INPHARMD™ **MONOGRAPHS**

Imfinzi ®

(Durvalumab)

The latest evidence on drug efficacy & recommendations.

InpharmD™

UPDATED APRIL 2024

OVERVIEW

REGIMEN

Generic Name	Durvalumab
Trade Name	Imfinzi®
Manufacturer	AstraZeneca
FDA Approval	May 1, 2017
Dosage	Varies based on indication, weight, and regimen
Therapeutic Class	10:00 Antineoplastic Agents - Anti-PD-L1 Monoclonal Antibody; Immune Checkpoint Inhibitor; Antineoplastic Agent

Indications

Non-Small Cell Lung Cancer: Treatment of adult patients with unresectable Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy

In combination with tremelimumab-actl and platinum-based chemotherapy for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations

Small Cell Lung Cancer: In combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adult patients with extensive-stage SCLC (ES-SCLC)

Biliary Tract Cancers: In combination with gemcitabine and cisplatin for the treatment of adult patients with locally advanced or metastatic BTC

Hepatocellular Carcinoma: In combination with tremelimumab-actl for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC)

PHARMACOLOGY

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds to programmed cell death ligand-1 (PD-L1) and blocks the interaction of PD-L1 with programmed death receptor 1 (PD-1) and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody dependent cell-mediated cytotoxicity (ADCC).

PD-L1 blockade with durvalumab led to increased T-cell activation in vitro and decreased tumor size in co-engrafted human tumor and immune cell xenograft mouse models

PHARMACODYNAMICS

The steady state AUC, Ctrough, and Cmax in patients administered with 1,500 mg every 4 weeks are 6% higher, 19% lower, and 55% higher than those administered with 10 mg/kg every 2 weeks, respectively. Based on the modeling of pharmacokinetic data and exposure relationships for safety, there are no anticipated clinically meaningful differences in efficacy and safety for the doses of 1,500 mg every 4 weeks compared to 10 mg/kg every 2 weeks in patients weighing > 30 kg with NSCLC

PHARMACOKINETICS

Absorption/Onset	Time to reach steady state: 16 weeks
Distribution	Vss: 5.4 L
Metabolism	N/A
Half-life Elimination	~21 days
Excretion	CLss: 8 mL/h

CLINICAL DATA OVERVIEW

N= 713 • Antonia et al., 2018 • International, randomized, double-blind, international, phase 3 trial (PACIFIC)

POPULATION

To evaluate durvalumab in patients with stage III, unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy

N= 713

Placebo (n= 236)

Durvalumab (n= 473)

METHODS

Inclusion/ exclusion criteria: Historically or cytologically documented stage III, unresectable NSCLC, received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy, progression after chemoradiotherapy, received last radiation dose within 1 to 42 days before randomization

Intervention: Patients were randomized (2:1) to receive durvalumab IV 10 mg/kg or matching placebo every 2 weeks.

Duration: Up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxic events, or withdrawal of consent

RESULTS

Primary outcome:
24-month overall survival (OS): durvalumab 66.3% vs placebo 55.6% (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.47 to 0.997; p= 0.0025)

Median progression-free survival (PFS): 17.2% months vs 5.6 months (HR 0.51; 95% CI 0.41 to 0.63)

Secondary outcomes:
Median time to death or distant metastasis: 28.3 months vs 16.2 months (HR 0.53; 95% CI 0.41 to 0.68)

Median time to second progression or death: 28.3 months vs 17.1 months (HR 0.58; 95% CI 0.46 to 0.73)

Overall response rate: 30% vs 17.8% (p<0.001)

Safety outcomes:
Maximum grade 3 or 4 adverse events (AEs): 30.5% vs 26.1%

Discontinuation of trial regimen because of AEs: 16.4% vs 9.8%

Most frequent AEs leading to discontinuation: pneumonitis (4.8% vs 2.6%), radiation pneumonitis (1.3% vs 1.3%), pneumonia (1.1% vs 1.3%)

Serious AEs: 29.1% vs 23.1%

Death due to AEs: 4.4% vs 6.4%.

CONCLUSIONS

Conclusion: Durvalumab therapy resulted in significantly longer overall survival than placebo. No new safety signals were identified.

Critique: This trial displays the long-term efficacy and safety of durvalumab in stage III, unresectable NSCLC patients. Of note, these are updated results for an interim analysis of the PACIFIC trial.

N = 1,013 • Johnson et al., 2023 • International, randomized, open-label, phase 3 trial (POSEIDON)

POPULATION

Objective: To evaluate tremelimumab plus durvalumab and chemotherapy (T+D+CT) and durvalumab + chemotherapy (D+CT) versus chemotherapy alone (CT) in first-line metastatic NSCLC (mNSCLC)

N= 1,013

T+D+CT (n= 338)

D+CT (n= 338)

CT (n= 337)

METHODS

Inclusion/exclusion criteria: Aged ≥18 years, stage IV NSCLC, no previous systemic therapy for mNSCLC, Eastern Cooperative Oncology Group (ECOG) status 0 or 1, no sensitizing EGFR mutations or ALK rearrangements and PD-L1 expression

Intervention: Eligible patients were randomized (1:1:1) to tremelimumab 75 mg plus durvalumab 1,500 mg and platinum-based chemotherapy for up to four 21-day cycles, followed by durvalumab once every 4 weeks until progression and one additional tremelimumab dose; durvalumab plus chemotherapy for up to four 21-day cycles, followed by durvalumab once every 4 weeks until progression; or chemotherapy for up to six 21-day cycles (with or without maintenance pemetrexed; all arms).

Duration: June 27, 2017 to September 19, 2018

RESULTS

Primary outcome:
Median PFS:
D+CT vs CT: 5.5 months vs 4.8 months (HR 0.74; 95% CI 0.62 to 0.89; p= 0.0009)

T+D+CT vs CT: 6.2 months vs 4.8 months (HR 0.72; 95% CI 0.60 to 0.86; p= 0.0003)

Median OS:
D+CT vs CT: 13.3 months vs 11.7 months (HR 0.86; 95% CI 0.72 to 1.02; p= 0.0758)

T+D+CT vs CT: 14 months vs 11.7 months (HR 0.77; 95% CI 0.65 to 0.92; p= 0.003)

Safety outcomes:
Grade 3/4 treatment-emergent adverse events (TEAEs): 51.8% (T + D + CT) vs 44.6% (D + CT) vs 44.4% (CT)

CONCLUSIONS

Authors' conclusions: D + CT significantly improved PFS versus CT. A limited course of tremelimumab added to durvalumab and chemotherapy significantly improved OS and PFS versus CT, without meaningful additional tolerability burden, representing a potential new option in first-line mNSCLC.

Critique: Despite chemotherapy options being clearly stated, the results may be subject to potentials biases as the choice of chemotherapy was in discretion of investigators. Despite the significant improvement with T + D + CT versus CT for both PFS and OS, the study may not be powered to show significance for this secondary outcome. However, although PFS is a surrogate endpoint, the choice of OS outcome in addition to PFS can be considered a strength of the study

N = 802 • Heymach et al., 2023 • International, randomized, double-blind, placebo-controlled, phase 3 trial (AEGEAN)

POPULATION

Objective: To evaluate use of durvalumab administered perioperatively (I.e., as neoadjuvant and adjuvant therapy) along with neoadjuvant chemotherapy in patients with resectable NSCLC

N= 802
Placebo (n= 374)

Durvalumab (n= 366)

METHODS

Inclusion/exclusion: Newly diagnosed, previously untreated, histologically or cytologically documented, resectable NSCLC (stage IIA to stage IIIB [N2 node stage] disease), age ≥18 years, candidates for planned surgical treatment, ECOG performance-status score of 0 or 1, documented tumor PD-L1 status

Intervention: Patients were randomized (1:1) to receive four cycles of platinum-based chemotherapy plus either fixed-dose durvalumab (1,500 mg) or placebo administered intravenously every 3 weeks, followed by surgery. After surgery, patients continued to receive durvalumab or placebo intravenously every 4 weeks for up to 12 cycles.

Duration: Treatment up to 12 cycles

RESULTS

Primary outcome:
Event-free survival at 12 months: durvalumab 73.4% vs placebo 64.5% (HR 0.68; 95% CI 0.53 to 0.88; p= 0.004)

Pathological complete response: 17.2% vs 4.3% (p<0.001)

Event-free survival and pathological complete response benefit observed regardless of stage and PD-L1 expression.

Secondary outcomes:
Objective response rate (ORR): 56.3% vs 38.0%

Safety outcomes:
AEs of maximum grade 3 or 4: 42.4% vs 43.2%.

CONCLUSIONS

Authors' conclusions: In patients with resectable NSCLC, perioperative durvalumab plus neoadjuvant chemotherapy was associated with significantly greater event-free survival and pathological complete response than neoadjuvant chemotherapy alone, with a safety profile that was consistent with the individual agents.

Critique: Patients with EGFR or ALK mutations were excluded from the analysis, limiting generalizability of the findings.

N = 805 • Paz-Ares et al., 2022 • Multicenter, prospective, head-to-head, comparative, 12-month study (BEST-MS)

POPULATION

Objective: To assess first-line durvalumab, with or without tremelimumab in combination with etoposide plus either cisplatin or carboplatin (EP) in ES-SCLC

N= 805

Durvalumab + EP (n= 268)

Durvalumab + tremelimumab + EP (n= 268)

EP (n= 269)

METHODS

Inclusion/exclusion: Age ≥18 years with treatment-naïve, histologically or cytologically documented ES-SCLC stage IV or T-stage T3-4 due to multiple lung nodules that are too extensive or a tumor or nodal volume that is too large to be encompassed in a tolerable radiotherapy plan, World Health Organization performance status 0 or 1, life expectancy of at least 12 weeks

Intervention: Patients were randomized (1:1:1) to receive durvalumab + EP, durvalumab + tremelimumab + EP, or EP. Patients in the immunotherapy arms received four cycles of EP plus durvalumab 1,500 mg with or without tremelimumab 75 mg every 3 weeks, followed by maintenance durvalumab 1,500 mg every 4 weeks until disease progression. Patients in the durvalumab + tremelimumab + EP arm received an additional tremelimumab dose after EP. Patients in the EP arm received up to 6 cycles of EP and optional prophylactic cranial irradiation.

Duration: Until disease progression

RESULTS

Primary outcomes: OS at 36 months
Durvalumab + EP vs EP: 17.6% vs 5.8% (HR 0.71; 95% CI 0.60 to 0.86; p= 0.0003)

Durvalumab + tremelimumab + EP vs EP: 15.3% vs 5.8% (HR 0.81; 95% CI 0.67 to 0.97; p= 0.02)

Safety outcomes:
Serious AEs: durvalumab + EP 32% vs durvalumab + tremelimumab + EP 47% vs EP 36%

Any-cause AEs leading to death: 5% vs 11% vs 6%

CONCLUSIONS

Authors' conclusions: Three times more patients were estimated to be alive at 3 years when treated with durvalumab plus EP versus EP, with the majority still receiving durvalumab at data cut-off, further establishing durvalumab plus EP as first-line standard of care for ES-SCLC.

Critique: The addition of tremelimumab did not appear to improve overall survival rates..

N = 685 • Oh et. Al, 2022 • Double-blind, placebo-controlled, phase 3 trial (TOPAZ-1)

POPULATION

Objective: To evaluate durvalumab plus chemotherapy for patients with advanced BTC

N= 685

Placebo (n= 344)

Durvalumab (n= 341)

METHODS

Inclusion/exclusion: Age ≥18 years, histologically confirmed unresectable, locally advanced, or metastatic adenocarcinoma of the biliary tract, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma, ECOG performance status of 0 or 1, no prior exposure to immune-mediated therapy

Intervention: Patients were randomized (1:1) to receive durvalumab in combination with gemcitabine and cisplatin or placebo in combination with gemcitabine and cisplatin. Treatment was administered intravenously on a 21-day cycle for up to 8 cycles. Durvalumab (1,500 mg) or placebo was administered on day 1 of each cycle, in combination with gemcitabine (1,000 mg/m2) and cisplatin (25 mg/m2), which were administered on days 1 and 8 of each cycle. After completion of chemotherapy, 1,500 mg of durvalumab or placebo monotherapy was given once every 4 weeks.

Duration: Until clinical or imaging disease progression or until unacceptable toxicity, withdrawal of consent, or any other discontinuation criteria were met

RESULTS

Primary outcomes: Median OS: durvalumab 12.8 months vs placebo 11.5 months (HR 0.80; 95% CI 0.66 to 0.97; p= 0.021)

Median OS in patients with PD-L1 expression ≥1%: HR 0.79; 95% CI 0.61 to 1.00

OS rates:
- 12 months: 54.1% vs 48.0%
- 18 months: 35.1% vs 25.6%
- 24 months: 24.9% vs 10.4%

Secondary outcomes:
Median PFS: 7.2 months vs 5.7 months (HR 0.75; 95% CI 0.63 to 0.89; p= 0.001)

Objective response rate (ORR): 26.7% vs 18.7% (odds ratio [OR] 1.60; 95% CI 1.11 to 2.31)

Safety outcomes:
Any-grade AEs: 99.4% vs 98.8%

Grade 3 or 4 AEs: 75.7% vs 77.8%

Discontinuation due to AEs: 13% vs 15.2%

Deaths due to AEs: 3.6% vs 4.1%

CONCLUSIONS

Authors' conclusions: Durvalumab plus chemotherapy significantly improved overall survival versus placebo plus chemotherapy and showed improvements versus placebo plus chemotherapy in prespecified secondary end points including progression-free survival and objective response rate. The safety profiles of the two treatment groups were similar.

Critique: Overall survival was not significantly improved in patients with PD-L1 expression ≥1%. Thus, use of durvalumab in this subgroup may not be effective.

N = 1,171 • Abou-Alfa et al., 2022 • International, randomized, open-label, sponsor-blinded phase 3 trial (HIMALAYA)

POPULATION

Objective: To evaluate single tremelimumab regular interval durvalumab (STRIDE) and durvalumab monotherapy versus sorafenib in patients with unresectable hepatocellular carcinoma who had not been previously treated with systemic therapy

N= 1,171

STRIDE (n= 393)

Durvalumab (n= 389)

Sorafenib (n= 389)

METHODS

Inclusion/exclusion: Age ≥18 years with histologically confirmed hepatocellular carcinoma, had no prior systemic therapy, ineligible for locoregional therapy, Barcelona Clinic Liver Cancer stage B or C, Child-Pugh Score class A, ECOG performance status 0 or 1

Intervention: Patients were randomized (1:1:1) to receive the following: 300 mg tremelimumab for one dose plus 1,500 mg durvalumab every 4 weeks (STRIDE), 1,500 mg durvalumab every 4 weeks, or 400 mg sorafenib twice daily.

Duration: Until progression, unacceptable toxicity, consent withdrawal, or other discontinuation criteria were met

RESULTS

Primary outcomes:
Median OS: STRIDE 16.43 months vs durvalumab 16.56 months vs sorafenib 13.77 months

OS at 36 months: 30.7% vs 24.7% vs 20.2%

- STRIDE vs sorafenib: HR 0.78; 96.02% CI 0.65 to 0.93; p= 0.0035
- Durvalumab vs sorafenib: HR 0.86; 95.67% 0.73 to 1.03; met noninferiority criteria

Secondary outcomes:
No difference in PFS between groups

Safety outcomes:
Grade 3 or 4 AEs: 50.5% vs 37.1% vs 52.4%.

CONCLUSIONS

Authors' conclusions: STRIDE significantly improved overall survival versus sorafenib. Durvalumab monotherapy was noninferior to sorafenib for patients with unresectable hepatocellular carcinoma.

Critique: This trial initially included a treatment arm in which patients received 75 mg tremelimumab every 4 weeks for four doses plus 1,500 mg durvalumab every 4 weeks, but data from a pre-planned analysis of the phase 2 trial found the regimen did not meaningfully differentiate from durvalumab monotherapy.

N = 40 RCTs (22,526 participants) • Li et al., 2023 • Network meta-analysis

POPULATION

Objective: To compare the efficacy and safety of all currently available immune checkpoint inhibitors (ICIs)

N= 40 RCTs (22,526 participants)

METHODS

Literature search parameters:

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase databases were systematically searched for RCTs published up to August 8, 2022. Trials including patients with advanced NSCLC (stage III or IV) that investigated at least one type of ICI monotherapy or combination therapy were analyzed.

Comparisons: ICIs and combination regimens

Outcomes: OS, PFS

RESULTS

OS:

- Durvalumab + platinum-based chemotherapy (PBC) vs bevacizumab + PBC: HR 0.69; 95% CI 0.49 to 0.97
- Durvalumab + PBC vs PBC alone: HR 0.69; 95% CI 0.54 to 0.88
- Durvalumab + PBC vs avelumab: HR 0.67; 95% CI 0.48 to 0.93
- Durvalumab + PBC vs daratumumab + atezolizumab: HR 0.60; 95% CI 0.38 to 0.96
- Bayesian ranking profiles ranked cemiplimab first for OS, followed by sintilimab + PBC and pembrolizumab + PBC.
- Durvalumab + tremelimumab + PBC presented with the highest OS for patients with PD-L1 expression ≥ 50%

PFS: Pembrolizumab + docetaxel ranked first, followed by atezolizumab + bevacizumab + PBC and camrelizumab + PBC.

CONCLUSIONS

Authors' conclusions: Although ICI plus PBC likely resulted in superior survival outcomes compared to ICI treatment alone, it did increase toxicity. Cemiplimab presented a well-balanced efficacy and safety profile in advanced NSCLC treatment. Our findings with the current ICIs comparisons will aid future trials for cancer immunotherapy.

Critique: This analysis is based primarily on indirect comparison data.

N = 13 studies (4,352 participants) • Zhang et al., 2023 • Network meta-analysis

POPULATION

Objective: To investigate the efficacy and safety of first-line immunotherapy combinations with chemotherapy for patients with ES-SCLC

N= 13 studies (4,352 participants)

METHODS

Inclusion/exclusion: Databases including PubMed, Embase, Cochrane Library, Scopus, Google Scholars, and ClinicalTrials.gov, and major international conferences were searched for RCTs regarding comparing immunotherapy combinations with chemotherapy as first-line treatments for patients with advanced ES-SCLC from inception to November 1. Studies that were prospective, randomized, phase 3 or 2, controlled clinical studies and included patients with newly diagnosed with treatment-naïve histologically or cytologically documented ES-SCLC were included for analysis.

Comparisons: first-line immunotherapies

Outcomes: OS, PFS, ORR and AEs

RESULTS

OS:

- Durvalumab vs ipilimumab: HR 0.77 (95% CI 0.61 to 0.97)
- Durvalumab vs atezolizumab + tiragolumab: HR 0.70 (95% CI 0.51 to 0.94)
- No difference between durvalumab and pembrolizumab, nivolumab, adebrelimab, atezolizumab and serplulimab

PFS:

- Durvalumab vs atezolizumab + tiragolumab: HR 0.74 (95% CI 0.57 to 0.97)
- Serplulimab vs durvalumab: HR 0.59 (95% CI 0.44 to 0.78)
- Serplulimab vs durvalumab + tremelimumab: HR 0.56 (95% CI 0.42 to 0.75)
- No difference between durvalumab and ipilimumab, adebrelimab, nivolumab, pembrolizumab, and atezolizumab

ORR and AEs: No difference between any agents

CONCLUSIONS

Authors' conclusions: Considering OS, PFS, ORR, and safety profiles, serplulimab with chemotherapy should be recommended as the best therapy for patients with ES-SCLC. Certainly, more head-to-head studies are needed to confirm these findings.

Critique: This analysis is based primarily on indirect comparison data.

N = 22 RCTs (13,293 participants) • Ciliberto et al., 2023 • Network meta-analysis

POPULATION

Objective: To compare the efficacy and toxicity of a variety of therapeutic strategies for treatment of advanced HCC

N= 22 RCTs (13,293 participants)

METHODS

Literature search parameters: From 2008 to September 2022, a comprehensive search from available online (PubMed, Embase, MedLine, Cochrane Central Register) and meeting (ASCO and ESMO) databases was performed. Studies were included if they were randomized controlled trials and evaluated systemic first line treatments for advanced HCC.

Comparisons: ICIs and combination regimens

Outcomes:

Surface under the cumulative ranking area (SUCRA) for OS, PFS, ORR, and tolerability

RESULTS

SUCRA rankings:

- OS: camrelizumab + rivoceranib (100%), sintilimab + bevacizumab (95.2%), atezolizumab + bevacizumab (90.5%), lenvatinib + pembrolizumab (84.8%), durvalumab + tremelimumab (85.7%), donafenib (76%), tislelizumab (68.1%), nivolumab (68%), durvalumab (61.7%)
- PFS: lenvatinib + pembrolizumab (100%), sintilimab + bevacizumab (92.3%), atezolizumab + bevacizumab (84.6%), camrelizumab + rivoceranib (76.3%), durvalumab + tremelimumab (46.2%), durvalumab (23.1%)
- ORR: sintilimab + bevacizumab (95.9%), camrelizumab + rivoceranib (91.2%), lenvatinib + pembrolizumab (89.2%), durvalumab + tremelimumab (87.9%), durvalumab (80.2%)
- Tolerability: durvalumab (99.6%), durvalumab + tremelimumab (95.6%)

CONCLUSIONS

Authors' conclusions: Combination of camrelizumab + rivoceranib scored the best in OS, followed by sintilimab + bevacizumab, whereas lenvatinib + pembrolizumab showed higher probability to be the best treatment in PFS and sintilimab + bevacizumab performed best in ORR. Finally, durvalumab is the most tolerated treatment.

Critique: Due to the lack of direct comparisons, results of the performance of each treatment is inferred by Bayesian probabilistic methodology.

N = 17 studies (3,632 participants) • Feng et al., 2022 • Network meta-analysis

POPULATION

Objective: To compare the efficacy of different first-line treatment regimens for patients with advanced BTC

N= 17 studies (3,632 participants)

METHODS

Literature search parameters: PubMed, Web of Science, and Cochrane Library were searched from database inception up through May 2022 for abstracts and full-text articles published about the first-line treatment for patients with advanced biliary duct cancer.

Comparisons: first-line treatment regimens for BTC

Outcomes:

OS, PFS, SUCRA rankings

RESULTS

OS: no difference between gemcitabine + cisplatin (GemCis) + durvalumab versus GemCis alone

SUCRA: GemCis + cediranib (86.1%), GemCis + durvalumab (80.4%), GemCis + merestinib (74.7%)

PFS: GemCis + durvalumab significantly better versus GemCis alone (HR 0.22; 95% CI 0.08 to 0.62)

SUCRA: gemcitabine + oxaliplatin (GemOxa) + erlotinib (91.2%), GemCis + durvalumab (82.7%), GemOxa + panitumumab (81.2%), GemOxa + cetuximab (79%)

CONCLUSIONS

Authors' conclusions: GemCis + durvalumab might be the most promising regimen for advanced BTC when considering OS and PFS. GemOxa and GemS1 could be alternative options for advanced BTC patients with nontolerance to GemCis.

Critique: This analysis is primarily based on indirect comparison data.

ADVERSE EFFECTS

Regimen	Adverse effects (≥20% incidence)
As a single agent	Cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash
In combination with platinum-based chemotherapy	Nausea, fatigue/asthenia, and alopecia
In combination with gemcitabine and cisplatin	Fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia
In combination with tremelimumab-actl	Rash, diarrhea, fatigue, pruritus, musculoskeletal pain, and abdominal pain
In combination with tremelimumab-actl and platinum-based chemotherapy	Nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea

CONTRA-INDICATIONS

None

DRUG INTERACTIONS

None reported in prescribing information

How Supplied:

IMFINZI (durvalumab) Injection is a clear to opalescent, colorless to slightly yellow solution supplied in a carton containing one single-dose vial either as:

- 500 mg/10 mL (50 mg/mL) (NDC 0310-4611-50)
- 120 mg/2.4 mL (50 mg/mL) (NDC 0310-4500-12)

Storage and Stability:

- Original product: Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
- Infusion solution: If the infusion solution is not administered immediately and needs to be stored, the time from preparation until the completion of the infusion should not exceed 28 days in a refrigerator at 2°C to 8°C (36°F to 46°F) or 8 hours at room temperature up to 25°C (77°F). Do not freeze. Do not shake.

SAFETY CONSIDERATIONS

BOXED WARNINGS

None

WARNINGS & PRECAUTIONS

- **Immune-Mediated Adverse Reactions:** Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, solid organ transplant rejection, and immune-mediated pancreatitis. Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. Withhold or permanently discontinue based on severity and type of reaction.
- **Infusion-Related Reactions:** Interrupt, slow the rate of infusion, or permanently discontinue durvalumab based on the severity of the reaction.
- **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT):** Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

IMMUNOGENICITY

Of the 2,280 patients who received durvalumab 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent, 69 patients (3%) tested positive for anti-drug antibodies (ADAs) and 12 (0.5%) tested positive for neutralizing antibodies. The development of ADAs against durvalumab appears to have no clinically relevant effect on its pharmacokinetics or safety.

- CASPIAN study: No patients tested positive for ADAs.
- TOPAZ-1 study: 2 (0.8%) patients tested positive for treatment-emergent ADAs and neutralizing antibodies, respectively. There were insufficient numbers of patients with ADAs or neutralizing antibodies (2 patients each) to determine whether ADAs have an impact on pharmacokinetics, pharmacodynamics, safety and/or effectiveness of durvalumab.

- HIMALAYA study: Among the 9 patients who tested positive for ADA, 55.6% (5/9) tested positive for neutralizing antibodies against durvalumab. There was no identified clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab; however, the effect of ADAs on the pharmacokinetics and effectiveness of durvalumab is unknown.
- POSEIDON study: 10% (29/286) of patients tested positive for anti-durvalumab antibodies with predose sampling at week 0, week 3 and week 12. Among the 29 patients who tested positive for ADAs, 10% (3/29) tested positive for neutralizing antibodies against durvalumab. The geometric mean of durvalumab concentration in patients with ADA positive was 46 mcg/mL compared to 89 mcg/mL in patients with ADA negative. There was no clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab; however, there is insufficient data to assess whether the observed ADA associated pharmacokinetic changes reduce effectiveness of durvalumab

USE IN SPECIFIC POPULATIONS

Renal impairment	There were no clinically significant differences in the pharmacokinetics of durvalumab based on mild or moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics of durvalumab is unknown.
Hepatic impairment	There were no clinically significant differences in the pharmacokinetics of durvalumab based on mild or moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of durvalumab is unknown.
Geriatrics	There were no clinically significant differences in the pharmacokinetics of durvalumab based on age. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients in clinical trials.
Pediatrics	Safety and effectiveness have not been established in pediatric patients.
Reproductive potential	Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiating treatment. Contraception: Durvalumab can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 3 months following the last dose. Refer to the Prescribing Information for the agents administered in combination with durvalumab for recommended contraception duration, as appropriate.
Pregnancy	Based on findings from animal studies and its mechanism of action, durvalumab can cause fetal harm when administered to a pregnant woman. There are no available data on the use of durvalumab in pregnant women.
Lactation	There are no data on the presence of durvalumab in human milk, its effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to durvalumab are unknown. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death. Because of the potential for adverse reactions in a breastfed child, advise women not to breastfeed during treatment with durvalumab and for 3 months after the last dose. Refer to the Prescribing Information for the agents administered in combination with durvalumab for recommended duration to not breastfeed, as appropriate.

DOSAGE & ADMINISTRATION

Administer as an intravenous infusion after dilution.

Recommended dosages:

Indication	Recommended Dosage	Duration of Therapy
Single Agent		
Unresectable stage III NSCLC	Patients with a body weight of ≥ 30 kg: 10 mg/kg every 2 weeks or 1,500 mg every 4 weeks Patients with a body weight of < 30 kg: 10 mg/kg every 2 weeks	Until disease progression, unacceptable toxicity, or a maximum of 12 month
Combination with Other Therapeutic Agents		
ES-SCLC	Patients with a body weight of ≥ 30 kg: 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of < 30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 10 mg/kg every 2 weeks as a single agent	Until disease progression or unacceptable toxicity
BTC	Patients with a body weight of ≥ 30 kg: 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) up to 8 cycles followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of < 30 kg:	Until disease progression or until unacceptable toxicity

	20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) up to 8 cycles followed by 20 mg/kg every 4 weeks as a single agent	
uHCC	Patients with a body weight of ≥ 30 kg and more: Durvalumab 1,500 mg following a single dose of tremelimumab-actl† 300 mg at Day 1 of Cycle 1; Continue durvalumab 1,500 mg as a single agent every 4 weeks Patients with a body weight of < 30 kg: Durvalumab 20 mg/kg following a single dose of tremelimumab-actl† 4 mg/kg at Day 1 of Cycle 1; Continue durvalumab 20 mg/kg as a single agent every 4 weeks	After Cycle 1 of combination therapy, administer durvalumab as a single agent every 4 weeks until disease progression or unacceptable toxicity

*Administer durvalumab prior to chemotherapy on the same day. Refer to the Prescribing Information for the agent administered in combination with durvalumab for recommended dosage information, as appropriate.

†Administer tremelimumab-actl prior to durvalumab on the same day. When tremelimumab-actl is administered inc ombination with durvalumab, refer to the Prescribing Information for tremelimumab –actl dosing information.

Treatment of metastatic NSCLC:

- Calculate the appropriate dosing using the table below based on the patient's weight and tumor histology.
- See Prescribing Information for the recommended dosage schedule.

Tumor Histology	Patient Weight	Dosage	Tremelimumab-actl Dosage	Platinum-based Chemotherapy Regimen
Non-Squamous	≥30 kg	1,500 mg	75 mg	Carboplatin and nab-paclitaxel OR Carboplatin or cisplatin and pemetrexed
	≥30 kg	20 mg/kg	1 mg/kg	
Squamous	≥30 kg	1,500 mg	75 mg	Carboplatin and nab-paclitaxel OR Carboplatin or cisplatin and gemcitabine

Administration

Administer infusion solution intravenously over 60 minutes. Administer all drug products as separate intravenous infusions. Do not co-administer other drugs through same infusion line. For platinum-based chemotherapy, refer to Prescribing Information for adminstration information. For pemetrexed therapy, refer to Prescribing Information for administration information.

Combination Regimens: Order of Infusions

- Durvalumab In Combination with Tremelimumab-actl: Infuse tremelimumab-actl first, followed by durvalumab on the same day of dosing.
- Durvalumab in Combination with Tremelimumab-actl and Platinum-Based Chemotherapy: Infuse tremelimumab-actl first, followed by durvalumab and then platinum-based chemotherapy on the day of dosing.

- Durvalumab in Combination with Tremelimumab-actl and Pemetrexed Therapy: Infuse tremelimumab-actl first, followed by durvalumab and then pemetrexed therapy on the day of dosing.

Combination Regimens: Infusion Instructions

- Durvalumab in Combination with Tremelimumab-actl: Administer tremelimumab-actl over 60 minutes followed by a 60-minute observation period. Then administer durvalumab as a separate intravenous infusion over 60 minutes.
- Durvalumab in Combination with Tremelimumab-actl and Platinum-Based Chemotherapy/Pemetrexed Therapy:
- Cycle 1: Infuse tremelimumab-actl over 1 hour. One to two hours after completion of tremelimumab-actl infusion, infuse durvalumab over 1 hour. One to two hours after completion of durvalumab infusion, administer platinum-based chemotherapy.

Subsequent Cycles: If there are no infusion reactions during cycle 1, subsequent cycles of durvalumab can be given immediately after tremelimumab-actl. The time between the end of the durvalumab infusion and the start of chemotherapy can be reduced to 30 minutes.

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