There were no significant difference between groups in HbA1c changes at 26 weeks (-0.73% with IDegAsp vs. -0.68% with detemir). *T2DM.* In BOOST-START 1 (n=530) and BOOST-INTESIFY-BASAL (n=465) IDegAsp met the primary outcome at 26 weeks by demonstrating non-inferiority for HbA1c lowering compared with IGlar. ***Safety:*** As for IDeg above.				

Hydro-cortisone oral modified release (MR) *Plenadren* ViroPharma	***Indication:*** Adrenal insufficiency.	***Current status:*** Approved in EU Nov 2011.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** NHSC May 2010, UKMi due Sep 2012.
Target population: Primary adrenal insufficiency affects about 10 in 100,000 people. ***Sector:*** Secondary care initiated.		***Implications:*** A once daily formulation that mimics natural rhythms. ***Financial:*** This will compete with currently available immediate-release, generic preparations and is likely to be considerably more expensive. ***PbR:*** Likely in tariff.		
Pharmacology: Dual-release once-daily tablet combining immediate release hydrocortisone (peak at 20-40 minutes post-dose) plus extended-release hydrocortisone (over 12-16 hours). ***Efficacy:*** In a published PIII open-label crossover study (n=64), daily dual-release hydrocortisone produced a sustained serum cortisol profile 0 to 4 hours after the morning intake and reduced late afternoon and 24-hour cortisol exposure compared with 3 times daily immediate release hydrocortisone. At 12 weeks, differences in mean weight (-0.7kg, p=0.005), systolic blood pressure (-5.5mmHg, p=0.0001), diastolic blood pressure (-2.3mmHg, p=0.03) and HbA1c (-0.1%, p=0.0006) were seen with daily vs. 3 times daily dosing. ***Safety:*** Similar safety profile to that of the immediate-release tablets.				
Pasireotide injection *Signifor* Novartis	***Indication:*** Acromegaly.	***Current status:*** PIII in EU with orphan status and plans to file in 2012.	***Predicted UK launch:*** 2013	***National guidance:*** None relevant. ***Reviews:*** NHSC Dec 2010.
Target population: Acromegaly affects about 12 in 100,000 in the EU, with an estimated 3,000 patients in the UK. ***Sector:*** Secondary care.		***Implications:*** Pasireotide will compete with somatostatin analogues, pegvisomant and dopamine agonists. ***Financial:*** Pasireotide will have to compete with available options. ***PbR:*** Tariff excluded.		
Pharmacology: Somatostatin analogue given by twice daily s.c injection. ***Efficacy:*** In a published PII study, patients with active acromegaly due to a pituitary adenoma (n=60) were treated with octreotide 100mcg s.c. 3 times daily for 28 days; 9% achieved a biochemical response (reduction in growth hormone to ≤2.5mcg/L and normalisation of IGF-1). They were then switched to pasireotide 200, 400 or 600mcg twice daily and after 28 days, 19% achieved a biochemical response, which increased to 27% after 3 months. Two PIII studies are ongoing: one compares pasireotide with octreotide over one year and the other compares pasireotide with octreotide or lanreotide over 24 weeks. Long-acting injections are used in both studies, which are due to complete early 2013. ***Safety:*** In studies, the most frequently reported adverse events were gastrointestinal (nausea, diarrhoea, abdominal pain and flatulence), increased blood glucose, increased HbA1c, and diabetes mellitus.				
Pasireotide injection *Signifor* Novartis	***Indication:*** Cushing's disease.	***Current status:*** Licensed in EU Apr 2012 – see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** NETAG Jun 12, LNDG Feb 2012.
Target population: Incidence of Cushing's syndrome ranges from 0.7-2.4 per million people annually; 70% are due to an ACTH-producing adenoma and referred to as Cushing's disease. ***Sector:*** Secondary care.		***Implications:*** First-line treatment options include removal of the adenoma, radiation and removal of adrenal glands. Pasireotide will be a second-line option. It is the first drug treatment for Cushing's disease. ***Financial:*** Likely to be expensive. ***PbR:*** Tariff excluded.		
Pharmacology: Somastostatin analogue given by twice daily s.c. injection. ***Efficacy:*** In the published PIII PASPORT-CUSHINGS study (n=162) in moderate to severe hypercortisolism, 14.6% achieved normalisation of urinary free cortisol (UFC) on pasireotide 600mcg twice daily vs. 26.3% on 900mcg twice daily, respectively. After 12 months, the responder rate was 13.4% and 25.0%, respectively. Patients who showed little to no improvement in UFC levels (<50% reduction from baseline) by month 2 were unlikely to show improvement by months 6 or 12. A long-acting formulation is in development. ***Safety:*** Most frequent reactions include gastrointestinal, hyperglycaemia and cholelithiasis.				

Mirabegron **oral** *Betanis* Astellas	***Indication:*** Overactive bladder (OAB) - with symptoms of urge urinary incontinence, urgency, and urinary frequency.	***Current status:*** Filed in EU Aug 2011. Approved in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Lower urinary tract symptoms in men, Urinary incontinence in women (update due Jul 2013), commissioning guide. Mirabegron due Jul 2013. **SIGN:** Urinary incontinence. ***Reviews:*** NHSC Dec 2010.

Target population: The prevalence of OAB is about 39 per 100,000 people and increases with age. Overall prevalence is similar in men and women, but more women have urge incontinence.

Sector: Primary care.

Implications: Bladder training and antimuscaric drugs are used first-line but the latter may produce unacceptable side effects. As first in class mirabegron could be attractive and provide an alternative in patients who are poor responders or intolerant to antimuscarinic agents.

Financial: It may be priced similarly to, or higher than, branded once daily antimuscarinic agents at ~£30/month.

PbR: Likely in tariff.

Pharmacology: First in class beta 3 adrenoceptor agonist.

Efficacy: In a pooled efficacy analysis of 12-week, PIII studies, ARIES, CAPRICORN and SCORPIO which randomised >4,600 patients, mirabegron resulted in a reduction of incontinence episodes per 24 hours vs. placebo of -0.40 ($p<0.001$) and a reduction of micturitions per 24 hours vs. placebo of -0.75 ($p<0.001$). In the 1-year safety study (TAURUS), mirabegron maintained efficacy over the study period as assessed by the same outcomes. TAURUS and SCORPIO included tolterodine as an active comparator, but as some subjects had previously used tolterodine and no longer wanted to continue use, direct efficacy comparison vs. mirabegron is not possible.

Safety: In the US use of mirabegron is cautioned in uncontrolled hypertension, end-stage kidney disease and major liver impairment. There have been reports of hypersensitivity reactions, urinary tract-related adverse effects and neoplasms.

Botulinum A toxin (onabotulinum toxin A) **injection** *Botox* Allergan	***Indication:*** Overactive bladder (OAB) – idiopathic in adults who have an inadequate response/ are intolerant of antimuscarinic medication.	***Current status:*** Filed in EU Mar 2012.	***Predicted UK launch:*** 2013.	***National guidance:*** As for mirabegron above. ***Reviews:*** None.

Target population: As for mirabegron above. In studies, first-line oral therapy discontinuation rates ranged from 54-71% depending on the drug used.

Sector: Secondary care.

Implications: After first-line therapy has failed or not been tolerated, options include botulinum A, neuromodulation therapy or surgery which moves treatment into secondary care. Around 10% of women will have to self-catheterise after botulinum A which will make it unacceptable for some.

Financial: *Botox* costs £138 for a 100unit vial and £276 for 200units. Administration and catheterisation costs are additional but may be offset by reduced use of continence pads. Incontinence is second only to dementia as the main factor for nursing home admission, the costs of which are considerable.

PbR: Tariff excluded.

Pharmacology: Purified neurotoxin complex given as a single injection into the detrusor muscle and repeated if needed.

Efficacy: Two 12-week PIII trials, (n=548 and 557), met the primary outcome of reducing the number of urinary incontinence episodes vs. placebo ($p<0.001$); improvements in QoL were also reported. An ongoing, long-term follow-up study (n=750) has completed enrolment. The effects of a single injection can last for between 3-10 months.

Safety: In the PIII trials, 15-20% of patients had urinary tract infections and 5-6% had urinary retention.

Botulinum A toxin (onabotulinum toxin A) injection *Botox* Allergan	***Indication:*** Urinary incontinence due to detrusor overactivity in a neurologic condition in those unresponsive to / intolerant of antimuscarinic medication.	***Current status:*** Recommended for approval in EU Aug 2011. Launched in US- see prescribing data.	***Predicted UK launch:*** 2012.	***National guidance:*** As for mirabegron above. ***Reviews:*** None.
Target population: 60-80% of people with MS and 75-80% of people with SCI have some degree of bladder dysfunction including urinary incontinence. The severity and nature of incontinence depends on many factors so estimates of who require treatment is difficult. ***Sector:*** Secondary care.		***Implications:*** EU guidelines already recommend botulinum toxin as the most effective minimally invasive treatment for neurogenic detrusor overactivity. Licensing may have little impact if its use is already adopted. ***Financial:*** The economic impact of neurogenic urinary tract dysfunction is substantial due to costs of assessment, use of catheters and pads, and carer, nursing and medical support. A 200unit vial of *Botox* costs £276. ***PbR:*** Tariff excluded.		
Pharmacology: Purified neurotoxin complex given as a single injection into the detrusor muscle and repeated if needed. ***Efficacy:*** In a published PIII study (n=416), the mean number of urinary incontinence episodes at week 6 decreased by 21 and 23 per week after 200 and 300units of botulinum A toxin, respectively, vs. 9 in the placebo group (each dose p<0.001). The median time to re-treatment request was about 255 days for botulinum A and 92 days for placebo. A second PIII study (n=275) has also been published with similar results. These studies comprise the DIGNITY programme from which there is an ongoing 3-year open-label extension study (n=397). In this study, the 300unit dose has been discontinued. ***Safety:*** The most common adverse effects are urinary tract infection and retention requiring catheterisation.				
Dapoxetine oral *Priligy* Menarini	***Indication:*** Premature ejaculation (PME) in men aged 18-65 years.	***Current status:*** Approved in UK Mar 2012. UK pharmacies import and supply via private prescription.	***Predicted UK launch:*** Uncertain.	***National guidance:*** None relevant. ***Reviews:*** NYRDTC due TBC.
Target population: PME is the most common form of male sexual dysfunction with a prevalence of 20-30% and is not affected by age. The prevalence of life-long PME is 2-5%. ***Sector:*** Primary care.		***Implications:*** Dapoxetine is already available in the UK via private prescription at a cost of about £76 for three tablets. Most men with PME do not seek medical help but demand may increase if treatment becomes available on NHS prescription. Media attention is likely to be high. ***Financial:*** Cost could be large unless prescribing guidance is issued. ***PbR:*** Likely in tariff.		
Pharmacology: Short-acting selective serotonin reuptake inhibitor given on demand 1-3 hours prior to sexual intercourse. ***Efficacy:*** A published meta-analysis of five studies (n=4,433) of 9-24 weeks duration, reported that dapoxetine increased intravaginal ejaculatory latency time by 1.38 minutes more than placebo (p<0.001). Differences in favour of dapoxetine were also reported for patient-reported impression of change, patient satisfaction with sexual intercourse, perceived control over ejaculation and personal distress related to ejaculation (all p<0.001). ***Safety:*** Adverse effects are those commonly associated with selective serotonin reuptake inhibitors.				
Collagenase clostridium histolyticum injection *Xiapex* Pfizer	***Indication:*** Peyronie's disease (PsD).	***Current status:*** PIII.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Extracorporeal shock waves for PsD. ***Reviews:*** None.
Target population: PsD prevalence is 3-9%. The average age of onset is in the fifth decade with many cases undiagnosed. In the US, the incidence is 23-40 per 100,000 people; about 2 per 100,000 are treated. ***Sector:*** Secondary care.		***Implications:*** Current therapy incudes intralesional interferon-alpha or verapamil, and surgery. ***Financial:*** Current cost of *Xiapex* 900microgram is £650; several fold more than interferon-alpha, although doses of *Xiapex* used for Peyronie's disease are much lower than for Dupuytren's contracture. ***PbR:*** Uncertain.		
Pharmacology: Collagenase stimulant injected into penile plaque twice weekly every 6 weeks for up to 4 treatment cycles. ***Efficacy:*** Two 52-week PIII studies IMPRESS I and IMPRESS II, each randomised >300 men to collagenase or placebo. In IMPRESS I, mean reduction in penile curvature deformity was 37.6% for collagenase vs. 21.3% for placebo (p=0.0005). In IMPRESS II, the respective results were 30.5% vs. 15.2% (p=0.006). An open-label PIII study in the UK is ongoing. ***Safety:*** Local treatment site reactions are common and include injection site haematoma, pain and swelling. Across IMPRESS I and II, 3 cases of corporal rupture and 3 serious haematomas occurred.				

Sorafenib **oral** *Nexavar* Bayer	***Indication:*** Thyroid cancer, differentiated (DTC) - advanced.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2013	***National guidance:*** None relevant. ***Reviews:*** NHSC Dec 2010.

Target population: UK incidence of thyroid cancer is 3.5 per 100,000; DTC (papillary and follicular) accounts for 80-90%. 5-20% of patients develop local or regional recurrences and 10-15% have distant metastases.

Sector: Secondary or tertiary care.

Implications: Options for recurrent or metastatic disease include surgery, radioactive iodine and radiotherapy. Sorafenib will be the first drug licensed for progressive disease.

Financial: This is additional therapy that currently costs £2,980 a month. Median treatment duration in a PII trial was 16.5 months.

PbR: Chemotherapy is tariff excluded.

Pharmacology: Blocks Raf and tyrosine kinases, vascular endothelial and platelet derived growth factor receptors.

Efficacy: In a published PII study (n=31) of sorafenib in locally advanced or metastatic refractory DTC, 59% had a clinical response (25% a partial response and 34% stable disease); 22% had progressive disease. Median PFS was 58 weeks. In a published PII study (n=19), the radiological response rate was 18% and overall survival 79% at 12 months. The PIII DECISION study is recruiting 420 patients with advanced DTC. Results are expected in 2013.

Safety: See emc.medicines.org.uk.

Cabozantinib **oral** Exelixis	***Indication:*** Thyroid cancer, medullary (MTC).	***Current status:*** PIII. Filed in US May 2012 with fast track and priority review status.	***Predicted UK launch:*** 2013	***National guidance:*** None relevant. ***Reviews:*** NHSC Feb 2012.

Target population: MTC is rare, accounting for 5-10% of all thyroid cancers (about 0.2 per 100,000 people).

Sector: Secondary or tertiary care.

Implications: First-line therapy is thyroidectomy. Cabozantinib may slow disease progression in patients who cannot be managed by surgery alone and may be better tolerated than vandetanib.

Financial: Likely to be expensive but may offset other treatment costs. An alternative to vandetanib which costs £5,000 per month.

PbR: Chemotherapy is tariff excluded.

Pharmacology: Tyrosine kinase inhibitor that blocks vascular endothelial growth factor and MET proto-oncogene.

Efficacy: In the PIII EXAM trial (n=330) PFS was 11.2 months with cabozantinib vs. 4.0 months with placebo (HR 0.28, p<0.0001). One-year PFS was 47.3% and 7.2%, respectively; objective response rates were 28% and 0%, respectively (p<0.0001). In a published PI study (n=35), 29% had a partial response to cabozantinib, and 49% had tumour shrinkage of 30% or more.

Safety: Adverse effects include diarrhoea, hand-foot syndrome, weight loss, nausea, fatigue and hypertension.

Crizotinib **oral** *Xalkori* Pfizer	***Indication:*** Non-small cell lung cancer (NSCLC), advanced - second-line in ALK-positive patients.	***Current status:*** Recommended for approval in EU Jul 2012. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Lung cancer: pathway, quality standard; Crizotinib due Jul 2013. **SIGN:** Lung cancer. ***Reviews:*** NHSC Dec 2010.

Target population: UK incidence of advanced NSCLC is 40 per 100,000 people; 25% are able to have first-line therapy, of these 20-40% may receive second-line therapy. 3-13% of patients has ALK genes and will respond poorly to current options.

Sector: Secondary care.

Implications: Crizotinib is first in class and may be used in place of current therapies (docetaxel, pemetrexed, erlotinib) in selected patients.

Financial: Likely to be expensive and as first in class will attract interest. Cost in US is $9,600 per month. A PAS is in place for erlotinib and gefitinib in this setting. Median duration of treatment in studies was 5-8 months.

PbR: Chemotherapy is tariff excluded.

Pharmacology: Anaplastic lymphoma kinase (ALK) and mesenchymal epithelial transition growth factor (cMET) inhibitor.

Efficacy: In a published single-arm PI study (n=82) after a mean treatment duration of 6.4 months, the overall response rate was 57%; 33% had stable disease. The estimated probability of 6-month PFS was 72%. Analysis showed 1-year overall survival (OS) was 77% and 2-year OS was 64%; compared with 73% and 33%, respectively in 37 ALK-positive un-treated historical controls. PIII PROFILE 1007 study results comparing crizotinib with docetaxel or pemetrexed after failure of previous platinum-based chemotherapy are due in 2012. The PII PROFILE 1005 study is due to complete in 2013.

Safety: Adverse reactions include visual problems, gastrointestinal and oedema. QTc prolongation has been observed and crizotinib interacts with drugs metabolised by CYP3A route.

Afatinib **oral** *Tomtovok* Boehringer Ingelheim	***Indication:*** Non-small cell lung cancer (NSCLC) advanced with EGFR mutation - first-line.	***Current status:*** PIII.	***Predicted UK launch:*** 2013	***National guidance:*** As for crizotinib above. ***Reviews:*** NHSC Aug 2010.
Target population: As for crizotinib above. Epidermal growth factor receptor (EGFR) is overexpressed in 10-15% of tumours. ***Sector:*** Secondary care.		***Implications:*** Afatinib will compete with first generation EGFR inhibitors, erlotinib and gefitinib. It is a less complicated and less toxic alternative to i.v. chemotherapy in selected patients. ***Financial:*** Cost of erlotinib and gefitinib is about £1,600 and £2,000/month. PASs are in place for erlotinib and gefitinib for NSCLC. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Tyrosine kinase inhibitor blocking EGFR and human epidermal growth factor receptor 2 (HER2). ***Efficacy:*** In the PIII LUX-Lung 3 trial (n=345) comparing first-line afatinib with cisplatin and pemetrexed, PFS was 11.1 vs. 6.9 months, respectively (HR 0.58, p=0.0004). The objective response rate was 56% for afatinib vs. 23% in the control group (p<0.0001). Afatinib also delayed the time to deterioration of cancer-related symptoms of cough (0.6, p=0.007) and dyspnoea (0.68, p<0.015). The ongoing PIII LUX-Lung 6 trial (n=364) is comparing afatinib with cisplatin and gemcitabine. ***Safety:*** Common adverse effects are diarrhoea, rash and paronychia.				
Amrubicin **injection** *Calsed* Celgene	***Indication:*** Small cell lung cancer (SCLC) - second-line.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Lung cancer pathway. **SIGN:** Lung cancer. ***Reviews:*** No recent reviews.
Target population: SCLC affects less than 15 per 100,000 people. For those with limited disease (25%), 45-75% achieve remission with first-line platinum-based chemotherapy but median PFS is only 12 months. 20-30% of those with extensive disease achieve remission and median PFS is 4 months. ***Sector:*** Secondary care.		***Implications:*** Amrubicin may improve survival with less toxicity than topotecan. ***Financial:*** Amrubicin will be an alternative to topotecan (approx. £1,500 per cycle), but is likely to be more expensive. ***PbR:*** Chemotherapy drugs are excluded.		
Pharmacology: Topoisomerase II inhibitor given i.v. for 3 consecutive days, starting on day 1 of a 21-day cycle for a mean of 3-4 cycles. ***Efficacy:*** Data from the PIII ACT-1 trial (n=637) showed that in relapsed or refractory SCLC amrubicin improved response rate vs. topotecan (31% vs. 17%, p=0.0002, NNT 7), but not overall survival (OS), except in the subgroup with refractory disease (6.2 vs. 5.7 months, HR 0.77, p=0.047). PFS was 4.1 vs. 4.0 months, respectively (p=0.98). In a PII study (n=76) in relapsed SCLC, the overall response rate was 44% with amrubicin vs.15% with topotecan (p=0.02, NNT 3). Median PFS and median OS were 4.5 months and 9.2 months with amrubicin, vs. 3.3 and 7.6 months with topotecan, respectively. ***Safety:*** Neutropenia, thrombocytopenia and anaemia occur less often with amrubicin than topotecan.				
Trastuzumab and hyaluronidase **injection** *Herceptin SC* Roche	***Indication:*** Breast cancer (BC), early and metastatic HER2-positive disease (all indications for which trastuzumab is currently indicated).	***Current status:*** Filed in EU Mar 2012.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** BC pathways - early/locally advanced, advanced and familial, BC quality standard. **SIGN:** Breast cancer. ***Reviews:*** NHSC Jan 2011.
Target population: The incidence of BC in the UK is about 78 per 100,000 people. HER2-positive disease accounts for up to 25% of all BCs. About 40% of women develop metastatic disease; 20% of these are HER2-positive which has a worse prognosis. ***Sector:*** Secondary care.		***Implications:*** Compared to the i.v. formulation which is usually prepared in pharmacy and given as a 30 minute infusion, s.c. trastuzumab will reduce preparation and administration time, and may decrease the incidence of infusion-related reactions. ***Financial:*** Cost unknown. This will be used in place of i.v. trastuzumab and may reduce overall costs and clinic time. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Anti-HER2 monoclonal antibody co-formulated with recombinant human hyaluronidase to facilitate absorption of trastuzumab through subcutaneous tissue. Given by s.c. injection every 3 weeks. ***Efficacy:*** The published PIII HannaH study compared the efficacy and pharmacokinetics of s.c and i.v. trastuzumab in 596 women with early HER2-postive BC. The s.c. formulation produced plasma concentrations at least as high as the i.v. formulation (69.0 and 51.8 microgram/mL, respectively). In addition, efficacy as determined by pathological complete response was similar in both groups (45.4% and 40.7%, respectively). ***Safety:*** See emc.medicines.org.uk. Adverse effects are consistent with those of i.v. trastuzumab.				

Pertuzumab **injection** *Omnitarg* Roche	***Indication:*** Breast cancer (BC), advanced HER2-positive disease - first-line.	***Current status:*** Filed in EU Dec 2011. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** As for trastuzumab above and **NICE:** Pertuzumab due Nov 2013. ***Reviews:*** NHSC Dec 2010.
Target population: As for trastuzumab above. ***Sector:*** Secondary care.		***Implications:*** Pertuzumab will be used as add on to standard therapy. ***Financial:*** Likely to be expensive and will be additive to the cost of current therapy. Delaying BC progression will also increase trastuzumab and docetaxel costs. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: First in class HER dimerisation inhibitor. It may be synergistic with trastuzumab, which binds to a different HER receptor region. Given as a 3-weekly i.v. infusion. ***Efficacy:*** The published PIII CLEOPATRA trial (n=808), compared pertuzumab or placebo, both with trastuzumab and docetaxel. Median PFS was 18.5 months for pertuzumab vs. 12.4 months in the control group (HR for progression or death 0.62, p<0.001). The ongoing PIII PERUSE trial (n=1,500) is assessing first-line triple combination therapy with pertuzumab, trastuzumab and a taxane. In a published PII study, 66 patients received pertuzumab plus trastuzumab. The objective response rate was 24.2%. Median PFS was 5.5 months. ***Safety:*** Adverse effects include diarrhoea, fatigue, nausea, rash and arthralgia. Cardiac dysfunction appears minimal.				
Everolimus **oral** *Afinitor* Novartis	***Indication:*** Breast cancer (BC), advanced HER2-positive disease - first-line.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2014	***National guidance:*** As for trastuzumab above. ***Reviews:*** NHSC Apr 2012.
Target population: As for trastuzumab above. ***Sector:*** Secondary care.		***Implications:*** About 70% of patients who receive trastuzumab monotherapy are resistant to treatment. The addition of everolimus may improve response rates and delay the need for second-line chemotherapy. ***Financial:*** Costs will be additive to existing therapies. Current cost of everolimus 10mg daily is about £2,970 per month. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: mTOR inhibitor. ***Efficacy:*** The PIII BOLERO-1 trial (n=717) is assessing addition of first-line everolimus to trastuzumab and paclitaxel. Results are due in 2012. This study was initiated following published PI trial results. Disease was controlled for more than 6 months in 74% of 27 women with prior resistance to trastuzumab given everolimus in addition to paclitaxel and trastuzumab. Overall response rate was 44% and PFS was 8.5 months. A pooled analysis of PII data from 47 women with trastuzumab resistance showed adding everolimus to trastuzumab produced partial responses in 7 patients (15%) and persistent stable disease (lasting 6 months or longer) in 9 patients (19%), with a clinical benefit rate of 34%. Median PFS was 4.1 months. ***Safety:*** See emc.medicines.org.uk.				
Lapatinib **oral** *Tyverb* GlaxoSmith-Kline	***Indication:*** Breast cancer (BC), advanced HER2-positive disease - second-line.	***Current status:*** Filed in EU Feb 2012. US filing withdrawn Jul 2012.	***Predicted UK licence extension:*** 2012	***National guidance:*** As for trastuzumab above. ***Reviews:*** NHSC Feb 2012.
Target population: As for trastuzumab above. About 70% of patients do not respond to first-line trastuzumab and the rest develop resistance within the first year. ***Sector:*** Secondary care.		***Implications:*** Current options for patients resistant to trastuzumab produce low response rates and short durations of response. Lapatinib may act synergistically with trastuzumab and avoid need for chemotherapy. ***Financial:*** The current cost of lapatinib 1g daily is £1,600 per month. Median treatment duration in trials was 12.8 months. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Dual inhibitor of HER1 and HER2 receptor tyrosine kinases. ***Efficacy:*** The published EGF104900 PIII trial (n=296) in women who received a median of 3 prior trastuzumab-containing regimens, showed that lapatinib plus trastuzumab increased PFS vs. lapatinib alone (12.0 vs. 8.1 weeks, respectively, HR 0.73, p=0.008). 28% in the combination arm vs. 13% in the monotherapy arm were progression free at 6 months (p=0.003). Final published data showed median overall survival (OS) was 14 months for combination therapy vs. 9.5 months for lapatinib alone (0.74, p=0.02). There was a 10% improvement in absolute OS rate at 6 months and 15% improvement at 12 months in the combination arm vs. monotherapy arm. ***Safety:*** See emc.medicines.org.uk. Diarrhoea, a common side effect of lapatinib and trastuzumab, is more frequent with combination therapy but incidence of decreased left ventricular ejection fraction is not higher than with either drug alone.				

Trastuzumab emtansine **injection** Roche	***Indication:*** Breast cancer (BC), advanced, HER2-positive disease -second/ third-line.	***Current status:*** PIII.	***Predicted UK launch:*** 2013	***National guidance:*** As for trastuzumab above. ***Reviews:*** NHSC Jan 2011.
Target population: As for lapatinib above. ***Sector:*** Secondary care.		***Implications:*** This will compete with other second-line options including biological therapies, chemotherapies and hormonal therapies. ***Financial:*** Cost unknown but will displace other expensive treatments. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: First in class trastuzumab emtansine (T-DM1) is an antibody conjugate of trastuzumab and an anti-mitotic agent, maytansinoid DM1 given by 3-weekly i.v. infusion. ***Efficacy:*** Initial data from the EMILIA study (n=991) in BC that progressed after first-line trastuzumab and a taxane show median PFS was 9.6 months for T-DM1 vs. 6.4 months for lapatinib and capecitabine (LC). Response rates were 43.6% and 30.8%, respectively. Median overall survival (OS) had not been reached in the T-DM1 group and was 23.3 months in the LC group. Final analysis is expected by 2014. 1-year and 2-year survival rates with T-DM1 were 84.7% and 65.4%; with LC they were 77% and 47.5%, respectively. The PIII TH3RESA study is comparing T-DM1 with treatment of the physician's choice in 795 women who have received at least 2 prior HER2 regimens. Results are expected in 2015. ***Safety:*** Compared with the combination of lapatinib and capecitabine, trastuzumab emtansine more commonly causes thrombocytopenia and raised liver enzymes, but less often causes diarrhoea, vomiting and hand-foot syndrome.				
Regorafenib **oral** Bayer	***Indication:*** Gastrointestinal stromal tumours (GIST), metastatic - third-line.	***Current status:*** PIII. Filed in US Aug 2012 with fast track status.	***Predicted UK licence extension:*** 2014	***National guidance:*** **NICE:** GIST - imatinib, sunitinib. ***Reviews:*** None.
Target population: The incidence of metastatic GIST is 0.4 per 100,000 people. About two thirds of patients do not respond, or develop resistance, to first-line imatinib. Sunitinib is a second-line option. ***Sector:*** Secondary care.		***Implications:*** Regorafenib will provide another treatment option for patients who have failed on imatinib and sunitinib. ***Financial:*** Cost unknown but will be additive to other therapies. A PAS is in place for sunitinib in GIST. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Multi-targeted inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases. Taken once daily for 3 weeks of every 4-week cycle. ***Efficacy:*** In the PIII GRID study (n=199) patients whose disease has progressed despite prior treatment received regorafenib or placebo, in addition to best supportive care. Median PFS was 4.8 months for regorafenib vs. 0.9 months for placebo (HR 0.27, p<0.0001). PFS rates at 3 and 6 months were 60% and 38% with regorafenib vs. 11% and 0% with placebo. The disease control rate (defined as the rate of partial response (PR) plus stable disease (SD) lasting for ≥12 weeks) was 53% vs. 9%, respectively. In a published PII study (n=33), the clinical benefit rate (defined as complete or PR, and SD ≥16 weeks) was 79%. Four patients achieved PR, and 22 exhibited SD ≥16 weeks. Median PFS was 10.0 months. ***Safety:*** Adverse effects include hand-foot syndrome, fatigue, diarrhoea, hypertension, oral mucositis and alopecia.				
Tertomotide **injection** KAEL-GemVax	***Indication:*** Pancreatic cancer, advanced.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** Uncertain.	***National guidance:*** **NICE:** Pancreatic cancer - gemcitabine. ***Reviews:*** No recent reviews.
Target population: UK incidence of pancreatic cancer is 13 per 100,000 people; 80% have advanced disease at diagnosis and less than 5% survive 5 years. 90% of pancreatic cancers express telomerase. ***Sector:*** Secondary care.		***Implications:*** Tertomotide will be used in addition to chemotherapy and may improve survival of patients with a very poor prognosis. Studies have used adjuvant GM-CSF which is not available in the UK. It is uncertain what impact this has on the potential use of tertomotide in the UK. ***Financial:*** Cost of tertomotide will be additive to current therapies. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Anti-telomerase vaccine that stimulates the immune system to destroy cancer cells by recognising telomerase, a protein specific to cancer cells. Given with adjuvant granulocyte macrophage colony stimulating factor (GM-CSF; not available in the UK), both by multiple intradermal injections over 4 weeks, and then once every month. ***Efficacy:*** The PIII TeloVac study (n=1,110) is comparing gemcitabine plus capecitabine with or without tertomotide, given concurrently or after chemotherapy is complete. Results are due in 2012. The PIII PrimoVax study was halted early when initial results showed no survival benefit for tertomotide. In 365 chemotherapy-naïve patients randomised to tertomotide (plus gemcitabine at first sign of disease progression) or gemictabine, median overall survival was 5.9 months vs. 7.3 months, respectively. Median PFS was 1.9 vs. 3.7 months, respectively. ***Safety:*** Tertomotide appears to be well tolerated and no serious adverse effects have been reported.				

Doxorubicin heat-sensitive liposomes injection *ThermoDox* Celsion	***Indication:*** Hepatocellular carcinoma (HCC), inoperable - first-line.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** HCC - sorafenib not recommended, microwave ablation. ***Reviews:*** NHSC Dec 11.
Target population: UK incidence of HCC is 5 per 100,000 people; 90% present with advanced disease and 5-year survival rates are 5%. Potentially curative options are surgery (suitable for <25% of patients) and microwave or radiofrequency ablation (RFA). Chemotherapy has limited benefits and surgery is not an option in advanced disease. ***Sector:*** Secondary care.	***Implications:*** For patients with limited treatment options, *ThermoDox* offers the possibility of greater efficacy and fewer systemic adverse effects because of the combined effects of targeted cytotoxicity and ablation. Sorafenib is licensed for HCC but not recommended by NICE. ***Financial:*** Likely to be more expensive than standard doxorubicin. ***PbR:*** Chemotherapy is tariff excluded.			
Pharmacology: A heat-activated liposomal formulation of doxorubicin, which is released when the tumour site is heated by microwave or radiofrequency ablation (RFA) to 39-42°C. Given by 30-minute i.v. infusion, 15 minutes prior to ablation. ***Efficacy:*** The PIII HEAT trial is investigating the efficacy and safety of *ThermoDox* in combination with RFA vs. RFA alone. Enrolment of 700 patients was completed in May 2012 and final data collection for the primary outcome of PFS is due at the end of 2012. In a published dose-finding PI study (n=24), median time to treatment failure was 374 days. ***Safety:*** Pre-medication is required to minimise infusion-related reactions.				
Aflibercept injection *Zaltrap* Sanofi-Aventis	***Indication:*** Colorectal cancer (CRC), metastatic - second-line.	***Current status:*** Filed in EU Dec 2011. Approved in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** CRC: pathway, quality standard due Aug 2012 (draft). **SIGN:** CRC. ***Reviews:*** No recent reviews.
Target population: UK incidence of CRC is 67 per 100,000 people. 20- 55% of patients present with metastatic disease. Management is mainly palliative with surgery and chemo/radiotherapy for symptom control. ***Sector:*** Secondary care.	***Implications:*** Aflibercept will be used in combination with FOLFIRI, as an alternative to other second-line options including irinotecan and/or oxaliplatin plus 5-fluorouracil and folinic acid (FOLFOX). ***Financial:*** Likely to be expensive but will displace other options. A PAS is in place for cetuximab in this setting. ***PbR:*** Chemotherapy is tariff excluded.			
Pharmacology: A vascular endothelial growth factor (VEGF) receptor fusion protein that binds VEGF-A and placental growth factor, preventing angiogenesis. Given every 2 weeks by i.v. infusion. ***Efficacy:*** In the PIII VELOUR study (n=1,200) previously-treated patients with inoperable metastatic CRC, were randomised to aflibercept or placebo, both followed by FOLFIRI (irinotecan, 5-fluorouracil and folinic acid), every 2 weeks. Aflibercept improved overall survival vs. placebo (HR 0.8, p<0.004) and PFS (HR 0.8, p=0.00007). In a PII study (n=51), in bevacizumab-naïve patients disease control rate was 29% and median PFS was 2 months. In bevacizumab previously-treated patients, disease control rate was 30% and median PFS was 3.4 months. ***Safety:*** Adverse effects include diarrhoea, stomatitis, hypertension, neutropenia.				
Regorafenib oral Bayer	***Indication:*** Colorectal cancer (CRC), metastatic disease - third- or fourth-line.	***Current status:*** Filed in EU and US May 2012 (US with priority review).	***Predicted UK launch:*** 2013	***National guidance:*** As for aflibercept above. ***Reviews:*** NHSC Aug 2011.
Target population: As for aflibercept above. ***Sector:*** Secondary care.	***Implications:*** For patients with no further treatment options, regorafenib may delay disease progression and improve quality of life. ***Financial:*** Cost unknown but will be additive to other therapies. A PAS is in place for cetuximab in this setting. ***PbR:*** Chemotherapy is tariff excluded.			
Pharmacology: Multi-targeted inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases. ***Efficacy:*** The PIII CORRECT study, in 754 adults with metastatic CRC that had progressed after receiving all approved drugs for CRC, was stopped early after meeting its primary outcome. Initial data show overall survival was 6.4 months in patients randomised to regorafenib plus best supportive care (BSC) vs. 5.0 months for placebo plus BSC (HR 0.77, p=0.052). Median PFS was 1.9 vs. 1.7 months, respectively (0.49, p<0.0001). The expanded-access PIII CONSIGN study is expected to report safety data in 2014. ***Safety:*** Most common adverse effects are hand-foot syndrome, fatigue, diarrhoea, hyperbilirubinaemia and hypertension.				

Axitinib **oral** *Inlyta* Pfizer	***Indication:*** Renal cell carcinoma (RCC), advanced - first-line.	***Current status:*** PIII with orphan status.	***Predicted UK licence extension:*** 2014	***National guidance:*** **NICE:** RCC, RCC – sunitinib, pazopanib, Urological cancer. ***Reviews:*** NHSC Jul 2012.
Target population: The UK incidence of RCC is about 14 in 100,000 people, about 60% have advanced disease which is treated with interferon and/or interleukin, and is largely resistant to chemo/radiotherapy. ***Sector:*** Secondary care.		***Implications:*** An alternative to NICE-approved sunitinib and pazopanib for first-line treatment of advanced disease. ***Financial:*** Likely to be expensive but will displace other options. Current monthly list price for sunitinib and pazopanib are about £2,100 and £2,200, respectively but PASs are in place for both in this setting. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: An angiogenesis inhibitor that blocks endothelial growth factor receptors, platelet derived growth factor receptor-beta and c-kit, a cytokine receptor. ***Efficacy:*** A PIII trial is comparing axitinib with sorafenib in 447 adults who are treatment naïve or have progressive disease after one prior systemic first-line regimen for metastatic disease. Data collection for the primary outcome of PFS is due in 2012. Data on overall response rates for a PII trial (n=200) is due by the end of 2013. ***Safety:*** Adverse events occurring more often with axitinib than sorafenib include diarrhoea, hypertension and hypothyroidism.				
Tivozanib **oral** Astellas	***Indication:*** Renal cell carcinoma (RCC), advanced - first-line.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** As for axitinib above. ***Reviews:*** NHSC Jan 2011.
Target population: As for axitinib above. ***Sector:*** Secondary care.		***Implications:*** As for axitinib above. ***Financial:*** As for axitinib above. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Triple vascular endothelial growth factor (VEGF) receptor inhibitor. ***Efficacy:*** The PIII TIVO-1 study is comparing tivozanib with sorafenib in 517 patients who have undergone nephrectomy and are treatment naïve (70%) or have received only one prior systemic therapy for metastatic disease. Overall, median PFS was 11.9 months with tivozanib vs. 9.1 months for sorafenib (HR 0.8, p=0.042); in treatment naïve patients it was 12.7 vs. 9.1 months, respectively (0.8, p=0.037). In a published PII study (n=272), tivozanib produced an objective response rate (ORR) after 16 weeks of 18%. 118 patients with less than 25% tumour shrinkage were then randomised to tivozanib or placebo. After a further 12 weeks, 49% on tivozanib were progression-free vs. 21% on placebo (p=0.001). Overall, the ORR was 24% and median PFS was 11.7 months. ***Safety:*** The most common adverse effect is hypertension. Like sorafenib, tivozanib causes diarrhoea, fatigue and neutropenia but is less likely to cause hand-foot syndrome or alopecia.				
Axitinib **oral** *Inlyta* Pfizer	***Indication:*** Renal cell carcinoma (RCC), advanced - second-line.	***Current status:*** Recommended for approval in EU May 2012 with orphan status. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** RCC (second-line): axitinib due May 2013; not recommended - sorafenib, sunitinib, everolimus. ***Reviews:*** NHSC Aug 2010.
Target population: As for axitinib above. There is no standard therapy for metastatic RCC when first-line immunotherapy has failed, or is unsuitable. Sunitinib, sorafenib and everolimus are licensed for second-line use but none are recommended by NICE. ***Sector:*** Secondary care.		***Implications:*** Axitinib may benefit patients who have few therapeutic options. ***Financial:*** Likely to be expensive and additive to existing therapy. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: An angiogenesis inhibitor that blocks endothelial growth factor receptors, platelet derived growth factor receptor-beta and c-kit, a cytokine receptor. ***Efficacy:*** In the published PIII AXIS 1032 study (n=723), axitinib showed a median PFS of 6.7 months vs. 4.7 months for sorafenib (HR 0.7, p<0.001). PFS was longer in axitinib-treated patients than those on sorafenib, regardless of prior therapy with sunitinib (4.8 vs. 3.4 months) or cytokines (12.1 vs. 6.5 months). In a published PII study of 62 patients previously treated with sorafenib, the objective response rate (ORR) was 22.6%, and median duration of response 17.5 months. Median PFS and overall survival (OS) times were 7.4 months and 13.6 months, respectively. In another published PII study (n=52) axitinib produced an ORR of 44%. Median time to progression was 15.7 months and median OS was 29.9 months. ***Safety:*** As for axitinib above.				

Apaziquone **intravesical** *Neoquin* Spectrum	***Indication:*** Bladder cancer, non-invasive.	***Current status:*** PIII.	***Predicted UK launch:*** Uncertain.	***National guidance:*** **NICE:** Urological cancer. **SIGN:** Bladder cancer. ***Reviews:*** None.
Target population: UK incidence of non-invasive (or superficial) bladder cancer is about 12 per 100,000 people. After surgery, intravesical chemotherapy reduces risk of recurrence by 39% together with BCG vaccine that reduces risk of progression by 27%, depending on tumour grade. ***Sector:*** Secondary care.		***Implications:*** Apaziquone will be an alternative to intravesical mitomycin, epirubin and doxorubicin in patients at risk of recurrence or progression. ***Financial:*** May displace current options. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: An indoloquinone mitomycin analogue prodrug, metabolised to an alkylating agent by the DT-diaphorase enzyme, which is over-expressed by bladder cancer cells. ***Efficacy:*** Two PIII trials (SPI-611 and SPI-612) each recruiting 800 patients have investigated use of a single dose of apaziquone following transurethral resection of bladder tumours. Individually they did not meet their primary outcomes but pooled analysis showed apaziquone produced a significant reduction in rate of tumour recurrence at 2 years (p=0.017). In a published PII study of 46 patients who underwent surgical excision of all but one superficial lesion, 67% had complete histological disappearance of the remaining lesion 2-4 weeks after 6 once-weekly instillations of apaziquone. After 24 months, 49% of responders were recurrence-free, with a median response duration of 18 months. Overall recurrence-free survival was 39%. Two ongoing PIII studies (SPI-1011 and SPI-1012) are investigating 6-weekly instillations. ***Safety:*** Local adverse effects include cystitis, dysuria, haematuria, bladder spasm, abdominal pain and fatigue.				
Abiraterone acetate **oral** *Zytiga* Janssen-Cilag	***Indication:*** Prostate cancer (PC), metastatic castration-resistant - first-line.	***Current status:*** Filed in EU Jun 2012.	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** PC pathway, Abiraterone - metastatic, castration resistant (no chemotherapy) due Nov 2013. ***Reviews:*** None.
Target population: In the UK, the crude incidence of PC is 134 per 100,000 people, 55-65% develop metastatic disease and all eventually become resistant to standard hormonal therapy (castration-resistant). ***Sector:*** Secondary care.		***Implications:*** First-line therapy with oral abiraterone will delay the need for chemotherapy. ***Financial:*** Based on current prices, 30 weeks' treatment with abiraterone is £20,510 vs. £7,200 for 10 cycles of docetaxel, excluding added costs of i.v. administration (based on a body surface area of 1.7m^2). A PAS is in place for second-line abiraterone in this setting. ***PbR:*** Hormonal therapies for cancer are in tariff. Various funding mechanisms are currently in use including the cancer drug fund.		
Pharmacology: Anti-androgen that irreversibly inhibits the cytochrome P450 enzyme involved in testosterone production. ***Efficacy:*** Interim data from the PIII COU-AA-302 trial in 1,088 chemotherapy-naïve men on prednisone showed abiraterone increased PFS (median not yet reached) vs. placebo (8.3 months, HR 0.43, p<0.0001). There was a 33% improvement in overall survival (OS), a co-primary outcome; in patients on abiraterone median OS was not reached vs. 27.2 months in the control arm (0.75; p=0.0097). Due to positive results, the trial was stopped early and control patients offered abiraterone. ***Safety:*** See emc.medicines.org.uk.				
Enzalutamide **oral** Astellas	***Indication:*** Prostate cancer (PC), metastatic castration-resistant - second-line.	***Current status:*** Filed in EU Jun 2012.	***Predicted UK launch:*** 2013	***National guidance:*** As for abiraterone above. ***Reviews:*** NHSC Feb 2012.
Target population: As for abiraterone above. About 40% of men with metastatic disease will receive first-line therapy and of these about 75% may receive second-line therapy (about 3,300 men). ***Sector:*** Secondary care.		***Implications:*** This will compete with oral abiraterone for second-line use. ***Financial:*** Likely to be similar to abiraterone for which a PAS is in place. ***PbR:*** Hormonal therapies for cancer are in tariff. Various funding mechanisms are currently in use including the cancer drug fund.		
Pharmacology: Androgen receptor antagonist. ***Efficacy:*** The published PIII AFFIRM study (n=1199) was stopped early after an interim analysis showed a survival benefit for enzlutamide vs. placebo. The median overall survival was 18.4 months for enzalutamide vs. 13.6 months for placebo group (HR 0.63, p<0.001). Prostate-specific antigen (PSA) level reduced by ≥50% (secondary outcome) in 54% vs. 2% of patients, respectively (p<0.001) and the time to PSA progression was 8.3 vs. 3.0 months (HR 0.25, p<0.001), respectively. ***Safety:*** Adverse effects include fatigue, diarrhoea and hot flushes. Seizures were reported in the AFFIRM study.				

Radium-223 chloride **injection** *Alpharadin* Bayer	***Indication:*** Prostate cancer (PC), castration-resistant (patients with bone metastases).	***Current status:*** PIII. Priority review granted in the US.	***Predicted UK launch:*** 2013	***National guidance:*** As for abiraterone above. ***Reviews:*** NHSC Dec 2010.
Target population: As for abiraterone above. Over 90% of patients with advanced disease will develop bone metastases which can lead to fractures and debilitating bone pain. ***Sector:*** Secondary care.		***Implications:*** Radium-233 could improve quality of life and delay disease progression and is potentially an alternative/ additive to palliative therapies. ***Financial:*** Cost is unknown but may displace other therapies. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: A first in class radiopharmaceutical that targets bone metastases. Given monthly for up to 6 cycles. ***Efficacy:*** The PIII ALSYMPCA study (n=921) was stopped early after meeting its primary outcome. Median overall survival (OS) was 14.9 months in the radium-223 group vs. 11.3 months for placebo (HR 0.7, p<0.0001). In a published PII study (n=64), median change in alkaline phosphatase was -65.6% in the radium-223 group vs. 9.3% in the placebo group (p<0.001); median OS was 16.3 months vs. 11.6 months (p=0.066). In a published PII study (n=100), pain was significantly reduced at 8 weeks in 56% of men given a single dose of radium-223. ***Safety:*** Most common adverse effects are bone pain, nausea, diarrhoea, vomiting and anaemia.				
Sipuleucel-T **injection** *Provenge* Dendreon	***Indication:*** Prostate cancer (PC), metastatic castration-resistant - first-line.	***Current status:*** Filed in EU Jan 2012. Launched in US - see prescribing data.	***Predicted UK launch:*** 2013	***National guidance:*** As for abiraterone above. ***Reviews:*** NHSC Apr 2011.
Target population: As for abiraterone above. ***Sector:*** Secondary care.		***Implications:*** Sipuleucel-T will compete with abiraterone acetate. It may prolong survival and have improved tolerability over existing therapies. ***Financial:*** Cost in the US is $93,000 for 3 doses. A PAS is in place for second-line abiraterone in this setting. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: First therapeutic vaccine for PC that stimulates a T-cell response against prostatic acid phosphatase, an antigen expressed in PC but not in non-prostate tissue. Given by one-hour i.v. infusion at 2-week intervals for 3 doses. ***Efficacy:*** In published PIII trials patients had leukapheresis followed 3 days later by infusion of sipuleucel-T or control (autologous peripheral blood mononuclear cells that had not been activated). In the IMPACT study (n=512), median overall survival (OS) was 25.8 months for sipuleucel-T vs. 21.7 months for placebo (HR 0.78, p=0.03). Median time to objective disease progression was 14.6 weeks vs. 14.4 weeks, respectively (p=0.63). In the D9901 study (n=127), median time to disease progression for sipuleucel-T was 11.7 weeks vs. 10.0 weeks for placebo (1.45, p=0.052) and median OS was 25.9 months and 21.4 months, respectively (1.7, p=0.01). In an analysis of 2 studies (n=98), sipuleucel-T produced a 33% relative reduction in risk of death (1.5, p=0.011). ***Safety:*** Pre-medication to prevent acute infusion reactions (commonly chills, fever and fatigue) is required.				
Bevacizumab **injection** *Avastin* Roche	***Indication:*** Ovarian cancer (OC), platinum-sensitive - second-line.	***Current status:*** Filed in the EU 2011.	***Predicted UK licence extension:*** 2012	***National guidance:*** **NICE:** OC pathway, quality standard; OC metastatic - bevacizumab -first-line due Apr 2013, -recurrent, advanced due Jun 2013. **SIGN:** Ovarian cancer. ***Reviews:*** NHSC Dec 2010.
Target population: The UK incidence of OC is 21 per 100,000 people. 75% have advanced disease and up to 80% respond to first-line platinum chemotherapy; of these 55-75% relapse within 2 years. ***Sector:*** Secondary care.		***Implications:*** Bevacizumab will be used in addition to current chemotherapies and may delay disease progression. ***Financial:*** Current cost of 12 doses for a 65kg woman is £28,000. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Vascular endothelial growth factor antagonist given by i.v. infusion every 3 weeks. ***Efficacy:*** The published PIII OCEANS trial randomised 484 women, whose disease had recurred after first-line chemotherapy, to bevacizumab 15mg/kg or placebo together with carboplatin and gemcitabine. Median PFS was 12.4 months for bevacizumab vs. 8.4 months for placebo (HR 0.5, p<0.0001). The objective response rate was 78.5% vs. 57.4%, respectively. Overall survival data are due in 2013 for the PIII GOG-0213 trial (n=660) studying bevacizumab plus carboplatin and paclitaxel. ***Safety:*** See emc.medicines.org.uk.				

Farletuzumab injection Eisai	***Indication:*** Ovarian cancer (OC), platinum-sensitive - second-line.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** As for bevacizumab above. ***Reviews:*** NHSC Apr 2012.
Target population: As for bevacizumab above. ***Sector:*** Secondary care.		***Implications:*** Farletuzumab will compete with bevacizumab and be used in addition to current chemotherapies. ***Financial:*** Cost unknown but could be expensive. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Humanised monoclonal antibody to the folate receptor-alpha which is over-expressed on most ovarian tumour cells. Given by once-weekly i.v. infusion in combination with carboplatin and a taxane. ***Efficacy:*** The PIII FAR-131 trial in 1,080 first-relapsed women is comparing 2 doses of farletuzumab (1.25mg/kg and 2.5mg/kg) plus carboplatin or cisplatin and a taxane, with second-line chemotherapy alone. Data collection is due for completion in 2012. In a PII trial in 44 women receiving farletuzumab plus chemotherapy, cancer antigen-125 (CA-125) levels normalised in 87% of patients. When comparing women with a first relapse less than 12 months after first-line therapy (n=12) or later (n=32), a complete or partial response was achieved in 64% and 71% of patients, respectively. ***Safety:*** Most common adverse effects are infusion-related fever and chills.			
Paclitaxel injection *Paclical* Oasmia	***Indication:*** Ovarian cancer (OC) - second- or third-line.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** 2013.	***National guidance:*** As for bevacizumab above. ***Reviews:*** NHSC Dec 2011.
Target population: As for bevacizumab above. ***Sector:*** Secondary care.		***Implications:*** Compared to current formulations, *Paclical* may cause fewer adverse effects, requires no pre-medication and may allow higher doses. ***Financial:*** Cost unknown but will displace other taxanes. Cost of currently available paclitaxel is £3,600 for six cycles (body surface area of $1.7m^2$). ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: A new formulation of paclitaxel encapsulated to increase its water solubility, removing the need for solvents which can cause hypersensitivity reactions. Given by i.v infusion every 3 weeks for 6 cycles. ***Efficacy:*** The PIII OAS-07OVA trial is comparing *Paclical* ($250mg/m^2$) with *Taxol* ($175mg/m^2$), both in combination with carboplatin, in 650 women with OC who have relapsed more than 6 months after first- or second-line chemotherapy. Interim analysis indicates *Paclical* reduces levels of the biomarker, cancer antigen-125 (CA-125), to similar levels as *Taxol.* ***Safety:*** Requires no pre-medication.			
Pazopanib oral *Votrient* GlaxoSmith-Kline	***Indication:*** Ovarian cancer (OC) – maintenance after first-line chemotherapy.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2013	***National guidance:*** As for bevacizumab above. ***Reviews:*** NHSC Apr 2011.
Target population: As for bevacizumab above. ***Sector:*** Secondary care.		***Implications:*** Pazopanib will be used in addition to current therapies but may delay need for second-line chemotherapy. ***Financial:*** Monthly cost of pazopanib 800mg daily is £2,200. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Multi-targeted tyrosine kinase receptor inhibitor. ***Efficacy:*** A PIII trial (n=900) is assessing the effect of 2 years pazopanib monotherapy on PFS in OC that has not progressed after first-line chemotherapy. Results are expected in 2013. In a published PII trial (n=36) with pazopanib monotherapy 31% of patients achieved the primary outcome of ≥50% decrease in cancer antigen-125 levels. Stable disease was seen in 56% of patients, with median duration of 80 days. At 6 months, 17% remained progression-free. ***Safety:*** See emc.medicines.org.uk.			

Vintafolide **injection** Merck	***Indication:*** Ovarian cancer (OC), platinum-resistant, folate receptor (FR)-positive.	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** As for bevacizumab above. Vintafolide – proposed appraisal. ***Reviews:*** NHSC Dec 2011.
Target population: As for bevacizumab above. 90% of patients have FR-positive tumours and most eventually relapse and develop platinum-resistant disease. ***Sector:*** Secondary care.		***Implications:*** Vintafolide will be used in addition to doxorubicin, to provide a more targeted treatment for patients with a poor prognosis and few options, none of which have demonstrated improved survival. ***Financial:*** Likely to be expensive. Cost of the radiopharmaceutical diagnostic test technetium Tc99m etarfolatide is unknown. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Vinca alkaloid conjugated to a folate molecule. It enters tumour cells via the folate receptor, which is over-expressed by most OC tumour cells. Given as an i.v. infusion in combination with pegylated liposomal doxorubicin (PLD). ***Efficacy:*** The PII PRECEDENT study involved 162 women with folate receptor-positive OC that had relapsed within 6 months of platinum chemotherapy. PFS was 21.7 weeks in those on vintafolide plus PLD and 11.7 weeks in those on PLD alone (HR=0.63, p=0.03). PFS in patients with at least one FR-positive tumour site was 24.6 weeks in the vintafolide plus PLD group vs. 7.6 weeks in the PLD only group (0.6, p=0.04); in patients in whom all tumour sites were FR-positive it was 24.0 vs. 6.6 weeks, respectively (0.4, p<0.02). The PIII PROCEED trial (n=640) is similar in design with results due in 2014. ***Safety:*** Adverse effects include neutropenia, anaemia, fatigue and hand/foot syndrome.				
Ridaforolimus **oral** *Jenzyl* Merck	***Indication:*** Bone and soft tissue sarcoma, advanced - maintenance.	***Current status:*** Filed in EU Jul 2011 with orphan status. Recommended against approval in US Jun 2012 due to concerns about its risk-benefit profile.	***Predicted UK launch:*** Uncertain.	***National guidance:*** **NICE:** STS- trabectedin, Sarcoma. ***Reviews:*** No recent reviews.
Target population: As for pazopanib above. Current therapy consists of a combination of chemotherapy, surgery and radiotherapy. ***Sector:*** Secondary care.		***Implications:*** Ridaforolimus is to be used in patients who have responded to chemotherapy. ***Financial:*** This is additive to current options and likely to be expensive. PASs are in place for trabectedin in advanced soft tissue sarcoma and for mifamurtide in resectable non-metastatic osteosarcoma. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: mTOR inhibitor. ***Efficacy:*** In the PIII SUCCEED trial, 711 patients aged ≥13 years with metastatic disease successfully treated with first-line chemotherapy were randomised to ridaforolimus or placebo. Ridaforolimus reduced the risk of progression vs. placebo (HR 0.7, p=0.0001). Median PFS was 17.7 weeks with ridaforolimus vs. 14.6 weeks with placebo. The median overall survival (secondary outcome) was 90.6 weeks for ridaforolimus and 85.3 weeks for placebo (HR 0.93, p=0.46). ***Safety:*** Common adverse effects include stomatitis, infections, fatigue, thrombocytopenia, diarrhoea and cough.				
Vismodegib **oral** *Erivedge* Roche	***Indication:*** Basal cell carcinoma (BCC), locally advanced or metastatic.	***Current status:*** Filed in EU Dec 2011. Launched in US - see prescribing data.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Skin tumours. ***Reviews:*** NHSC May 2010.
Target population: The incidence of BCC is underestimated but is likely to be about 100 per 100,000 people. Metastases occur rarely (in ≤0.5% of cases). Treatment options for advanced disease are very limited and prognosis depends on site of spread. ***Sector:*** Secondary care.		***Implications:*** Vismodegib is an option for first and second-line use in advanced disease, where surgery or radiotherapy is inappropriate. ***Financial:*** Used in patients with no other therapeutic options and continued until disease progression. US cost is about $7,500/month and average duration of treatment is 10 months. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Hedgehog pathway inhibitor, first in class. ***Efficacy:*** In the published PII ERIVANCE BCC study, 96 patients with advanced BCC unsuitable for surgery received vismodegib daily until disease progression. The overall response rate was 43% and 30% in patients with locally advanced and metastatic disease, respectively. Median PFS was 9.5 months. ***Safety:*** Common adverse effects include muscle spasm, hair loss, altered taste sensation, weight loss and fatigue.				

Dabrafenib **oral** GlaxoSmith-Kline	***Indication:*** Malignant melanoma, $BRAF^{V600}$-positive - first-line.	***Current status:*** Filed in EU Aug 2012.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** As for vismodegib above. **Reviews:** NHSC Aug 2011.
Target population: The UK incidence of malignant melanoma is about 21 per 100,000 people, and is doubling every 10-20 years. About 50% are $BRAF^{V600}$-positive (80-90% V600E and 10-20% V600K) which is associated with increased tumour aggressiveness. ***Sector:*** Secondary care.		***Implications:*** Dabrafenib will compete with vemurafenib as an alternative to the current first-line choice of i.v. dacarbazine, which has a response rate of 5-15% and improves PFS by only a few months. A test is needed to identify $BRAF^{V600}$-positive patients. ***Financial:*** Likely to be similarly priced to vemurafenib (£7,000 per month) but will offset administration costs of dacarbazine. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: $BRAF^{V600E}$ inhibitor. ***Efficacy:*** In the published BREAK-3 trial, 250 adults with previously untreated, stage IV or unresectable stage III $BRAF^{V600E}$-positive melanoma were randomised to dabrafenib or 3-weekly cycles of i.v. dacarbazine. Median PFS was 5.1 months for dabrafenib vs. 2.7 months for dacarbazine; dabrafenib reduced the risk of disease progression or death by 70% (HR 0.30, p<0.0001). There was no difference in overall survival (HR 0.61) but data are immature. 50% of patients on dabrafenib had a confirmed objective response vs. 6% on dacarbazine. ***Safety:*** Most common adverse events are cutaneous (hyperkeratosis, papillomas, hand-foot syndrome), pyrexia, fatigue, headache, and arthralgia. Photosensitivity, which is common with vemurafenib, occurs rarely with dabrafenib.				
Rituximab **injection** *MabThera* Roche	***Indication:*** Non-Hodgkin's lymphoma (NHL) - s.c. formulation.	***Current status:*** PIII with plans to file in 2012.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Follicular NHL- rituximab, Haemato-oncology. ***Reviews:*** None.
Target population: All patients with NHL for whom i.v. rituximab is currently indicated. Those with poor venous access may be initial candidates. ***Sector:*** Secondary care.		***Implications:*** Subcutaneous administration could reduce outpatient time and may facilitate homecare delivery. ***Financial:*** Likely to be the same cost as the current i.v. formulation. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Anti-CD20 monoclonal antibody plus recombinant human hyaluronidase for s.c. administration. ***Efficacy:*** A PIII open-label study with rituximab 1400mg s.c. or 375 mg/m² i.v. plus standard chemotherapy in 530 patients with previously untreated follicular NHL followed by maintenance treatment with either rituximab s.c. or i.v. is ongoing. Primary outcome measures include the ratio of trough serum concentrations following s.c. and i.v. injection at day 21 and the overall response rate after induction treatment. ***Safety:*** Injection site reactions in addition to drug associated adverse effects are possible. See emc.medicines.org.uk.				
Bendamustine **injection** *Levact* Napp	***Indication:*** Non-Hodgkin's lymphoma (NHL), advanced low-grade - first-line with rituximab.	***Current status:*** PIII with plans to file in 2012.	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** NHL- bendamustine first-line due Oct 2013. Haemato-oncology. ***Reviews:***
Target population: The UK incidence of NHL is about 20 per 100,000 people and 40-50% have indolent (low-grade) disease, usually advanced at presentation. ***Sector:*** Secondary care.		***Implications:*** Bendamustine plus rituximab could be used instead of standard chemotherapy regimens which have more adverse effects. ***Financial:*** Bendamustine is currently licensed for second-line use. Cost of a 12-dose course is about £5,000. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: An alkylating agent with antimetabolite activity, given by i.v. infusion for up to six cycles. ***Efficacy:*** In a PIII trial in 513 patients with low-grade NHL including follicular and mantle-cell lymphoma, first-line bendamustine (90mg/m^2) and rituximab was associated with better PFS (54.8 vs. 34.8 months, p<0.001), complete response rate (40% vs. 31%, p<0.05), and event-free survival (54 vs. 31 months, p<0.001) than rituximab and CHOP. The ongoing PIII BRIGHT study is comparing complete response rate in 447 patients randomised to bendamustine or standard chemotherapy, both in addition to rituximab, for first-line treatment of low-grade NHL. ***Safety:*** See emc.medicines.org.uk				

Pixantrone **injection** *Pixuvri* Cell Therapeutics	***Indication:*** Non-Hodgkin's lymphoma (NHL), relapsed or refractory aggressive disease - monotherapy.	***Current status:*** Conditional approval granted in EU May 12. See prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** NHL- pixantrone due TBC. Haemato-oncology. ***Reviews:*** No recent reviews.
Target population: About 50-60% of people with NHL have aggressive disease (10-12 per 100,000). 50-60% can be cured with combination chemotherapy. ***Sector:*** Secondary care.		***Implications:*** Pixantrone will be an option for patients resistant to or intolerant of standard therapies, those who have exceeded their lifetime limit of anthracyclines, and those unsuitable for stem cell transplantation. ***Financial:*** Likely to be expensive. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Topoisomerase II inhibitor structurally similar to anthracyclines. ***Efficacy:*** In the published PIII EXTEND (PIX301) study, 140 patients were given third-line pixantrone or a physician's choice single agent. Complete or unconfirmed complete response rates (primary outcome) were 20.0% vs. 5.7%, respectively (p=0.02). Median overall survival was 10.2 months vs. 7.6 months (HR 0.79, p=0.25), respectively. ***Safety:*** See prescribing data.				
Brentuximab vedotin **injection** *Adcetris* Takeda	***Indication:*** Hodgkin's lymphoma – relapsed/ refractory post autologous stem cell transplant (ASCT) or when ASCT unsuitable.	***Current status:*** Recommended for approval in EU Jul 2012 with orphan status. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Haemato-oncology. ***Reviews:*** NHSC Jan 2011.
Target population: UK incidence of Hodgkin's lymphoma is about 3 per 100,000 people. About 80% are cured with first-line therapy but 5-10% have primary refractory disease; 20-30% will relapse. Second-line chemotherapy and ASCT cure about 50%. ***Sector:*** Secondary or tertiary care.		***Implications:*** Current standard of care for patients who relapse following second-line therapy and ASCT is palliative chemotherapy with generally poor outcomes and median survival of 26 months. Brentuximab is an option for these patients. ***Financial:*** Brentuximab will be additive to current options and is likely to be expensive. Cost in the US is $13,500 per dose. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Anti-CD30 antibody conjugated to an antimicrotubule agent given as an i.v. infusion every 21 days. ***Efficacy***: Published PII results (n=102) show that 75% of patients on brentuximab achieved an objective response (34% complete and 40% partial remission). Median PFS was 5.6 months, and median duration of response for those in complete remission was 20.5 months. The ongoing PIII AETHERA trial in 322 patients is due to complete in 2013. ***Safety:*** Adverse effects include gastrointestinal effects, peripheral neuropathy and immunosuppression.				
B cell lymphoma vaccine **injection** *BiovaxID* Biovest International	***Indication:*** Non-Hodgkin's lymphoma (NHL), low-grade follicular disease.	***Current status:*** PIII with orphan status and plans to file in EU in 2012. Available on compassionate use basis.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Follicular NHL- rituximab, Haemato-oncology. ***Reviews:*** NHSC May 2010.
Target population: The UK incidence of follicular NHL is 3-7 per 100,000 and most (90%) will present with stage III or IV disease. These patients are considered for chemotherapy and will be eligible for this vaccine if they have prolonged remission. ***Sector:*** Secondary care.		***Implications:*** Further data are needed to define *BiovaxID*'s place in therapy, as the standard of care has changed since initial trials began. The company believe *BiovaxID* may eliminate the risk of rituximab resistance and may increase the utility of other therapies. ***Financial:*** Additive to current options after first-line treatment but may delay need for other therapies. ***PbR:*** Uncertain.		
Pharmacology: An autologous vaccine consisting of a conjugated lymphoma-associated antigen given about 6 months after chemotherapy. Five s.c. injections are given over a 6 month period. Booster vaccination may be required after 3 years. ***Efficacy:*** In a prematurely closed PIII trial, 117 patients who maintained a complete response to initial chemotherapy were given *BiovaxID* or control vaccine. Median disease-free survival was 44.2 months vs. 30.6 months, respectively (p<0.05). At 36 months, 61% of patients on *BiovaxID* were disease-free vs. 37% of control patients (NNT=4). In another PIII study, in 35 patients with IgM tumour isotype given *BiovaxID* made with IgM isotype, median time to relapse was 52.9 months vs. 28.7 months in the control group (HR 0.34, p=0.002). In 40 patients with IgG tumour isotype given *BiovaxID* made with an IgG isotype, median time to relapse was 35.1 months, vs. 32.4 months in 15 control-treated patients (HR 1.1, p=0.81). ***Safety:*** To date no serious adverse effects have been reported.				

Brentuximab vedotin injection *Adcetris* Takeda	***Indication:*** Relapsed/ refractory systemic anaplastic large cell lymphoma (ALCL).	***Current status:*** Recommended for approval in EU Jul 2012 with orphan status. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** NHSC Jan 2011.
Target population: ALCL accounts for between 2-3% of all cases of NHL and affects about 2 in 100,000 people in the EU. ***Sector:*** Secondary or tertiary care.	***Implications:*** ALCL is treated with chemotherapy and radiotherapy, followed by stem cell transplant if appropriate. Brentuximab may be considered in those who relapse despite these options. ***Financial:*** Brentuximab will be additional to current therapy. The US cost is $13,500 per dose/cycle. Patients receive an average of 3 cycles but up to a maximum of 16. ***PbR:*** Chemotherapy is tariff excluded.			
Pharmacology: Anti-CD30 antibody conjugated to an antimicrotubule agent and given by i.v. infusion every 21 days. ***Efficacy:*** Results of a PII single-arm study in 58 patients given brentuximab 1.8 mg/kg every 21 days for up to 16 doses show an objective response in 86% of patients. Complete remission was achieved in 57%, partial remissions in 33%, 3% of patients had stable disease, and 5% had progressive disease. Median duration of overall objective response was 12.6 months and median duration of response in those with complete remission was 13.2 months. ***Safety:*** Adverse effects include gastrointestinal effects, peripheral neuropathy and immunosuppression.				
Bortezomib injection *Velcade* Janssen-Cilag	***Indication:*** Multiple myeloma (MM) - s.c. administration.	***Current status:*** Recommended for approval in EU Jun 2012. Launched in US – see prescribing data.	***Predicted UK licence extension:*** 2012	***National guidance:*** **NICE:** MM - bortezomib and thalidomide, bortezomib, Haemato-oncology. ***Reviews:*** None.
Target population: The UK incidence of MM is 7.7 per 100,000 people and prevalence is about 16 in 100,000 people. ***Sector:*** Secondary care.	***Implications:*** Administration by s.c. injection may reduce treatment time. Note i.v and s.c doses are administered as different concentrations of the same formulation (i.v.-1mg/mL, s.c.- 2.5mg/mL) with potential for error. ***Financial:*** The formulation is the same as that currently available. PASs are in place for bortezomib and lenalidomide in this setting. ***PbR:*** Chemotherapy is tariff excluded.			
Pharmacology: A proteasome inhibitor given by s.c. instead of i.v. route. ***Efficacy:*** In a published PIII trial 222 patients with relapsed MM were randomised to 21-day cycles of bortezomib by s.c. injection or i.v. infusion. After 4 cycles overall response rate difference was -0.4%, showing non-inferiority (p=0.002). After a median follow-up of 11.8 months in the s.c. group and 12.0 months in the i.v. group, there were no differences in median time to progression (10.4 vs. 9.4 months, respectively) and 1-year overall survival (73% vs. 77%). ***Safety:*** See emc.medicines.org.uk.				
Bortezomib injection *Velcade* Janssen-Cilag	***Indication:*** Multiple myeloma (MM), induction and consolidation with autologous stem-cell transplant (ASCT).	***Current status:*** PIII.	***Predicted UK licence extension:*** Uncertain.	***National guidance:*** **NICE:** As for bortezomib above, MM - bortezomib (induction) due Oct 2013. ***Reviews:*** LNDG Mar 2012, NHSC Apr 2011.
Target population: As for bortezomib above. Induction followed by melphalan and ASCT gives the greatest chance of prolonged survival; less than 50% of newly diagnosed patients are eligible. ***Sector:*** Secondary care.	***Implications:*** Bortezomib will be additive to current treatment strategies involved in stem-cell transplantation. ***Financial:*** Average cost of a 20-dose course of i.v. bortezomib is £15,240. Use will be additive to current management options. ***PbR:*** Chemotherapy is tariff excluded.			
Pharmacology: A proteasome inhibitor. ***Efficacy:*** A published PIII study in 480 newly diagnosed patients assessed addition of bortezomib to thalidomide plus dexamethasone (VTD) vs. TD alone for induction therapy before double ASCT. Complete or near complete response (CR) was achieved in 31% on VTD vs. 11% on TD alone (p<0.0001). In the published PIII PETHEMA/GEM study (n=386), the CR rate was 35% with VTD, 14% with TD and 22% with VBMCP/VBAD/Bortezomib (*VBMCP*= Vincristine, BCNU, Melfalan, Cyclophosphamide, Prednisone, *VBAD*= Vincristine, BCNU, Adriamycin, Dexamethasone) regimen (p=0.0001 and p=0.01, respectively). In the published IFM 2005-01 study (n=482) bortezomib plus dexamethasone improved post-induction and post-transplantation CR or near CR vs. vincristine plus doxorubicin plus dexamethasone (14.8% vs. 6.4%, respectively). ***Safety:*** See emc.medicines.org.uk.				

Pomalidomide **oral** *Actimid* Celgene	***Indication:*** Multiple myeloma (MM), relapsed or refractory.	***Current status:*** Filed in EU Jun 2012 with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** As for bortezomib above, Lenalidomide. ***Reviews:*** None.
Target population: As for bortezomib above. Almost all patients eventually relapse. ***Sector:*** Secondary care.		***Implications:*** Initially likely to be used after lenalidomide and bortezomib in patients who have few remaining options. ***Financial:*** Will compete with others aiming for third-line treatment and will have to be competitive. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Interleukin stimulant and tumour necrosis factor inhibitor, analogue of thalidomide. ***Efficacy:*** The PIII NIMBUS open-label study (n=426) is underway to assess use of pomalidomide plus low-dose dexamethasone vs. high-dose dexamethasone in patients who have had ≥2 prior treatment lines. Data from 5 PII trials (n=224) involving use of pomalidomide with dexamethasone showed that 6 month PFS ranged from 37-73% and 6 month overall survival rates ranged from 67-95%. ***Safety:*** Myelosuppression is the main adverse effect.				
Carfilzomib **injection** *Kyprolis* Onyx	***Indication:*** Multiple myeloma (MM), relapsed and refractory.	***Current status:*** PIII in EU with orphan status. Approved in US- see prescribing data.	***Predicted UK launch:*** Uncertain.	***National guidance:*** As for pomalidomide above. ***Reviews:*** None.
Target population: As for pomalidomide above. ***Sector:*** Secondary care.		***Implications:*** Studies suggest the initial place in therapy for carfilzomib would be last-line monotherapy prior to palliative care. It may have safety advantages vs. current options but i.v. administration is a disadvantage. ***Financial:*** Likely to be similarly priced to current options for relapsed/refractory disease but additive to current therapy. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Second generation selective and irreversible proteasome inhibitor. ***Efficacy:*** The US licence is based on the results of a published PII open-label, single-arm study where patients had median of 5 prior lines of therapy, including bortezomib, lenalidomide, and thalidomide. The primary outcome of overall response rate was achieved in 23.7% of 266 patients. Median overall survival, a secondary outcome was 15.6 months. In a published PII study (n=129), the objective response rate was 42-52% in those who received up to 12 cycles of therapy. In an extension of this study interim data for 61 patients on maintenance carfilzomib therapy, show disease control was maintained for a median of 18 months. The ongoing PIII FOCUS study compares carfilzomib with best supportive care following treatment with at least 3 prior therapies. The primary outcome is overall survival. Comparative studies with bortezomib and studies in combination with lenalidomide and dexamethasone are ongoing. ***Safety:*** Common adverse reactions include fatigue, anaemia, nausea, thrombocytopenia, dyspnoea, diarrhoea and pyrexia.				
Bosutinib **oral** *Bosulif* Pfizer	***Indication:*** Chronic myeloid leukaemia (CML), Philadelphia positive - first-line.	***Current status:*** Filed in EU Aug 2011 with orphan status.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** CML- dasatinib, imatinib and nilotinib. ***Reviews:*** NHSC May 2010.
Target population: The annual incidence of CML is 1-2 per 100,000 people; 95% are Philadelphia chromosome positive. ***Sector:*** Secondary care.		***Implications:*** Imatinib is recommended by NICE for use in the first-line setting with nilotinib for use in patients resistant to, or intolerant of, standard dose imatinib. Dasatinib is not recommended. Bosutinib could be an alternative to imatinib or nilotinib. A PAS is in place for nilotinib in CML. ***Financial:*** Cost is likely to be similar to other licensed options. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Dual inhibitor of Src-Abl and Bcr-Abl kinases. ***Efficacy:*** One-year results from the PIII BELA study in 502 patients show that bosutinib did not meet the primary outcome of superior complete cytogenetic response rate vs. imatinib (70% vs. 68%, p=0.6). 39% vs. 26%, respectively, experienced a major molecular response (MMR), a secondary outcome (p=0.002). Preliminary data suggest fewer patients on bosutinib progressed to an advanced phase (1.6%) vs. imatinib (4.0%), and fewer deaths occurred (1.2% vs. 3.2%). ***Safety:*** Diarrhoea, nausea, vomiting and rash are the most frequent adverse effects.				

Ponatinib oral *Actimid* Arid Pharma-ceuticals	***Indication:*** Chronic myeloid leukaemia (CML) and Acute lymphoblastic leukaemia (ALL), Philadelphia positive post dasatinib or nilotinib or with T315I mutation.	***Current status:*** Filed in EU Aug 2012 with accelerated assessment.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** CML- imatinib resistant/ intolerant patients. ***Reviews:*** None.
Target population: The annual incidence of CML is 1-2 per 100,000 people; 95% are Philadelphia chromosome positive and ALL incidence is 1 in 100,000 people. ***Sector:*** Secondary care.		***Implications:*** Bcr-Abl mutation testing prior to treatment. ***Financial:*** Likely to be similar cost to other treatments for CML but is an additional option in those who are resistant/intolerant to standard therapies. A PAS is in place for nilotinib in CML. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: Inhibitor of Src-Abl and Bcr-Abl kinases and other tyrosine kinases. ***Efficacy:*** In the PII PACE trial patients with chronic, acute or blast phase CML or Philadelphia-positive ALL resistant to nilotinib or dasatinib or with T315I mutation were enrolled (n=449) and treated with ponatinib. Latest results suggest, of 404 evaluable patients, after a median 6.6 months, primary outcomes were achieved by 49% with chronic phase CML, 67% with acute phase CML and 37% with ALL. PIII studies are due to start. ***Safety:*** Most common adverse effects in the PACE trial were thrombocytopenia, rash and dry skin.				
Decitabine **injection** *Dacogen* Janssen-Cilag	***Indication:*** Acute myeloid leukaemia (AML), newly diagnosed or secondary acute AMLin patients aged ≥65 years, unsuitable for standard chemotherapy.	***Current status:*** Recommended for approval in EU Jul 2012 with orphan status.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** AML - decitabine due TBC. ***Reviews:*** No recent reviews.
Target population: The incidence of AML is 5-8 per 100,000 people. Treatment options (stem-cell transplant or chemotherapy) differ according to age. Patients aged >60 are usually given palliative chemotherapy. ***Sector:*** Secondary care.		***Implications:*** Current first-line option is low dose cytarabine with hydroxycarbamide, etoposide and 6-mercaptopurine as alternatives. ***Financial:*** Decitabine will compete with comparatively inexpensive alternatives but may be used in those unsuitable for standard therapy. A PAS is in place for azacitidine in AML. ***PbR:*** Chemotherapy is tariff excluded.		
Pharmacology: DNA methyl transferase inhibitor, given by i.v. infusion for 5 days of every 28-day cycle. ***Efficacy:*** In the published PIII DACO-016 trial, 485 patients aged ≥65 years with AML received decitabine or control (cytarabine or best supportive care). Median overall survival was 7.7 months for decitabine vs. 5.0 months for the control group (HR 0.85, p>0.05). However, the US licensing authority concluded these results do not show sufficient evidence of efficacy and tolerability. In a published PII trial in 55 elderly patients a complete response rate was achieved by 24% with a median overall survival of 7.7 months and median time to response of 3 months. ***Safety:*** Adverse effects include neutropenia, anaemia, thrombocytopenia, fever and pneumonia.				
Rituximab **injection** *MabThera* Roche	***Indication:*** Vasculitis, anti-neutrophil cytoplasmic antibody (ANCA)-associated.	***Current status:*** Filed in EU early 2012. Approved in US - see prescribing data.	***Predicted UK licence extension:*** 2012	***National guidance:*** **NICE:** Rituximab for vasculitis proposed appraisal. ***Reviews:*** NHSC Dec 2011.
Target population: ANCA associated vasculitides are the most common primary systemic small-vessel vasculitis to occur in adults and include disorders such as microscopic polyangiitis, granulomatosis with polyangitis and Churg-Strauss syndrome. UK incidence of vasculitides is 5 per 100,000. ***Sector:*** Secondary care.		***Implications:*** Current treatment is induction with cyclophosphamide (CYP) plus high-dose corticosteroids for 3-6 months, then replace CYP with azathioprine or methotrexate plus steroid tapering for maintenance. Rituximab would be an alternative, especially where CYP is unsuitable. ***Financial:*** Based on current cost of *MabThera* a treatment course will cost about £4,000, considerably more than a regimen involving CYP. ***PbR:*** Tariff excluded.		
Pharmacology: CD20 antibody given by i.v. infusion (375mg/m^2 weekly for 4 weeks). ***Efficacy:*** In the published RAVE study (n=197) rituximab was compared with oral cyclophosphamide (CYP) for remission induction. At 6 months, the primary outcome was achieved by 64% and 53% of patients, respectively, p<0.001 for noninferiority. In the published RITUXIVAS study (n=44), patients received either rituximab plus two i.v. CYP pulses (n=33, rituximab group) or i.v. CYP for 3-6 months followed by azathioprine (n=11, control group). At 12 months, 76% and 82%, respectively, had a sustained remission (p=0.68), indicating rituximab was not superior to CYP. ***Safety:*** See emc.medicines.org.uk.				