AdisInsight: Drugs

AdisInsight: Drugs (önceki adı Adis R&D Insight) dünya çapında, ticari ilaç geliştirme üzerine kanıta dayalı bilimsel ve pazar bilgisini sağlar. İlaç ve hücre bazlı ürünler, keşiften lansmana kadar tüm terapötik alanlarda ve tüm geliştirme süreci boyunca izlenir.
AdisInsight drug aşağıdaki konu başlıklarını içerir:

- Key development milestones
- Development status and history
- Drug properties
- Chemical synopses
- Generic name, syonyms, brand names
- Pharmacokinetics data
- Pharmacodynamics data
- Company agreements
- Trial landscape and details
- Related safety reports
- Patent information
- Related drugs
- Drug limitations
- Immunogenicity
- Developing companies
- Forecasts of approval probability

Veriler, 2,300 den fazla biyomedikal dergiden toplanmatadır. Bu veriler, ilaç ve terapötikler, haber servisleri, gazeteler, yıllık şirket raporları, toplantı ve konferanslardan sağlanmaktadır.

AdisInsight profilleri ayrıca 10.000'den fazla değerlendirilmiş Adis bilimsel özeti ve 63.000 bibliyografik referansla desteklenmektedir.

AdisInsight: Drugs aşağıdaki gibi sorulara yanıt vermektedir:

- Nivolumab üzerine hangi pipeline rapoları bulunmaktadır?
- TSR 042 nerede geliştirilmiştir? Hangi endikasyonlar için?
- Fransa da glioblastoma için belirtilen Faz III çalışmasında olan ilaçlar hangileridir?
- Celgene hangi ilaçları geliştiriyor??
- En yüksek Faz I de yer alan akne için hangi ilaçlar bulunmaktadır?

Tarih Kapsamı

1995–günümüze

Kapsam

Uluslararası

Güncelleme Sıklığı

Haftalık

Doküman Türü

Rapor

TI Ipilimumab - Bristol-Myers Squibb

PD **AdisInsight: Drugs**. (May 22, 2019). Pricing

TX **Full Text** Translate

DRUG PROFILE - Ipilimumab - Bristol-Myers Squibb

Ipilimumab, a recombinant, human anti-CTLA-4 monoclonal antibody that activates the immune system by targeting CTLA-4, a protein receptor that down regulates the immune system is being developed by by Bristol-Myers Squibb for treatment of cancer. The agent originated from Medarex, which was later acquired by Bristol-Myers Squibb. The drug has been launched worldwide, for treatment of patients with malignant melanoma. The drug is approved as a combination therapy with nivolumab for malignant melanoma in Japan and South Korea, for metastatic renal cell carcinoma in the US and Canada. and is awaiting regulatory approval for colorectal cancer in the US. The drug is registered as monotherapy for the treatment of malignant melanoma in the EU, Iceland, Norway, Liechtenstein, Japan and Taiwan. Ipilimumab is approved in the European Union, Norway, Iceland, Liechtenstein and Japan for combination and first-line therapy in patients with metastatic renal cell carcinoma. The drug is under regulatory review in the EU and the US for nivolumab plus ipilimumab combination for the first-line treatment of metastatic Non-small cell lung cancer and and in the US for renal cell carcinoma. Clinical development is underway for adrenocortical carcinoma, breast cancer, CNS cancer, carcinomatous-meningitis, colorectal cancer, gastric cancer, gastrointestinal cancer, genitourinary disorders, glioblastoma, gynaecological cancer, head and neck cancer, hepatocellular carcinoma, liver cancer, lung cancer, mesothelioma, diffuse large B-cell lymphoma, myelodysplastic syndromes, neuroendocrine tumours, non-small cell lung cancer, oesophageal cancer, ovarian cancer, pancreatic cancer, penile cancer, prostate cancer, renal cell cancer.

COMPANY AGREEMENTS

In June 2017, Bristol-Myers Squibb (BMS) and Novartis entered into a clinical research collaboration to conduct a phase I/II trial to assess the safety, tolerability and efficacy of combination of nivolumab (Opdivo ®) and

(...)

KEY DEVELOPMENT MILESTONES

Breast Cancer: In January 2018, Oslo Uniersity Hospital and Bristol-Myers Squibb initiated a phase II trial to assess the combination therapy of nivolumab and ipilimumab in patients with metastatic luminal B breast cancer (ICON-CA209-9FN; NCT03409198). The randomised trial will enrol 72 patients in Norway (Reference: 700292614).

In September 2017, Northwestern University, NCI and Bristol-Myers Squibb initiated a phase II trial to evaluate the safety and efficacy of combination therapy of nivolumab and ipilimumab in patients with metastatic recurrent HER2-inflammatory breast cancer (NCI2016-01038; NU16B07; P30CA060553; STU00203191; NCT02892734). The open label trial intends to enrol 29 patients in the US (Reference: 700276367).

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PATENT INFORMATION

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BMS owns a composition of matter patent covering ipilimumab in the USA and EU which expires in 2022 and 2020, respectively. The company also holds the rights to method of use patents owned by Medarex that expire in the USA in 2015. BMS has rights to a Medarex composition of matter patent that expires in 2020 (extended to 2022 by a patent term adjustment) and also has pending Medarex patent applications covering composition of matter and method of use of ipilimumab. BMS also has data exclusivity rights in the USA and EU which expires in 2023 and 2021, respectively.

Adverse Event

Malignant melanoma

Phase III (first-line therapy): No unexpected adverse events occurred in a phase III registrational trial (study 024) of ipilimumab in combination with dacarbazine as a first-line treatment for patients with unresectable stage III or IV metastatic melanoma. The double-blind, two-arm study included 502 patients with previously-untreated stage III or IV metastatic melanoma who were randomised to receive dacarbazine with or without ipilimumab (10 mg/kg). Treatments were administered once every three weeks for up to four doses, and patients without disease progression at week 24 continued to receive treatment in a maintenance phase where a single dose of ipilimumab was administered once every 12 weeks until disease progression. The overall incidence of grade 3/4 adverse events was 56% in the ipilimumab plus dacarbazine arm and 28% in the dacarbazine only arm. Adverse events (all grades) that occurred more frequently with combination therapy versus monotherapy included alanine transaminase elevation (33% vs 6%), aspartate transaminase elevation (29% vs 6%), diarrhoea (36% vs 25%), pruritus (30% vs 9%) and rash (25% vs 7%). There were no gastrointestinal perforations in either arm of the study, and no treatment-related deaths occurred with combination therapy. One fatal gastrointestinal haemorrhage was reported in the dacarbazine only arm. Discontinuation due to treatment-related toxicity occurred in 36% of patients in the ipilimumab plus dacarbazine arm and 4% in the dacarbazine only arm (Reference: 803055485) (Reference: 809125654). There were few new immune-related adverse events which were reported beyond 2 years of treatment in patients who were still alive after 4 years and who remained on therapy (Reference: 809141735).

Adverse Event

Phase III (second-line therapy): the most frequently reported adverse events in a phase III trial investigating ipilimumab alone, or in combination with a gp100 peptide vaccine, were immune-related events. Study 002 included 676 HLA-A2-positive, previously-treated patients with unresectable stage III or IV metastatic melanoma. Patients were randomised to receive ipilimumab 3 mg/kg plus gp100 (n = 403), ipilimumab 3 mg/kg plus placebo (n = 137) or gp100 plus placebo (n = 136) every three weeks for four doses. Grade 3/4 drug-related adverse events occurred in 17% of patients who received ipilimumab plus gp100, 23% of those who received ipilimumab alone, and 11% of those who received gp100 alone. Grade 3/4 immune-related events occurred in 10-15% of patients in the ipilimumab arms and 3% of patients in the gp100 monotherapy arm. A total of 14 drug-related deaths occurred during the study, including seven that were attributed to an immune-related event (five in the ipilimumab + gp100 arm and two in the ipilimumab monotherapy arm) (Reference: 809113380) (Reference: 809113383).

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Drug Interaction

Coadministration of ipilimumab with either paclitaxel plus carboplatin or dacarbazine does not require ipilimumab dosage adjustments, according to pharmacokinetic data from a phase I trial in patients with previously-untreated malignant melanoma. The pharmacokinetics of ipilimumab were determined in patients who received either ipilimumab alone, or in combination with paclitaxel/carboplatin or dacarbazine. Ipilimumab was administered at a dosage of 10 mg/kg every 3 weeks for 4 doses; in the combination therapy arms, chemotherapy was administered every 3 weeks for 8 doses prior to the first ipilimumab dose and concomitantly there after. Coadministration with ipilimumab and paclitaxel/carboplatin or dacarbazine decreased serum ipilimumab concentrations (AUC_{τ}) by 13% and 8%, respectively. It was also shown that ipilimumab increased paclitaxel and carboplatin plasma concentrations (AUC_{∞}) by 7% and decreased AUC_{∞} of dacarbazine and its metabolite (AIC) by 9% and 5%, respectively. However, none of the pharmacokinetic interactions were considered to be clinically-relevant (Reference: 803043600).

Drug Interaction

Ipilimumab clearance did not appear to be affected by concomitant budesonide administration in patients with advanced melanoma. This was the finding from a pharmacokinetic modelling study that used data from three clinical trials of ipilimumab monotherapy (Reference: 802053389).

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Immunogenicity
Cancer
Malignant melanoma

A 12-week induction regimen of ipilimumab (10 mg/kg every 3 weeks) resulted in activation of T cells in the majority of patients with stage III or IV melanoma in a phase II trial (Study 007). The double-blind trial randomised 115 patients to treatment with ipilimumab alone or in combination with prophylactic budesonide. The results showed that by week 4, the mean number of activated CD4+ and CD8+ T-cells had increased by approximately 10% from baseline and the number of naive CD4+ and CD8+ T-cells had decreased by approximately 6%. At the 4-week assessment, 96% of evaluable patients had an increase in activated T-cells and 82% of evaluable patients had a decrease in naive T-cells. In more than 50% of patients, these changes continued to evolve between weeks 4 and 12 (Reference: 801125366).

Immunogenicity
Cancer
Prostate cancer

In a phase I clinical trial assessing GVAX ® and ipilimumab combination treatment in patients with castrate-resistant prostate cancer, significant increases in $CD4^+$ and/or $CD8^+$ T-cells were seen with ipilimumab administered at dosages of 3 or 5 mg/kg. HLA-DR, programmed death-1, FoxP3 and inducible costimulator marker expression, and effector/memory T-cell or Treg levels were differentially associated with survival. Up-regulation of $CD4^+$ interleukin-5 $^+$ T-cell frequencies were associated with improved overall survival, as was increased seroreactivity to prostate-specific membrane antigen, pyridoxamine 5'-phosphate oxidase and/or neuropilin-2. Significantly increased rates of Th17 were only seen in patients who experienced partial responses and stable disease (Reference: 803056331).

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Pharmacodynamics
Cancer

High pre-existing immune activity appears to favour clinical response to ipilimumab, according to preliminary results of a retrospective analysis of a phase II trial of the drug in patients with primary or metastatic malignant melanoma. Biopsies obtained at baseline, prior to treatment, from 46 tumours showed that most over-expressed transcripts and pathways linked to favourable clinical activity were immune-related. Differential analysis of mRNA from pre- and post-treatment tumour biopsies indicated that there was an increase in expression of these genes after treatment with ipilimumab. In addition, within 3 weeks following the first dose of ipilimumab, several melanoma-associated transcripts in the tumours were down-regulated (Reference: 803056347).

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Pharmacokinetics

In patients with hormone-refractory prostate cancer, ipilimumab had a mean terminal elimination half-life ($t_{½}$) of 12.5 hour, indicating that antibody levels would be sustained at 10 µg/mL for 60 days. In this pilot study, 12 patients received a single 3 mg/kg dose of ipilimumab and two patients received two 3 mg/kg doses. The median time to maximum ipilimumab concentration (T_{max}) was 1.9h and the observed mean maximum concentration (C_{max}) was 155.94 µg/mL (Reference: 801077655).

Therapeutic Trials
Cancer
Malignant melanoma

Phase III (first-line therapy): A phase III registrational trial (study 024) of ipilimumab in combination with dacarbazine as a first-line treatment for patients with unresectable stage III or IV metastatic melanoma met its primary endpoint of overall survival. The double-blind, two-arm study included 502 patients with previously-untreated stage III or IV metastatic melanoma who were randomised to receive dacarbazine with or without ipilimumab (10 mg/kg). Treatments were administered once every three weeks for up to four doses and patients without disease progression at week 24 continued to receive treatment in a maintenance phase where a single dose of ipilimumab was administered once every 12 weeks until disease progression. A significant improvement in overall survival was observed in the ipilimumab plus dacarbazine arm, compared with the dacarbazine only arm (hazard ratio of 0.72; $p<0.001$). The median overall survival in patients treated with ipilimumab plus dacarbazine was 11.2 months, compared with 9.1 months in those who received dacarbazine alone. The estimated rates of overall survival in the combination versus monotherapy arms were 47.3% versus 36.3% at 1 year and 28.5% versus 17.9% at 2 years. The best objective response rates in the ipilimumab plus dacarbazine and dacarbazine only arms were 15.2% and 10.3%, respectively. Among those patients who achieved an objective response, the median durations of response were 19.3 months and 8.1 months, respectively (Reference: 803055485) (Reference: 809125654). The 4-year overall survival rates were 19.0% and 9.6% in the ipilimumab plus dacarbazine arm, and dacarbazine-only arm, respectively. The 3-year survival rate was 21.2% in the ipilimumab plus dacarbazine arm. The 3-and 4-year survival rates in patients who received placebo plus dacarbazine were 12.1% and 9.6%, respectively (Reference: 809141735).

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ADVERSE EVENTS

Diarrhoea, Frequent
Fatigue, Frequent
Hypothyroidism, Frequent
Nausea, Frequent
Pruritus, Frequent
Adrenal-insufficiency, Occasional
Arthritis, Occasional
Colitis, Occasional
Dermatitis, Occasional
Hepatitis, Occasional
Hypopituitarism, Occasional
Laryngospasm, Occasional
Neutropenia, Occasional
Pancreatitis, Occasional
Skin-eruptions, Occasional
Uveitis, Occasional
Death, Rare

(...)

History of Drug Development

Event date	Update date	Update type	Significant	Details
19960516	19960516	New Profile	true	New profile
19960516	19960516	Phase Change	true	Preclinical development for Cancer in USA (IV)
19981103	19981103	Scientific Update	true	A preclinical study has been added to the pharmacodynamics section (715750)
19991201	19991201	Scientific Update	true	A preclinical study has been added to the pharmacodynamics section (755426)
20000118	20000118	Licensing Status	true	Anti-CTLA-4 monoclonal antibodies are available for licensing from Medarex (http://www.medarex.com)
20011108	20011108	Scientific Update	true	A phase I/II study has been added to the Cancer therapeutic trials section (885561)
20011108	20011108	Phase Change	true	Phase-II clinical trials for Malignant melanoma in USA (IV)
20011108	20011108	Phase Change	true	Phase-II clinical trials for Prostate cancer in USA (IV)
20020930	20070108	Phase Change	true	Phase-II clinical trials in Lymphoma in USA (IV)

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Development Phases

Phase	Country	Indication	Route of Administration	Formulation	On Fast Track	Qualifiers and Comments
Marketed	Argentina	Malignant-melanoma	IV	Infusion	false	Late-stage disease, Second-line therapy or greater
Marketed	Australia	Malignant-melanoma	IV	Infusion	false	Late-stage disease, Second-line therapy or greater
Marketed	Austria	Malignant-melanoma	IV	Infusion	false	Late-stage disease, Metastatic disease, Second-line therapy or greater
Marketed	Belgium	Malignant-melanoma	IV	Infusion	false	Late-stage disease, Metastatic disease, Second-line therapy or greater
Marketed	Canada	Malignant-melanoma	IV	Infusion	false	Combination therapy, First-line therapy, Inoperable/Unresectable, Late-stage disease, Metastatic disease, In combination with nivolumab

(...)

Indexing (details) Cite

RF, CTI, CAU, CPUB, CYR, CVO

References

1. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody blockade in patients previously vaccinated with irradiated, autologous tumor cells engineered to secrete granulocyte-macrophage colony stimulating factor (GM-CSF). Hodi FS, Seiden M, Butler M, Haluska FG, Lowy I, et al.. 40th Annual Meeting of the American Society of Clinical Oncology. : 172, Jun 2004, Language: English, Country: USA (Adis Number: 800982695);
2. Tumor regression in patients with metastatic renal cancer treated with a monoclonal antibody to CTLA4 (MDX-010). Yang JC, Beck KE, Blansfield JA, Tran KQ, Lowy I, et al.. Journal of Clinical Oncology. 23 (Suppl.): 166 (plus oral presentation) abstr. 2501, No. 16, Part I, 1 Jun 2005, Language: English, Country: USA (Adis Number: 800994676);
3. CTLA-4 blockade-based immunotherapy for hormone-refractory prostate cancer. Kavanagh B, Rini B, Weinberg V, Shaw V, Small E, Fong L. 2006 Prostate Cancer Symposium. : abstr. 255, 24 Feb 2006, Language: English, Country: Unknown (Adis Number: 801036744);
4. A pilot trial of CTLA-4 blockade with human anti-CTLA-4 in patients with hormone-refractory prostate cancer. Small EJ, Tchekmedyian NS, Rini BI, Fong L, Lowy I, Allison JP. Clinical cancer research: an official journal of the American Association for Cancer Research. 13: 1810-1815, No. 6, 15 Mar 2007, Language: English, Country: USA (Adis Number: 801077655);

(...)

SU	**Subject**	Monoclonal-antibodies
SUBST	**Substance**	Substance: Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulphide with human κ-chain, dimer CAS: 477202-00-9
SYN	**Drug synonym**	Anti CTLA-4 monoclonal antibody - Medarex, BMS 734016, BMS-734016, BMS734016, MDX 010, MDX CTLA-4, MDX CTLA4, MDX-010, MDX-CTLA-4, MDX-CTLA4
MF	**Molecular formula**	C6472H9972N1732O2004S40
GN	**Generic name**	Ipilimumab - Bristol-Myers Squibb
ORD	**Orphan drug**	Indication: Malignant-melanoma Region: USA Company: Bristol-Myers Squibb
TN	**Trade name**	Yervoy® (Malignant-melanoma, Australia, Bristol-Myers Squibb) Yervoy® (Malignant-melanoma, Canada, Bristol-Myers Squibb) Yervoy® (Malignant-melanoma, Europe, Bristol-Myers Squibb) Yervoy® (Malignant-melanoma, USA, Bristol-Myers Squibb)
OS	**Origin of substance**	Fixed combination: No
RO	**Route of administration**	IV, Parenteral, SC
MEC	**Mechanism of action**	Cytotoxic-T-lymphocyte-antigen-4-inhibitors, Immunomodulators
PK	**Pharmacokinetics**	Cl (L/h), unspecified, .015 - .015 t (1/2) beta (h), unspecified, 12.500 - 12.500 tmax (h) [oral], unspecified, 1.900 - 1.900
TC	**Therapeutic class**	L1G: Monoclonal Antibody Antineoplastics L01X-C11: Ipilimumab
IND	**Indication**	Adrenocortical-carcinoma Breast-cancer Cancer Carcinomatous-meningitis Chronic-lymphocytic-leukaemia Chronic-myeloid-leukaemia CNS-cancer Colorectal-cancer Gastric-cancer Gastrointestinal-cancer Genitourinary-disorders Glioblastoma Gynaecological-cancer Head-and-neck-cancer Hepatocellular-carcinoma HIV-infections Liver-cancer Lung-cancer Lymphoma Malignant-melanoma Mesothelioma Myelodysplastic-syndromes Myelofibrosis Myeloid-leukaemia Neuroendocrine-tumours Non-small-cell-lung-cancer Oesophageal-cancer Ovarian-cancer Pancreatic-cancer Penile-cancer Prostate-cancer Renal-cell-carcinoma Small-cell-lung-cancer Solid-tumours Thyroid-cancer Urogenital-cancer
DST	**Drug status**	Active

CO, DOR, LCO	**Company information**	Name: Aduro BioTech, Public, Not-Large-Pharma Type: Biotechnology Role: Collaborator Region: USA Name: AIO Studien gGmbH, Private, Not-Large-Pharma Type: ContractResearchOrganization Role: Collaborator Region: Germany Name: Australia and New Zealand Melanoma Trials Group, Public, Not-Large-Pharma Type: Institution Role: Collaborator Region: Australia Name: Australian and New Zealand Urogenital and Prostate Cancer Group, Not-Large-Pharma Type: Unknown Role: Collaborator Region: Australia Name: Bavarian Nordic, Public, Not-Large-Pharma Type: Biopharmaceutical Role: Collaborator Region: Denmark Name: Big Ten Cancer Research Consortium, Private, Not-Large-Pharma Type: Unknown Role: Collaborator Region: USA

(...)

TI	**Title**	Ipilimumab - Bristol-Myers Squibb
HP	**Highest phase**	Marketed
LG	**Language**	English
DTYPE	**Document type**	Report
PUB	**Publication title**	AdisInsight: Drugs
PSTYPE	**Publication type**	Reports
PD	**Publication date**	Mar 22, 2018
DCRE	**Date created**	1996-05-21
DREV	**Date revised**	2018-03-22
	Source attribution	AdisInsight: Drugs, © Publisher specific
AN	**Accession number**	6680
	Document URL	https://2018r2nightly.aa1.proquest.com/professional/docview/16341325?accountid=100557
	First available	2011-11-11
FAV	**Updates**	2012-07-30 2016-10-10 2018-03-22 2018-03-28
UD		
	Database	AdisInsight: Drugs; 1995 to date (1995 - current)