The Clinical Cancer Letter

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Lung Cancer Screening

Model Projects 54,900 New Lung Cancer Cases In 5 Years with Nationwide LDCT Screening

A model projecting outcomes for nationwide low-dose CT screening for lung cancer estimated that gradual implementation of the program would detect roughly 54,900 more cases over five years in a high-risk Medicare population. The large majority of new cases would be early-stage disease.

The model assumes that over a five-year period, an additional 20 percent of high risk patients are offered screening each year. Investigators considered three different screening use scenarios for the implementation: an expected-use scenario based on historic experience with mammography (50 percent of patients offered screening undergo screening every year), a low-use scenario (25 percent), and a high-use scenario (75 percent).

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Breast Cancer

ASCO Publishes Two Clinical Guidelines For Treating HER2-Positive Breast Cancer

The American Society of Clinical Oncology published two clinical practice guidelines on treating women with advanced, HER2-positive breast cancer.

The first guideline lists appropriate systemic therapies for women newly-diagnosed with advanced disease and those whose early-stage disease progressed to advanced cancer. The second provides recommendations for treating brain metastases. Both guidelines were published in the Journal of Clinical Oncology.

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Prostate Cancer

Study: Delaying ADT Until Symptoms Appear Can Be Safe in Men with a PSA-based Relapse

A study found that it may be safe to postpone androgen deprivation therapy in men with a PSA-only based relapse after prostate surgery or radiation therapy.

Delaying ADT until the onset of symptoms or appearance of cancer on a scan does not substantially compromise long-term survival, according to the population-based observational study.

"Rising PSA levels trigger a lot of anxiety, and many men want to start treatment as soon as possible," said lead study author Xabier Garcia-Albeniz, a research associate at Harvard University School of Public Health.

"These findings suggest that there may be no need to rush to ADT."

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54,900 New Cases Expected Following LDCT Implementation`

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The study, funded by Genentech, will be presented June 2 at the American Society of Clinical Oncology annual meeting in Chicago.

In the expected screening use scenario, the screening would yield 11.2 million more LDCT scans over five years, compared to no screening.

It is estimated that this program would increase the proportion of early-stage diagnoses from 15 percent to 33 percent. The total five-year Medicare expenditure for LDCT imaging, diagnostic workup, and cancer care would be $9.3 billion, amounting to a $3.00-per-month premium increase for each Medicare member.

In the low- and high-screening use scenarios, the total five-year Medicare expenditure would be $5.9 and $12.7 billion, respectively.

The U.S. Preventive Services Task Force recommended LDCT largely based on findings from the National Lung Cancer Screening Trial, which demonstrated a 20 percent reduction of lung cancer deaths with LDCT screening compared to X-ray screening. Annual LDCT screening is recommended for persons age 55-80 years with a 30 pack-year smoking history who currently smoke or quit within the past 15 years.

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Non-Small Cell Lung Cancer

Two Phase III Afatinib Trials Demonstrate Prolonged Survival

Two phase III clinical trials, LUX-Lung 3 and LUX-Lung 6, demonstrated that patients with advanced non-small cell lung cancer whose tumors have the most common epidermal growth factor receptor mutation lived longer if treated with first-line afatinib compared to chemotherapy.

The data will be discussed at an oral presentation at the American Society of Clinical Oncology annual meeting June 2.

In the updated, pooled analysis, afatinib (Gilotrif) prolonged survival of lung cancer patients whose tumors have common EGFR mutations compared with standard chemotherapy by a median of 3 months (24.3 to 27.3 months) and significantly reduced the risk of death by 19 percent (HR=0.81, p=0.037).

The most pronounced reduction in risk of death was 41 percent (HR=0.59, CI 0.45, 0.77) in patients whose tumors have the most common EGFR mutation, exon 19 deletion.

For patients with the exon 21 mutation there was no impact on overall survival (HR=1.25, CI 0.92, 1.71). Exon 19 deletions occur with a frequency of approximately 48 percent in EGFR-mutant lung tumors.

The progression-free survival analysis and adverse events associated with afatinib in comparison with standard chemotherapy were consistent with previously published results of the primary data from these two trials.

The LUX-Lung 3 clinical trial compared afatinib with chemotherapy (pemetrexed/cisplatin) as a first-line treatment in patients with advanced NSCLC with EGFR mutations. LUX-Lung 6 evaluated afatinib versus chemotherapy (gemcitabine/cisplatin) as a first-line treatment for Asian patients with advanced NSCLC with EGFR mutations.

A third phase III study of afatinib in NSCLC patients presented at the ASCO annual meeting, LUX-Lung 5, met its primary endpoint by showing an improvement in progression-free survival when continuing treatment with afatinib in combination with chemotherapy after the tumor started to grow on afatinib alone.

This study compared afatinib and paclitaxel versus investigator's choice of chemotherapy alone in patients with late-stage NSCLC whose disease has progressed after afatinib alone and have also failed

several treatments, including chemotherapy, erlotinib or gefitinib.

Those patients who continued afatinib treatment with the addition of chemotherapy, after progressing on afatinib alone, had a further delay in tumor growth compared to the group who stopped afatinib treatment and received chemotherapy only (tumor growth was delayed by 5.6 months and 2.8 months respectively, p=0.003). This corresponded to a 40 percent reduction in risk of disease progression (HR=0.60).

Afatinib is an oral, once-daily kinase inhibitor that is designed to irreversibly bind and inhibit EGFR (ErbB1), HER2 (ErbB2) and ErbB4. Sponsored by Boehringer Ingelheim, afatinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test.

EGFR Inhibitor Shrinks Tumors In Phase I Study of Patients With Treatment-Resistant Mutation

A phase I study of a mutant selective EGFR tyrosine kinase inhibitor demonstrated tumor shrinkage in roughly 50 percent of patients with advanced, EGFR-mutant, non-small cell lung cancer resistant to standard EGFR inhibitors.

The drug, AZD9291, worked particularly well in patients with the T790M mutation, which causes the most common form of EGFR therapy resistance. The study will be presented at the annual meeting of the American Society of Clinical Oncology in Chicago on May 31.

EGFR mutations are found in 10-15 percent of Caucasian patients and about 40 percent of Asian patients with NSCLC. Many of these patients initially respond well to approved EGFR inhibitors erlotinib and afatinib, but all ultimately become resistant to this therapy, generally within 10 to 14 months.

In the study, 199 patients with advanced NSCLC harboring EGFR mutations whose disease progressed after one or more standard EGFR therapies received different doses of AZD9291. Responses were observed at all dose levels and in all subgroups of patients, including those with brain metastasis.

Among the 89 patients with the T790M mutation, 64 percent responded to AZD9291, compared to 23 percent of T790M-negative patients. The responses were still ongoing in nearly all patients at data cut-off, with the longest response lasting more than eight months. Longer follow up is needed to determine overall survival.

AZD9291 selectively targets EGFR in tumors and appears to cause fewer skin toxicities than approved EGFR TKIs. Existing drugs block both the mutant EGFR in the tumor and the normal EGFR in the skin, often leading to debilitating skin rash or acne. The study was funded by Astra Zeneca, the drug's sponsor.

VeriStrat Biomarker Test Predicts Treatment Outcomes In Phase III NSCLC Trial

A phase III study showed that the VeriStrat biomarker test was predictive of differential treatment outcomes between two standard treatment options for advanced non-small cell lung cancer.

The study, named PROSE, examined patients who have progressed after first-line treatments and who are EGFR wild-type or whose EGFR status is unknown, and tested between single-agent chemotherapy and Tarceva (erlotinib).

Data from the multi-center, randomized proteomic stratified study of 285 patients was published in The Lancet Oncology.

For patients whose EGFR status is unknown, VeriStrat identifies those who can still be considered for the targeted therapy. VeriStrat also helps rule out the roughly 30 percent of patients who are highly unlikely to benefit from erlotinib and should receive chemotherapy.

The VeriStrat test is sponsored by Biodesix Inc. Tarceva is a trademark of OSI Pharmaceutical LLC, an affiliate of AstellasPharma US, and Genentech Inc. All other trademarks are the property of their respective owners.

Breast Cancer

ASCO Publishes Two Guidelines Ahead of 2014 Annual Meeting

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The first guideline, Systemic Therapy for Patients with Advanced HER2-Positive Breast Cancer, involved a review of 19 phase III clinical trials on HER2-targeted therapies, which helped an expert panel make recommendations for three lines of therapy. The key recommendations of the guideline are:

For first-line therapy: a combination of chemotherapy, trastuzumab and pertuzumab. For select patients, such as those with contraindications and/or slow growing hormone receptor-positive cancer, hormonal therapy administered with or without either trastuzumab or lapatinib may be substituted for a chemotherapy-based HER2-targeted regimen because it may have fewer side effects.However, hormonal therapy is not appropriate for all patients with advanced, hormone receptor-positive breast cancer and it has not been associated with a survival benefit in this setting.

For second-line therapy: trastuzumab emtansine. For third-line line therapy and beyond, treatment depends on what patients have received in the first- and second-lines. Options may include trastuzumab emtansine, hormonal therapy or chemotherapy with tratuzumab and in some cases with lapatinib, the combination of trastuzumab and lapatinib, or pertuzumab-based regimen if the patient had not previously received pertuzumab.

The second clinical practice guideline provides consensus-based recommendations for use of local and systemic therapies in patients with HER2 positive breast cancer that has spread to the brain and is the first guideline specifically for patients with HER2-positive metastatic breast cancer.

The key recommendations of the second guideline, Recommendations on Disease Management for Patients with Advanced HER2-Positive Breast Cancer and Brain Metastases, are: for patients with favorable prognosis for survival, surgery and/or radiotherapy are recommended, depending on the size and number of metastases, resectability, and symptoms.

For patients with a poor prognosis for survival, options include surgery, whole brain radiation therapy and systemic therapies with some evidence of activity in the setting of brain metastases, such as lapatinib and capecitabine. Additional options include best supportive care, enrollment in a clinical trial, and/or palliative care.

Researchers Link Obesity With 34% Higher Death Risk In Pre-Menopausal Women

Researchers found that obesity is associated with a 34 percent higher risk of deaths related to breast cancer in pre-menopausal women with estrogen receptor positive disease. Obesity had little effect in post-menopausal ER-positive disease or in ER-negative disease.

"Obesity substantially increases blood estrogen levels only in post-menopausal women, so we were surprised to find that obesity adversely impacted outcomes only in pre-menopausal women," said Hongchao Pan, a researcher at the University of Oxford. "This means we don't understand the main biological mechanisms by which obesity affects prognosis."

The study examined the cases of 80,000 women with early breast cancer in 70 clinical trials. Researchers compared records from women who received the same treatment in the same clinical trial.

Body-mass index was used to define normal weight, overweight, and obesity (20-25, 25-30 and ≥30 kg/m2, respectively). To assess the independent effects of BMI on prognosis, the researchers adjusted the findings for tumor characteristics such as size and nodal spread, and for any differences in treatment.

Among the 20,000 pre-menopausal patients with ER-positive disease, the breast cancer mortality rate was one-third higher in obese women than in women of normal weight. This would, for example, change a 10-year breast cancer mortality risk of 15 percent into a 10-year risk of 20 percent.

In contrast, obesity had little effect on breast cancer outcome either among the 40,000 post-menopausal women with ER-positive disease or among the 20,000 with ER-negative disease. The study, funded by Cancer Research UK, the MRC and the British Heart Foundation, will be presented at the annual meeting of the American Society of Clinical Oncology in Chicago on May 31.

Prostate Cancer

Study: Delaying ADT Can Be Safe In Men with PSA-based Relapse

(Continued from page 1)

"If our results are confirmed in randomized trials, patients could feel more comfortable waiting until they develop symptoms or signs of cancer that are seen on a scan, before initiating ADT," said Garcia-Albeniz.

The study will be presented June 1 at the American Society of Clinical Oncology annual meeting in Chicago.

The study provided novel data on patients with so-called "PSA relapse," where PSA levels are increased but patients have no symptoms, and there is no evidence of a tumor on a CT or bone scan. There are no standard guidelines for timing of ADT initiation in such patients.

The study analyzed national prospective registry data (CaPSURE: Cancer of the Prostate Strategic Urologic Research Endeavor, based at the University of California, San Francisco) on over 14,000 patients, 2,012 of whom had a PSA relapse after radical prostatectomy or radiation therapy with curative intention. Patients were assigned to the "immediate" strategy if they received ADT within three months of PSA relapse. They were assigned to the "deferred" strategy if they started ADT at least two years after the PSA relapse, or when they presented with metastasis, symptoms, or a short PSA doubling time.

The median time from primary treatment to PSA relapse was 27 months. After a relapse, patients were followed for a median period of 41 months. The estimated five-year overall survival was similar between the two ADT timing strategies: 87.2 percent for deferred ADT vs. 85.1 percent for immediate ADT, suggesting that there was little or no survival benefit of immediate ADT initiation compared with deferred initiation.

In practice, deferred initiation could help delay ADT by two or more years for some men, according to the authors, offering men substantially better quality of life by avoiding common and often debilitating side effects.

Targeted Biopsy More Effective At Selecting Men For Active Surveillance, Study Says

Researchers found that selection of men for active surveillance for prostate cancer should be based not on conventional biopsy, but with imaging-guided targeted biopsy.

Conventional "blind" biopsy failed to reveal the true extent of presumed low-risk prostate cancers, and that when targeted biopsy was used, more than a third of these men had more aggressive cancers than they thought, according to researchers at UCLA.

Their aggressive cancers were not detected by conventional blind biopsy using ultrasound alone, and the men were referred to UCLA's active surveillance program thinking they were at no immediate risk. The new biopsy method is now a routine part of the UCLA active surveillance program.

The study was published in Urology. The targeted biopsy method is performed by combining MRI with real-time ultrasound. This study is the first to show the value of using it early in the selection process for men interested in active surveillance.

"These findings are important as active surveillance is a growing trend in this country," said study senior author Leonard Marks, a professor of urology and director of the UCLA Active Surveillance Program. "It's touted as the best course for many men thought to have slow-growing cancers. But we show here that many men thought to be candidates for active surveillance based on conventional biopsies really are not good candidates."

Researchers identified 113 men enrolled in the UCLA active surveillance program who met the criteria for having low-risk cancers based on conventional biopsies. Study volunteers underwent an MRI to visualize the prostate and any lesions. That information was then combined with three-dimensional ultrasound, allowing the urologist to visualize and target lesions during the biopsy.

Of the 113 volunteers enrolled in the study, 41 men, or 36 percent, were found to have more aggressive cancer than initially suspected.

Colorectal Cancer

New Biomarker Findings Show Improvement in KRAS Subtype In Phase III Erbitux Trial

Merck announced new biomarker findings from a retrospective analysis of the completed phase III study that compared Erbitux (cetuximab) plus FOLFIRI with FOLFIRI alone.

The analysis involved a subgroup of patients with KRAS wild-type (exon 2) metastatic colorectal cancer. A significant clinical improvement was observed in patients with RAS wild-type tumors when Erbitux was added to FOLFIRI in first-line mCRC. The data will be presented at the American Society of Clinical Oncology annual meeting June 2.

In the study, named CRYSTAL, 430 patient tumor samples with wild-type KRAS (exon 2) status were assessed for additional RAS mutations (defined as mutations in exons 3 or 4 of KRAS and/or exons 2, 3 or 4 of NRAS). Of these, 367 were RAS wild-type, while 63 presented a mutation.

The analysis showed a 27.7 percent increase in response rate, from 66.3 percent to 38.6 percent (95% CI: 2.03-4.78; $p<0.0001$). Median progression free survival increased by 3.0 months, 11.4 months compared to 8.4 months (HR: 0.56; 95% CI: 0.41-0.76; $p=0.0002$).

An 8.2-month increase in median overall survival was observed in mCRC patients with RAS wild-type tumors (n=367), at 28.4 months vs. 20.2 months, respectively (HR: 0.69; 95% CI: 0.54-0.88; $p=0.0024$).

In the patient group with either KRAS exon 2 mutations identified in the initial KRAS analysis (n=397) or other RAS mutations (n=63) receiving Erbitux plus FOLFIRI (n=246) no benefit was observed, compared with FOLFIRI alone (n=214). This subgroup analysis helps confirm the findings of other studies which have shown that patients with RAS mutations do not benefit from anti-EGFR therapy.

Following an update to the Erbitux label that was approved by the European Commission in December 2013, Erbitux is now indicated for the treatment of patients with epidermal growth factor receptor-expressing RAS wild-type mCRC in combination with irinotecan-based chemotherapy, in firstline in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Erbitux is contraindicated in combination with oxaliplatin-containing chemotherapy in patients with mutant RAS mCRC or for whom RAS mCRC status is unknown.

Erbitux is a highly active IgG1 monoclonal antibody targeting the epidermal growth factor receptor. As a monoclonal antibody, the mode of action of Erbitux is distinct from standard non-selective chemotherapy treatments in that it specifically targets and binds to the EGFR. This binding inhibits the activation of the receptor and the subsequent signal-transduction pathway, which results in reducing both the invasion of normal tissues by tumor cells and the spread of tumors to new sites.

Merck licensed the right to market Erbitux outside the U.S. and Canada from ImClone LLC, a wholly-owned subsidiary of Eli Lilly and Company, in 1998. In Japan, ImClone, Bristol-Myers Squibb Company and Merck jointly develop and commercialize Erbitux. Merck has an ongoing commitment to the advancement of oncology treatment and is currently investigating novel therapies in highly targeted areas.

Childhood Neuroblastoma

Immunotherapy Shrinks Tumors In Phase I Study at St. Jude

In a phase I study, tumors shrank or disappeared and disease progression was temporarily halted in 15 children with advanced neuroblastoma enrolled in a safety study of an experimental antibody produced at St. Jude Children's Research Hospital.

Four patients are still alive after more than two-and-a-half years and without additional treatment. Findings from the phase I study were published in the Journal of Clinical Oncology.

The results prompted St. Jude to expand clinical trials of the monoclonal antibody hu14.18K322A to include patients newly diagnosed with neuroblastoma. Monoclonal antibodies are engineered in the laboratory to recognize and attach to specific markers carried on the cell surface.

In the study, 38 patients received one of nine different doses of hu14.18K322A. The immunotherapy is designed to activate the immune system to attack and kill tumor cells. Every 28 days, patients received an infusion of hu14.18K322A once daily for four days.

Of the 31 patients evaluated after two or more rounds of treatment, the disease stabilized in nine patients, tumors shrank in two patients and were undetectable in four more, researchers reported.

Hu14.18K322A is engineered to attach to the GD2 antigen, found on the surface of almost all neuroblastoma cells as well as other tumors, including the skin cancer melanoma, the bone cancer osteosarcoma and soft-tissue sarcomas. The antigen is found on the normal cells of just a few tissues.

The monoclonal antibody in this study is one of several antibodies targeting GD2 that are in clinical development for treatment of neuroblastoma.

In this study, pain remained the most common side effect associated with hu14.18K322A treatment. While 68 percent of patients reported severe pain during the first round of treatment, Navid said the pain was manageable with medication and resolved within 24 hours of receiving the experimental antibody. The pain also lessened with each round of therapy.

Clinical trials involving hu14.18K322A continue at St. Jude. Researchers are testing the impact of giving the monoclonal antibody weekly rather than every 28 days and in combination with other therapies.

Chemotherapy

Anti-Nausea Drug Successful In Phase III Trial in Highly Emetogenic Chemotherapy

A phase III trial of rolapitant, an investigational neurokinin-1 receptor antagonist in development for the prevention of chemotherapy-induced nausea and vomiting, was successful in achieving statistical significance for its primary and all secondary endpoints.

The trial enrolled patients receiving cisplatin-based, highly emetogenic chemotherapy. The international, multicenter, randomized, double-blind, active-controlled study enrolled 532 cancer patients receiving chemotherapy regimens at a dose equal to or greater than 60 mg/m2.

Patients were randomized to receive either control, which consisted of a 5-HT3 receptor antagonist plus dexamethasone, or 200 milligrams of oral rolapitant plus control. The rolapitant arm in this study successfully achieved statistical significance over the control arm for the primary endpoint of complete response in the delayed phase of CINV.

In addition, the rolapitant arm also successfully achieved statistical significance over the control arm for the key secondary endpoints of CR in the acute and overall phases of CINV, for the secondary endpoint of no significant nausea, and for all other secondary endpoints.

Tesaro Inc., the drug's sponsor, plans to submit a new drug application to the FDA in mid-2014. Rolapitant is an investigational agent and has not been approved by the FDA or any regulatory agencies.

NCI CTEP-Approved Trials For the Month of May

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

Phase II

9543: A Phase 2 Study to Determine the Efficacy of the BTK Inhibitor Ibrutinib (PCI-32765) in Patients with Relapsed or Refractory Precursor-B Lymphoblastic Leukemia (B-ALL). MD Anderson Cancer Center; Burger, Jan A. (713) 792-1865

AMC-089: A Phase II Study of Gamma Secretase Inhibitor PF-03084014 in Patients with AIDS-Associated Kaposi Sarcoma. AIDS-Associated Malignancies Clinical Trials Consortium; Ratner, Lee. (314) 362-8836

CITN-07-FLT3L: A Phase II, Open-Label, Multicenter, Randomized Study of CDX-1401, a Dendritic Cell Targeting NY-ESO-1 Vaccine, in Patients with Malignant Melanoma Pre-Treated with Recombinant CDX-301, a Recombinant Human Flt3 Ligand. Cancer Immunotherapy Trials Network; Bhardwaj, Nina. (212) 263-5814

Phase Other

AALL14B1-Q: Deep Sequencing for Minimal Residual Disease Detection in Acute Lymphoblastic Leukemia ALL. Children's Oncology Group; Wood, Brent Lee. (206) 288-7115

AAML14B4-Q: Role of EVI-1 Hyperexpression in Pediatric and Young Adult Acute Myeloid Leukemia. Children's Oncology Group; Qian, Zhijian. (312) 355-3295

EA914LT1: Lab Testing of AML Patient Samples. ECOG-ACRIN Cancer Research Group; Wald, David. (216) 368-5668

S0016B: Use of Chromosome Genomic Microarray

Testing (CGAT) to Identify Novel Genetic Aberrations Impacting Patient Outcome in S0016 Follicular Lymphoma Patients. SWOG; Fang, Min (206) 288-1385

Pilot Phase

ABTC-1301: Pilot Study of MLN0128 in Preoperative Recurrent Glioblastoma (GBM) Patients. Adult Brain Tumor Consortium; Lee, Eudocia Quant. (617) 632-2166

Drug Approvals

Orphan Designation Granted To Advaxis HPV Immunotherapy

FDA granted orphan drug designation to ADXS-HPV for the treatment of stage II-IV invasive cervical cancer.

ADXS-HPV is an immunotherapy drug candidate, developed by Advaxis Inc., which is designed to target cells expressing the HPV gene E7. Expression of the E7 gene from high-risk HPV variants is responsible for the transformation of infected cells into dysplastic and malignant tissues.

ADXS-HPV is designed to infect antigen-presenting cells and direct them to generate a powerful, cellular immune response to HPV E7. The resulting cytotoxic T cells infiltrate and attack the tumors while specifically inhibiting tumor Tregs and MDSCs in the tumors that are protecting it, according to the drug's sponsor.

Orphan drug designation is granted to drug therapies intended to treat diseases or conditions that affect fewer than 200,000 people in the U.S. The designation entitles the sponsor to clinical protocol assistance with the FDA, as well as annual grant funding, tax credits, waiver of PDUFA filing fees, and potentially a seven-year market exclusivity period.

The European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion for Gardasil to be used for the prevention of anal precancerous lesions and anal cancers, causally related to oncogenic HPV types 16 and 18.

This new indication is supported by the results of a study showing the high efficacy of Gardasil against anal precancerous lesions linked to HPV types 6, 11, 16 & 18 (AIN 2/3) which are recognized as immediate precursors of anal cancers. A CHMP positive opinion is one of the final steps before a variation to the marketing authorization granted by the European Commission.

Gardasil is currently licensed from the age of nine years, for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic HPV types and genital warts causally related to specific HPV types.

Gardasil, manufactured by Merck, is a quadrivalent vaccine for protection against cancer of the cervix and other genital diseases caused by the human papillomavirus types 6, 11, 16 and 18: precancerous lesions of the cervix (CIN2/3), precancerous lesions of the vulva (VIN2/3) and vaginal (VaIN2/3) and genital warts.