PRODUCT MONOGRAPH

PrINLYTA®

Axitinib

Tablets, 1 mg, 3 mg, 5 mg and 7 mg

Kinase Inhibitor, Anti-Tumour Agent

®Pfizer Products ULC
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PRINLYTA®

Axitinib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 1 mg, 3 mg, 5 mg, 7 mg	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

- INLYTA (axitinib) is indicated for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib.

  The clinical effectiveness of INLYTA is based on progression-free survival (PFS) in patients with metastatic RCC in a Phase 3, controlled clinical trial which compared INLYTA to sorafenib. The overall median PFS increased by 2 months in patients treated with INLYTA as compared to those treated with sorafenib (HR = 0.67 [95% CI: 0.54, 0.81]). The difference in median PFS for patients previously treated with a cytokine was 5.6 months (HR = 0.46 [95% CI: 0.32, 0.68]), whereas the difference in patients previously treated with sunitinib was 1.4 months (HR = 0.74 [95% CI: 0.57, 0.96]). The overall survival and quality of life were not significantly different in patients treated with INLYTA as compared to those treated with sorafenib (see CLINICAL TRIALS).

- INLYTA, in combination with pembrolizumab, is indicated for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) with no prior systemic therapy for metastatic RCC (see CLINICAL TRIALS).

INLYTA should be prescribed by a qualified healthcare professional who is experienced in the use of anti-neoplastic therapy.

Geriatrics (≥65 years of age):

In a pivotal, Phase 3 controlled study with INLYTA for the treatment of metastatic RCC, 123/359 (34%) patients treated with INLYTA were ≥ 65 years old. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years old and patients younger than 65 years. No dosage adjustment is required in patients who are 65 years or older (see WARNING AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION).

Pediatrics (<18 years of age):

The safety and efficacy of INLYTA in pediatric patients have not been established.
Physeal dysplasia in immature mice and dogs and odontopathies in growing incisors of mice have been observed in toxicology studies. Other toxicities of potential concern to pediatric patients due to the anti-angiogenic mechanism of action of axitinib have not been evaluated in juvenile animals. Therefore, INLYTA should not be administered to children under 18.
(see WARNING AND PRECAUTIONS, Special Populations and Conditions and TOXICOLOGY).

CONTRAINDICATIONS

INLYTA (axitinib tablets) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

INLYTA should be prescribed by a qualified healthcare professional who is experienced in the use of anti-neoplastic therapy.

INLYTA has not been studied in patients with severe hepatic impairment (see Hepatic section below)

The following are clinically significant adverse events:

- Hypertension and Hypertensive Crisis (see Cardiovascular section below)
- Arterial Thromboembolism, including deaths (see Cardiovascular section below)
- Venous Thromboembolism, including deaths (see Cardiovascular section below)
- Hemorrhage (including gastrointestinal, cerebral and respiratory tract) (see Hematologic section below)
- Gastrointestinal perforation, including death and gastrointestinal fistulas (see Gastrointestinal section below)
- Reversible posterior leukoencephalopathy syndrome (see Neurologic section below)
- Congestive heart failure/Cardiomyopathy, including deaths (see Cardiovascular section below)

General

INLYTA contains lactose and should not be taken by patients with hereditary problems of lactose intolerance.

Drug-Drug Interactions

Co-administration of INLYTA with strong inhibitors of CYP3A4/5 is not recommended as this may increase axitinib concentrations and drug toxicity. If a strong CYP3A4/5 inhibitor must be co-administered a dose reduction of INLYTA is recommended (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Co-administration with strong inducers of CYP3A4/5 should be avoided due to the risk of reduced effectiveness of the drug. Moderate CYP3A4/5 inducers may also reduce the plasma exposure of axitinib and should be avoided if possible (see DRUG INTERACTIONS).

Effects on ability to drive and use machines

No studies on the effect of INLYTA on the ability to drive or use machines have been performed. However, patients should be informed that dizziness and fatigue have been reported during treatment with INLYTA.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with axitinib have not been conducted. Axitinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in an *in vitro* human lymphocyte chromosome aberration assay. Axitinib was genotoxic in an *in vivo* mouse bone marrow micronucleus test (see TOXICOLOGY).

Cardiovascular

Patients with uncontrolled hypertension at baseline or a recent history of myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, deep vein thrombosis or pulmonary embolism were excluded from clinical studies with INLYTA.

Hypertension and Hypertensive Crisis

Hypertension is a common adverse event in patients treated with INLYTA (see ADVERSE REACTIONS) and blood pressure should be well controlled prior to initiating treatment with INLYTA. Patients were required to have diastolic BP ≤90 mm Hg and systolic BP ≤140 mm Hg for entry into the controlled Phase 3 trial. During therapy patients should be monitored for hypertension early after starting treatment (no longer than one week after starting axitinib and frequently thereafter to ensure blood pressure control), and treated promptly with a combination of standard anti-hypertensive therapy and INLYTA dose reduction or interruption as clinically warranted. INLYTA should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy or if there is evidence of hypertensive crisis (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

In pooled clinical studies for the treatment of patients with RCC, hypertension was reported in 344/672 patients (51%) receiving INLYTA with 155/672 patients (23%) experiencing Grade 3/4 events.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving INLYTA and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) treated with INLYTA and none in patients treated with sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and increases in

blood pressure were observed as early as 4 days after the first dose of INLYTA. Hypertension was managed with standard anti-hypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib (see ADVERSE REACTIONS).

Patients with hypertension that is not controlled by medications should not be treated with INLYTA. If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension (see DOSAGE and ADMINISTRATION).

Serious cases of artery dissection have been reported in patients using VEGFR TKIs, including INLYTA, with or without hypertension.

Congestive Heart Failure/Cardiomyopathy Events

Congestive heart failure/cardiomyopathy events have been reported in patients receiving INLYTA in the post-market setting. Many events have resulted in hospitalizations and some have been fatal. In clinical studies for the treatment of patients with RCC, congestive heart failure/cardiomyopathy events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 12/672 patients (2%) receiving INLYTA and 11 patients were hospitalized. Grade 3/4 congestive heart failure/cardiomyopathy events were reported in 7 patients (1%) and 2 patients (<1%) receiving INLYTA had fatal events.

In a pivotal controlled Phase 3 clinical study with INLYTA for the treatment of patients with RCC, congestive heart failure/cardiomyopathy events (including cardiac failure, cardiopulmonary failure, left ventricular dysfunction, and right ventricular failure) were reported in 6/359 patients (2%) receiving INLYTA and 3/355 patients (<1%) receiving sorafenib. Grade 3/4 congestive heart failure/cardiomyopathy events were observed in 2 patients (<1%) receiving INLYTA and 1 patient (<1%) receiving sorafenib. Fatal events were reported in 2 patients (<1%) receiving INLYTA and 1 patient (<1%) receiving sorafenib (see ADVERSE REACTIONS).

Monitor for signs or symptoms of congestive heart failure/cardiomyopathy events at baseline and periodically throughout treatment with INLYTA. Management of these events may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy.

QT Prolongation

The effect of INLYTA on the QTc interval was investigated in a randomized, 2-way crossover study where, 35 healthy subjects were administered a single, oral 5 mg dose of INLYTA alone or with 400 mg ketoconazole. Although some tyrosine kinase inhibitors are associated with QT interval prolongation, INLYTA did not result in large mean changes in the QTc interval (>20 msec) up to 3 hours post-dose. However smaller increases in the QTc interval (<10 msec) cannot be ruled out.

Decreased Heart Rate

In clinical studies with INLYTA, events of decreased heart rate have occurred (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Caution should be observed in patients who are bradycardic or considered to be at risk for bradyarrhythmias or who are receiving other heart rate-lowering drugs.

Arterial Thromboembolic Events

In pooled clinical studies for the treatment of patients with RCC, arterial thromboembolic events were reported in 19/672 patients (3%) receiving INLYTA with 17/672 patients (3%) experiencing Grade 3/4 events. Fatal arterial thromboembolic events were reported in 2 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. A fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients (0%) receiving sorafenib (see ADVERSE REACTIONS).

INLYTA should be used with caution in patients who are at risk for or who have a history of these events. INLYTA has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

Venous Thromboembolic Events

In clinical studies with INLYTA, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. In pooled clinical studies for the treatment of patients with RCC, venous thromboembolic events were reported in 19/672 patients (3%) receiving INLYTA with 14/672 patients (2%) experiencing Grade 3/4 events. Fatal venous thromboembolic events were reported in 1/672 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events (including pulmonary embolism, deep vein thrombosis, and retinal-vein occlusion/thrombosis) were reported in 9/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib.

INLYTA should be used with caution in patients who are at risk for venous thromboembolic events or who have a history of these events. INLYTA has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

Endocrine and Metabolism

Thyroid Dysfunction

In clinical studies with INLYTA, events of hypothyroidism and hyperthyroidism have occurred (see ADVERSE REACTIONS). In pooled clinical studies for the treatment of patients with RCC,

hypothyroidism was reported in 165/672 patients (25%) receiving INLYTA. In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib.

In pooled clinical studies for the treatment of patients with RCC, hyperthyroidism was reported in 11/672 patients (2%) receiving INLYTA. In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, hyperthyroidism was reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving INLYTA and 25/232 patients (11%) receiving sorafenib (see ADVERSE REACTIONS).

Monitoring for thyroid function before initiation of, and periodically throughout, treatment with INLYTA is recommended. Hypothyroidism and hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Gastrointestinal

Gastrointestinal Perforation and Fistula Formation

In clinical studies with INLYTA, events of gastrointestinal (GI) perforation or fistula have occurred, including a fatal GI perforation (see ADVERSE REACTIONS). In pooled clinical studies for the treatment of patients with RCC, gastrointestinal perforation and fistula were reported in 13/672 patients (2%) receiving INLYTA. In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical studies with INLYTA, GI perforation was reported in 5/715 patients (1%), including one death, and GI fistulas were reported in 4/715 patients (1%).

Monitoring for symptoms of GI perforation or fistula formation periodically throughout treatment with INLYTA is recommended.

Hematologic

Elevation of Hemoglobin or Hematocrit

In clinical studies with INLYTA, events of elevated hemoglobin have occurred. Elevated hemoglobin above the upper limit of normal (ULN) was observed in 31/320 patients (10%) receiving INLYTA and 3/316 patients (1%) receiving sorafenib. An increase in red blood cell mass may increase the risk of thromboembolic events.

Monitoring hemoglobin or hematocrit before initiation of, and periodically throughout, treatment with INLYTA is recommended. If hemoglobin or hematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease hemoglobin or hematocrit to an acceptable level.

Hemorrhagic

In clinical studies with INLYTA, hemorrhagic events have been reported, some of which were fatal (see ADVERSE REACTIONS). In pooled clinical studies for the treatment of patients with RCC, hemorrhagic events were reported in 173/672 patients (26%) receiving INLYTA with 27/672 patients (3%) experiencing Grade 3/4 events. Fatal hemorrhagic events were reported in 3/672 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving INLYTA and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 patients (1%) receiving INLYTA (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 patients (3%) receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

Since INLYTA has not been studied in patients who have evidence of untreated brain metastasis, a history of pulmonary embolism in the previous 6 months, or a history of active bleeding in the previous 3 months, treatment with INLYTA is not recommended in these patients. INLYTA should be used with caution in patients with a significant risk for hemorrhage.

Hepatic

Elevation of Liver Enzymes when INLYTA is given as a single agent for RCC

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, alanine aminotransferase (ALT) elevations occurred in 74/331 patients (22%) receiving INLYTA and 68/313 patients (22%) receiving sorafenib. Grade 3/4 events were reported in 1/331 patients (<1%) receiving INLYTA and 5/313 patients (2%) receiving sorafenib (see ADVERSE REACTIONS).

Monitoring of ALT, aspartate aminotransferase (AST) and bilirubin before initiation of, and periodically throughout treatment with, INLYTA is recommended.

Elevation of Liver Enzymes when INLYTA is given in combination with pembrolizumab for RCC

When INLYTA is given with pembrolizumab, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (See ADVERSE REACTIONS). Monitor liver enzymes before initiation of and periodically throughout treatment.

Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. (See DOSAGE AND ADMINISTRATION and the Product Monograph for pembrolizumab).

Hepatic Impairment

In a clinical hepatic impairment study with INLYTA (N=24 subjects), the systemic exposure of INLYTA was approximately 2-fold higher in patients with moderate hepatic impairment (Child-Pugh class B) compared to patients with normal hepatic function. A dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this patient population (see DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY).

Neurologic

Reversible Posterior Leukoencephalopathy Syndrome

In pooled clinical studies for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 2/672 patients (<1%) receiving INLYTA.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, RPLS was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. Two additional events of RPLS were reported in other clinical trials with INLYTA (see ADVERSE REACTIONS).

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. INLYTA should be discontinued in patients with signs/symptoms of RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

Peri-Operative Considerations

Wound Healing Complications

No formal studies of the effect of INLYTA on wound healing have been conducted. Since vascular endothelial growth factor (VEGF) inhibitors may impair wound healing, treatment with INLYTA should be stopped at least 24 hours prior to scheduled surgery. The decision to resume INLYTA after surgery should be based on clinical judgement of adequate wound healing. INLYTA should be discontinued in patients with wound dehiscence.

Renal

Renal Impairment

Axitinib has not been studied in patients with renal impairment. Caution should be exercised when administering INLYTA to patients with end-stage renal disease. Population pharmacokinetic analyses, suggest that there is no significant change in axitinib clearance in patients with mild to severe renal impairment. No dose adjustments based on renal function are required in patients with mild to severe renal impairment (see DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY).

Proteinuria

In pooled clinical studies for the treatment of patients with RCC, proteinuria was reported in 142/672 patients (21%) receiving INLYTA with 33/672 patients (5%) experiencing Grade 3/4 events.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, proteinuria was reported in 39/359 patients (11%) receiving INLYTA and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving INLYTA and 6/355 patients (2%) receiving sorafenib (see ADVERSE REACTIONS).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with INLYTA is recommended. For patients who develop moderate to severe proteinuria, reduction of the dose or temporary interruption of INLYTA treatment is recommended.

Sexual Function/Reproduction

Based on nonclinical safety findings, male and female fertility may be impaired by treatment with axitinib (see TOXICOLOGY).

Skin and Subcutaneous Tissue Disorders

Palmar-Plantar Erythrodysesthesia Syndrome

In pooled clinical studies for the treatment of patients with RCC, palmar-plantar erythrodysesthesia syndrome (PPE) was reported in 216/672 patients (32%) receiving INLYTA with 51/672 patients (7.6%) experiencing Grade 3/4 events.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, PPE was reported in 98/359 patients (27%) receiving INLYTA and 181/355 patients (51%) receiving sorafenib (see ADVERSE REACTIONS). Grade 3 PPE was reported in 18/359 (5%) of patients in the INLYTA arm and 57/355 (16.1%) of patients in the sorafenib arm. PPE resulted in dose modification or temporary delay of treatment in 19/359 (5.3%) patients treated with INLYTA and 63/355 (17.7%) patients treated with sorafenib. PPE led to treatment discontinuation in 1/359 (0.3%) of patients treated with INLYTA and 4/355 (1.1%) of patients treated with sorafenib.

Consider initiating treatment with topical therapies as soon as symptoms occur.

Special Populations

Pregnant Women

INLYTA should not be used during pregnancy. There are no studies in pregnant women using INLYTA. Based on its anti-angiogenic mechanism of action, INLYTA is expected to cause fetal harm when used by pregnant women.

In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose (see TOXICOLOGY).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. It is recommended that men and women should use effective birth control during treatment with INLYTA.

Nursing Women

The safe use of axitinib during lactation has not been established. It is unknown whether INLYTA is excreted in human milk. Breastfeeding should be discontinued during treatment with INLYTA.

Many drugs are commonly excreted in human milk therefore INLYTA may be toxic to nursing infants.

Pediatrics (<18 years of age)

The safety and efficacy of INLYTA in pediatric patients have not been established.

Limited data are available on the use of INLYTA in pediatric patients. In a phase 1 dose-finding study, the safety of INLYTA was evaluated in 16 pediatric patients with recurrent/refractory solid tumours. The maximum tolerated dose was determined to be 2.4 mg/m^2/dose administered orally twice daily in 28-day cycles. There were three Grade 3 non-dose limiting toxicities (DLTs) reported: hemoglobin increased, hypertension, and lipase increased. DLTs (palmar-plantar erythrodysesthesia syndrome and intratumoural hemorrhage) occurred in 2/5 patients treated at 3.2 mg/m^2/dose.

Physeal dysplasia in immature mice and dogs and odontopathies in growing incisors of mice have been observed in toxicology studies. Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals (see TOXICOLOGY). Therefore, INLYTA should not be administered to children less than 18 years of age.

Geriatrics (≥65 years of age)

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, 123/359 (34%) of patients treated with INLYTA were ≥65 years of age. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years old and

patients younger than 65 years. No dosage adjustment is required in patients who are 65 years or older (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Prior to treatment and during the course of therapy with INLYTA, patients should be monitored for hypertension, signs or symptoms of congestive heart failure/cardiomyopathy events, decreased heart rate, thyroid dysfunction, increased hemoglobin or hematocrit, symptoms of gastrointestinal perforation and fistula formation, proteinuria and elevated liver enzymes and elevated creatinine (see WARNINGS and PRECAUTIONS, Hypertension, Thyroid Dysfunction, Elevation of Hemoglobin and Hematocrit, Gastrointestinal Perforation and Fistula Formation, Proteinuria, Elevation of Liver Enzymes).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of INLYTA has been evaluated in 672 patients with metastatic RCC. The data described in this section reflect exposure to INLYTA in 359 patients with metastatic RCC who participated in the pivotal Phase 3 controlled clinical study versus sorafenib (see CLINICAL TRIALS).

The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse event occurred in 199/359 patients (55%) receiving INLYTA and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse event occurred in 33/359 patients (9%) receiving INLYTA and 46/355 patients (13%) receiving sorafenib.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

INLYTA as a single agent

Potentially serious adverse reactions with INLYTA included congestive heart failure/cardiomyopathy events, hypertension and hypertensive crisis, arterial thrombotic events, venous thrombotic events, cardiac dysfunction, hemorrhagic events, gastrointestinal perforation and fistula formation, thyroid dysfunction, elevation of hemoglobin or hematocrit, wound healing complications, RPLS, proteinuria, palmar-plantar erythrodysesthesia syndrome, elevation of liver enzymes and fetal development (see WARNINGS AND PRECAUTIONS).

Table 1 presents the most common adverse reactions reported in ≥10% of patients who received INLYTA or sorafenib.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received INLYTA or Sorafenib

Adverse Reaction[a]	INLYTA (N=359)			Sorafenib (N=355)		
	All Grades[b]	Grade 3	Grade 4	All Grades[b]	Grade 3	Grade 4
	%	%	%	%	%	%
Endocrine disorders						
Hypothyroidism	19	<1	0	8	0	0
Gastrointestinal disorders						
Diarrhea	55	10	<1	53	7	1
Nausea	32	2	<1	22	1	0
Vomiting	24	3	<1	17	1	0
Constipation	20	1	0	20	1	0
Stomatitis	15	1	0	12	<1	0
Abdominal pain	14	2	<1	11	1	0
Dyspepsia	10	0	0	2	0	0
General disorders and administration site conditions						
Fatigue	39	11	1	32	5	<1
Asthenia	21[c]	5	1	14	2	<1
Mucosal inflammation	15	1	0	12	1	0
Investigations						
Weight decreased	25	2	0	21	1	0
Metabolism and nutrition disorders						
Decreased appetite	34[c]	5	<1	29	4	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	1	1	11	1	0
Pain in extremity	13	<1	<1	14	1	0
Nervous system disorders						
Headache	14	1	0	11	0	0
Dysgeusia	11	0	0	8	0	0
Renal and urinary disorders						
Proteinuria	11	3	0	7	2	0
Respiratory, Thoracic and Mediastinal disorders						
Dysphonia	31	0	0	14	0	0
Cough	15	1	0	17	1	0
Dyspnea	15[c]	2	1	12	2	1
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia syndrome	27	5	0	51	16	0
Rash	13	<1	0	32	4	0
Dry skin	10	0	0	11	0	0
Pruritus	7	0	0	12	0	0
Alopecia	4	0	0	32	0	0
Erythema	2	0	0	10	<1	0
Vascular disorders						
Hypertension	40	15	<1	29	11	<1
Haemorrhage[d]	16 [c]	1	<1	18	3	0

[a] Percentages are treatment-emergent, all-causality events; [b] National Cancer Institute Common Terminology Criteria for

Adverse Events, Version 3.0; [c]Includes Grade 5 <1%; [d]Hemorrhage includes the following preferred terms (All Grades frequency): epistaxis (6%), haematuria (3%), haemoptysis (2%), rectal haemorrhage (2%), cerebral haemorrhage (<1%), gastric haemorrhage (<1%), and lower gastrointestinal haemorrhage (<1%).

Less Common Clinical Trial Adverse Drug Reactions (<10%)

Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included the following:

Blood and lymphatic disorders: anemia (4%), neutropenia (<1%), leukopenia (<1%), polycythemia (1%), thrombocytopenia (2%)

Cardiac disorder: congestive heart failure/cardiomyopathy events including cardiac failure (1%), cardiopulmonary failure (<1%), left ventricular dysfunction (<1%), right ventricular failure (<1%)

Metabolism and nutrition disorders: dehydration (6%), hypercalcemia (3%), hyperkalemia (3%)

Nervous system disorders: dizziness (9%), RPLS (<1%)

Eye disorders: retinal artery occlusion (<1%)

Ear and labyrinth disorders: tinnitus (3%)

Endocrine disorders: hyperthyroidism (1%)

Vascular disorders: hypertensive crisis (1%); venous embolic and thrombotic events including pulmonary embolism (2%), retinal-vein occlusion/thrombosis (1%), and deep vein thrombosis (1%); arterial embolic and thrombotic events including transient ischaemic attack (1%), cerebrovascular accident (<1%), and myocardial infarction (<1%)

Respiratory, thoracic and mediastinal disorders: epistaxis (6%), hemoptysis (2%), pulmonary embolism (2%)

Gastrointestinal disorders: upper abdominal pain (8%), hemorrhoids (4%), fistula (<1%), anal fistula (<1%), gastrointestinal perforation (<1%)

Muscoskeletal and connective tissue disorders: myalgia (7%)

Renal and urinary disorders: renal failure (including acute renal failure) (2%)

Skin and subcutaneous tissue disorders: glossodynia (3%)

Investigations: lipase increased (3%)

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 presents the most common laboratory abnormalities reported in ≥10% patients who received INLYTA or sorafenib.

Table 2. Laboratory Abnormalities Occurring in ≥10% of Patients who Received INLYTA or Sorafenib

Laboratory Abnormality	N	INLYTA			N	Sorafenib		
		All Grades[a]	Grade 3	Grade 4		All Grades[a]	Grade 3	Grade 4
		%	%	%		%	%	%
Hematology								
Hemoglobin decreased	320	35	<1	0	316	52	4	<1
Lymphocytes (absolute) decreased	317	33	3	0	309	36	4	0
Platelets decreased	312	15	<1	0	310	14	0	0
White blood cells decreased	320	11	0	0	315	16	<1	0
Chemistry								
Creatinine increased	336	55	0	0	318	41	<1	0
Bicarbonate decreased	314	44	0	<1	291	43	0	0
Hypocalcemia	336	39	1	1	319	59	1	1
ALP increased	336	30	1	0	319	34	1	0
Hyperglycemia	336	28	2	0	319	23	2	0
Lipase increased	338	27	4	1	319	46	13	2
Amylase increased	338	25	2	0	319	33	2	<1
ALT increased	331	22	<1	0	313	22	1	1
AST increased	331	20	<1	0	311	25	1	0
Hypernatremia	338	17	1	0	319	13	<1	1
Hypoalbuminemia	337	15	<1	0	319	18	1	0
Hyperkalemia	333	15	3	0	314	10	3	0
Hypoglycemia	336	11	<1	0	319	8	<1	0
Hyponatremia	338	13	3	<1	319	11	2	<1
Hypophosphatemia	336	13	2	0	318	49	16	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Hemoglobin increases above the upper limit of normal were observed for 9% of patients treated with INLYTA as compared to 1% of patients treated with sorafenib. Neutrophils decreased was observed in 6% of patients treated with INLYTA and 8% of patients treated with sorafenib.

In clinical trials, INLYTA was associated with statistically significant mean increases from baseline in systolic and diastolic blood pressure. On day 15 of treatment, systolic blood pressure was increased by mean 8.0 mmHg and diastolic blood pressure by mean 5.5 mmHg. These blood pressure increases were associated with a statistically significant mean decrease from baseline in heart rate of approximately 4 to 6 beats per minute.

Hypercalcemia was observed in 6% of patients treated with INLYTA and 2% of patients treated with sorafenib.

Hyperbilirubinemia was observed in 1% of patients treated with INLYTA and 1% of patients treated with sorafenib.

INLYTA in combination with Pembrolizumab

Table 3 summarizes the treatment-related adverse events that occurred in at least 1% of patients with renal cell carcinoma treated with INLYTA in combination with pembrolizumab in KEYNOTE-426. The most common treatment-related adverse events (reported in at least 10% of patients) were: hyperthyroidism; hypothyroidism; diarrhea; nausea; stomatitis; asthenia; fatigue; mucosal inflammation; ALT increased; AST increased; decreased appetite; arthralgia; proteinuria; dysphonia; palmar-plantar erythrodysesthesia syndrome; pruritus; rash; and hypertension. Sixty three percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 adverse reactions were: hypertension (21.2%); ALT increased (12,1%); diarrhea (7.2%); AST increased (6.8%); and palmar-plantar erythrodysesthesia syndrome (5.1%).

In KEYNOTE-426, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%), as measured by laboratory tests, were observed in previously untreated patients with RCC receiving INLYTA in combination with pembrolizumab. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or INLYTA (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT >3 times ULN, and of those patients with recurrence of ALT >3 times ULN, all recovered (See DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Fatal treatment-related adverse events occurred in 0.9% of patients receiving pembrolizumab in combination with INLYTA. These included 1 case each of myasthenia gravis, myocarditis, necrotising fasciitis, and pneumonitis.

Serious treatment-related adverse events occurred in 24% of patients receiving INLYTA in combination with pembrolizumab. Serious treatment-related adverse events in ≥ 1% of patients receiving INLYTA in combination with pembrolizumab included: diarrhea (1.9%); ALT increased (1.4%); AST increased (1.2%); and pneumonitis (1.2%).

Pembrolizumab and INLYTA were simultaneously discontinued for treatment-related adverse events (Grades 1-4) in 6.3% of patients in KEYNOTE 426. The most common treatment-related adverse event leading to discontinuation of both study drugs was ALT increased (1.2%). The median time to discontinuation of both drugs for treatment-related adverse events was 63 days.

In KEYNOTE 426, pembrolizumab was discontinued for treatment-related adverse events in 18.6% of subjects, regardless of action taken with INLYTA; the most common treatment-related adverse events (≥ 2%) leading to discontinuation of pembrolizumab were: ALT increased (4.7%);

and AST increased (3.7%). INLYTA was discontinued for treatment-related adverse events in 15.4% of subjects, regardless of action taken with pembrolizumab; the most common treatment-related adverse event (≥ 2%) leading to discontinuation of INLYTA was ALT increased (3.7%).

Treatment-related adverse events leading to simultaneous interruption of both pembrolizumab and INLYTA occurred in 28% of patients; the most common treatment-related adverse events leading to interruption of both study drugs (≥ 2%) were: ALT increased (7.0%); AST increased (6.5%); and diarrhea (6.1%).

Treatment-related adverse events leading to interruption of pembrolizumab occurred in 41% of patients, regardless of action taken with INLYTA. The most common treatment-related adverse events leading to interruption of pembrolizumab (≥ 2%) were: ALT increased (9.1%); AST increased (8.4%); diarrhea (8.4%); and hyperthyroidism (2.1%).

INLYTA was interrupted due to treatment-related adverse events in 57.6% of patients, regardless of action taken with pembrolizumab. The most common treatment-related adverse events leading to interruption of INLYTA (≥ 2%) were: diarrhea (12.8%); hypertension (12.6%); ALT increased (11.9%); AST increased (11.4%); palmar-plantar erythrodysesthesia syndrome (6.8%); decreased appetite (4.4%); proteinuria (3.5%); fatigue (3.0%); mucosal inflammation (2.6%); stomatitis (2.6%); and nausea (2.3%). INLYTA was dose reduced in 21% of patients, regardless of action taken with pembrolizumab. The most common treatment-related adverse events leading to dose reduction (≥ 2%) were: hypertension (4.0%); diarrhea (3.5%); and palmar-plantar erythrodysesthesia syndrome (2.3%).

Table 3. Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Renal Cell Carcinoma treated with INLYTA in Combination with pembrolizumab in KEYNOTE-426

	INLYTA + pembrolizumab n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Blood and lymphatic system disorders								
Anemia	12 (2.8)	0 (0)	1 (0.2)	0 (0)	69 (16.2)	13 (3.1)	0 (0)	0 (0)
Leukopenia	5 (1.2)	0 (0)	0 (0)	0 (0)	37 (8.7)	6 (1.4)	0 (0)	0 (0)
Neutropenia	6 (1.4)	0 (0)	1 (0.2)	0 (0)	79 (18.6)	27 (6.4)	1 (0.2)	0 (0)
Thrombocytopenia	8 (1.9)	0 (0)	0 (0)	0 (0)	94 (22.1)	20 (4.7)	2 (0.5)	0 (0)
Endocrine disorders								
Adrenal insufficiency	9 (2.1)	1 (0.2)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Hyperthyroidism	52	4 (0.9)	0 (0)	0 (0)	14	0 (0)	0 (0)	0 (0)

	INLYTA + pembrolizumab n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
	(12.1)				(3.3)			
Hypophysitis	5 (1.2)	4 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypothyroidism	135 (31.5)	1 (0.2)	0 (0)	0 (0)	119 (28.0)	0 (0)	0 (0)	0 (0)
Thyroiditis	10 (2.3)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders								
Dry eye	5 (1.2)	0 (0)	0 (0)	0 (0)	7 (1.6)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders								
Abdominal	5 (1.2)	0 (0)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Abdominal pain	23 (5.4)	3 (0.7)	0 (0)	0 (0)	16 (3.8)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	13 (3.0)	1 (0.2)	0 (0)	0 (0)	20 (4.7)	1 (0.2)	0 (0)	0 (0)
Colitis	8 (1.9)	5 (1.2)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Constipation	31 (7.2)	0 (0)	0 (0)	0 (0)	29 (6.8)	0 (0)	0 (0)	0 (0)
Diarrhea	210 (49)	31(7.2)	0 (0)	0 (0)	175 (41.2)	19 (4.5)	0 (0)	0 (0)
Dry mouth	17 (4.0)	0 (0)	0 (0)	0 (0)	22 (5.2)	0 (0)	0 (0)	0 (0)
Dyspepsia	12 (2.8)	0 (0)	0 (0)	0 (0)	48 (11.3)	1 (0.2)	0 (0)	0 (0)
Dysphagia	9 (2.1)	1 (0.2)	0 (0)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Flatulence	13 (3.0)	0 (0)	0 (0)	0 (0)	9 (2.1)	0 (0)	0 (0)	0 (0)
Gastritis	6 (1.4)	0 (0)	0 (0)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Gastroesophageal reflux disease	6 (1.4)	0 (0)	0 (0)	0 (0)	34 (8.0)	3 (0.7)	0 (0)	0 (0)
Nausea	91 (21.2)	2 (0.5)	0 (0)	0 (0)	111 (26.1)	4 (0.9)	0 (0)	0 (0)
Oesophagitis	6 (1.4)	0 (0)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Oral pain	17 (4)	0 (0)	0 (0)	0 (0)	13 (3.1)	0 (0)	0 (0)	0 (0)
Stomatitis	61 (14.2)	3 (0.7)	0 (0)	0 (0)	86 (20.2)	9 (2.1)	0 (0)	0 (0)
Vomiting	34 (7.9)	1 (0.2)	0 (0)	0 (0)	56 (13.2)	3 (0.7)	0 (0)	0 (0)
General disorders and administration site conditions								
Asthenia	50 (11.7)	6 (1.4)	0 (0)	0 (0)	54 (12.7)	12 (2.8)	0 (0)	0 (0)
Chills	8 (1.9)	0 (0)	0 (0)	0 (0)	11 (2.6)	1 (0.2)	0 (0)	0 (0)
Fatigue	130 (30.3)	10 (2.3)	0 (0)	0 (0)	142 (33.4)	21 (4.9)	0 (0)	0 (0)
Malaise	8 (1.9)	1 (0.2)	0 (0)	0 (0)	13	0 (0)	0 (0)	0 (0)

	INLYTA + pembrolizumab n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
					(3.1)			
Mucosal inflammation	55 (12.8)	4 (0.9)	0 (0)	0 (0)	90 (21.2)	7 (1.6)	0 (0)	0 (0)
Oedema peripheral	7 (1.6)	1 (0.2)	0 (0)	0 (0)	14 (3.3)	0 (0)	0 (0)	0 (0)
Pyrexia	16 (3.7)	0 (0)	0 (0)	0 (0)	24 (5.6)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders								
Hepatic function abnormal	13 (3.0)	6 (1.4)	0 (0)	0 (0)	6 (1.4)	0 (0)	0 (0)	0 (0)
Hepatitis	6 (1.4)	4 (0.9)	2 (0.5)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Hyperbilirubinaemia	5 (1.2)	0 (0)	0 (0)	0 (0)	6 (1.4)	0 (0)	1 (0.2)	0 (0)
Infections and infestations								
Gingivitis	5 (1.2)	0 (0)	0 (0)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Investigations								
Alanine aminotransferase increased	102 (23.8)	48 (11.2)	4 (0.9)	0 (0)	54 (12.7)	10 (2.4)	1 (0.2)	0 (0)
Aspartate aminotransferase increased	97 (22.6)	26 (6.1)	3 (0.7)	0 (0)	59 (13.9)	7 (1.6)	0 (0)	0 (0)
Blood alkaline phosphatase increased	17 (4.0)	5 (1.2)	0 (0)	0 (0)	15 (3.5)	3 (0.7)	0 (0)	0 (0)
Blood bilirubin increased	19 (4.4)	1 (0.2)	1 (0.2)	0 (0)	20 (4.7)	1 (0.2)	0 (0)	0 (0)
Blood creatinine increased	24 (5.6)	0 (0)	0 (0)	0 (0)	30 (7.1)	1 (0.2)	0 (0)	0 (0)
Blood lactate dehydrogenase increased	8 (1.9)	0 (0)	0 (0)	0 (0)	12 (2.8)	0 (0)	0 (0)	0 (0)
Blood pressure increased	13 (3.0)	6 (1.4)	0 (0)	0 (0)	6 (1.4)	1 (0.2)	0 (0)	0 (0)
Blood thyroid stimulating hormone increased	22 (5.1)	0 (0)	0 (0)	0 (0)	22 (5.2)	0 (0)	0 (0)	0 (0)
Lymphocyte count decreased	6 (1.4)	1 (0.2)	0 (0)	0 (0)	13 (3.1)	2 (0.5)	1 (0.2)	0 (0)
Platelet count decreased	14 (3.3)	0 (0)	1 (0.2)	0 (0)	76 (17.9)	27 (6.4)	4 (0.9)	0 (0)
Weight decreased	41 (9.6)	6 (1.4)	0 (0)	0 (0)	36 (8.5)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders								
Decreased appetite	94 (21.9)	9 (2.1)	0 (0)	0 (0)	106 (24.9)	2 (0.5)	0 (0)	0 (0)
Dehydration	9 (2.1)	4 (0.9)	0 (0)	0 (0)	8 (1.9)	5 (1.2)	0 (0)	0 (0)

	INLYTA + pembrolizumab n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Hyperglycemia	13 (3.0)	5 (1.2)	1 (0.2)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Hyperkalemia	10 (2.3)	1 (0.2)	0 (0)	0 (0)	4 (0.9)	1 (0.2)	0 (0)	0 (0)
Hypoalbuminemia	6 (1.4)	1 (0.2)	0 (0)	0 (0)	5 (1.2)	1 (0.2)	0 (0)	0 (0)
Hyponatremia	13 (3.0)	5 (1.2)	0 (0)	0 (0)	13 (3.1)	6 (1.4)	2 (0.5)	0 (0)
Hypophosphatemia	6 (1.4)	2 (0.5)	0 (0)	0 (0)	26	11 (2.6)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders								
Arthralgia	52 (12.1)	3 (0.7)	0 (0)	0 (0)	15 (3.5)	2 (0.5)	0 (0)	0 (0)
Arthritis	5 (1.2)	2 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	9 (2.1)	0 (0)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Muscle spasms	8 (1.9)	0 (0)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Muscular weakness	5 (1.2)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Myalgia	23 (5.4)	0 (0)	0 (0)	0 (0)	16 (3.8)	0 (0)	0 (0)	0 (0)
Pain in extremity	18 (4.2)	0 (0)	0 (0)	0 (0)	20 (4.7)	2 (0.5)	0 (0)	0 (0)
Nervous system disorders								
Dizziness	10 (2.3)	0 (0)	0 (0)	0 (0)	14 (3.3)	0 (0)	0 (0)	0 (0)
Dysgeusia	40 (9.3)	1 (0.2)	0 (0)	0 (0)	129 (30.4)	0 (0)	0 (0)	0 (0)
Headache	35 (8.2)	3 (0.7)	0 (0)	0 (0)	33 (7.8)	1 (0.2)	0 (0)	0 (0)
Lethargy	9 (2.1)	0 (0)	0 (0)	0 (0)	8 (1.9)	1 (0.2)	0 (0)	0 (0)
Paresthesia	6 (1.4)	0 (0)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Psychiatric disorders								
Insomnia	6 (1.4)	0 (0)	0 (0)	0 (0)	8 (1.9)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders								
Acute kidney injury	7 (1.6)	4 (0.9)	0 (0)	0 (0)	4 (0.9)	1 (0.2)	0 (0)	0 (0)
Hematuria	8 (1.9)	2 (0.5)	0 (0)	0 (0)	8 (1.9)	1 (0.2)	0 (0)	0 (0)
Proteinuria	66 (15.4)	11 (2.6)	0 (0)	0 (0)	39 (9.2)	6 (1.4)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders								
Cough	32 (7.5)	1 (0.2)	0 (0)	0 (0)	12 (2.8)	0 (0)	0 (0)	0 (0)
Dysphonia	98 (22.8)	1 (0.2)	0 (0)	0 (0)	12 (2.8)	0 (0)	0 (0)	0 (0)
Dyspnea	28 (6.5)	2 (0.5)	0 (0)	0 (0)	16 (3.8)	2 (0.5)	0 (0)	0 (0)
Epistaxis	19 (4.4)	0 (0)	0 (0)	0 (0)	32 (7.5)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	13	1 (0.2)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)

	INLYTA + pembrolizumab n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
	(3.0)							
Pneumonitis	11 (2.6)	0 (0)	0 (0)	1 (0.2)	1 (0.2)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders								
Alopecia	11 (2.6)	0 (0)	0 (0)	0 (0)	13 (3.1)	0 (0)	0 (0)	0 (0)
Dermatitis	5 (1.2)	1 (0.2)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Dermatitis acneiform	5 (1.2)	1 (0.2)	0 (0)	0 (0)	6 (1.4)	0 (0)	0 (0)	0 (0)
Dry skin	27 (6.3)	1 (0.2)	0 (0)	0 (0)	35 (8.2)	0 (0)	0 (0)	0 (0)
Erythema	7 (1.6)	0 (0)	0 (0)	0 (0)	8 (1.9)	0 (0)	0 (0)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	119 (27.7)	22 (5.1)	0 (0)	0 (0)	168 (39.5)	15 (3.5)	0 (0)	0 (0)
Pruritus	53 (12.4)	1 (0.2)	0 (0)	0 (0)	18 (4.2)	0 (0)	0 (0)	0 (0)
Rash	46 (10.7)	1(0.2)	0 (0)	0 (0)	38 (8.9)	1 (0.2)	0 (0)	0 (0)
Rash maculo-papular	17 (4.0)	1 (0.2)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Skin exfoliation	5 (1.2)	0 (0)	0 (0)	0 (0)	8 (1.9)	0 (0)	0 (0)	0 (0)
Vascular disorders								
Hypertension	179 (41.7)	91 (21.2)	0 (0)	0 (0)	184 (43.3)	78 (18.4)	0 (0)	0 (0)
Hypotension	5 (1.2)	1 (0.2)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)

Treatment related adverse events attributable to pembrolizumab and reported in <1% patients with renal cell carcinoma treated with pembrolizumab in combination with INLYTA (n=429) in KEYNOTE-426 by SOC are shown below:

Blood and lymphatic system: lymphopenia
Eye disorders: uveitis
Cardiac disorders: myocarditis
Gastrointestinal disorders: pancreatitis
Metabolism and nutrition disorders: diabetic ketoacidosis, diabetes mellitus
Musculoskeletal and connective tissue disorders: myositis
Nervous system disorders: myasthenic syndrome
Injury, poisoning and procedural complications: infusion related reaction
Renal and urinary disorders: nephritis

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-426 in patients with renal cell carcinoma are presented in Table 4.

Table 4. Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with Renal Cell Carcinoma treated with pembrolizumab and INLYTA at a Higher Incidence than in the Sunitinib Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-426)

	INLYTA + pembrolizumab n=429		Sunitinib n=425	
Laboratory Test	**All Grades n (%)**	**Grades 3-4 n (%)**	**All Grades n (%)**	**Grades 3-4 n (%)**
Activated Partial Thromboplastin Time Increased	80 (18.6)	4 (0.9)	51 (12.0)	0 (0)
Alanine Aminotransferase Increased	253 (59.0)	85 (19.8)	186 (43.8)	23 (5.4)
Aspartate Aminotransferase Increased	241 (56.2)	57 (13.3)	234 (55.1)	19 (4.5)
Calcium Increased	112 (26.1)	3 (0.7)	64 (15.1)	8 (1.9)
Glucose Decreased	52 (12.1)	1 (0.2)	29 (6.8)	1 (0.2)
Glucose Increased	262 (61.1)	38 (8.9)	224 (52.7)	13 (3.1)
Lymphocytes Decreased	142 (33.1)	46 (10.7)	195 (45.9)	33 (7.8)
Potassium Decreased	71 (16.6)	15 (3.5)	49 (11.5)	10 (2.4)
Potassium Increased	145 (33.8)	26 (6.1)	92 (21.6)	7 (1.6)
Sodium Decreased	149 (34.7)	33 (7.7)	124 (29.2)	33 (7.8)

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of INLYTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorder: Acute pulmonary oedema, cardiac failure, cardiac failure congestive, cardiomyopathy, cardiopulmonary failure, central venous pressure increased, diastolic dysfunction, ejection fraction decreased, left ventricular dysfunction, left ventricular failure, stress cardiomyopathy, pulmonary oedema, and ventricular dysfunction

Vascular disorders: Artery dissection and artery aneurysm (including rupture) have been reported in association with VEGFR TKIs, including Inlyta.

DRUG INTERACTIONS

Overview

Axitinib is metabolized in the liver, undergoing oxidative metabolism mediated primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, as well as uridine diphosphate-glucuronosyltransferase (UGT) 1A1. The aqueous solubility of axitinib is pH dependent, with higher pH resulting in lower solubility.

In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations. *In vitro* studies indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2 and CYP2C8. Co-administration of INLYTA with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g., theophylline).

In vitro studies indicated that axitinib inhibits P-glycoprotein. However, INLYTA is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations.

Drug-Drug Interactions

CYP3A4/5 Inhibitors

Co-administration of INLYTA with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) should be avoided as they may increase the plasma concentration of axitinib. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose reduction of INLYTA is recommended (see DOSAGE AND ADMINISTRATION).

Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean AUC 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of INLYTA in healthy volunteers.

CYP3A4/5 Inducers

Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, and phenobarbital) should be avoided due to the potential for reduced effectiveness of the drug. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma concentration of axitinib and should be avoided if possible. Selection of concomitant medication with no or

minimal CYP3A4/5 induction potential is recommended (see DOSAGE AND ADMINISTRATION).

Rifampin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5-mg dose of INLYTA in healthy volunteers.

Agents that Increase Gastric pH

The solubility of axitinib is lowered with increasing pH and co-administration of drugs that increase the gastric pH (e.g. proton pump inhibitors, H2-receptor antagonists, and antacids) could result in decreased plasma exposure to axitinib. It is recommended that antacids should be avoided for 2 hours before through 2 hours after dosing with INLYTA.

The effect of rabeprazole, a proton pump inhibitor (administered 20 mg once a day), on the steady state exposure of axitinib (dosed at 5 mg twice a day) was examined in 6 patients with solid tumours. Although the mean AUC and Cmax of axitinib were decreased by 15% (geometric mean ratio of 0.85 [90% CI: 0.59, 1.23]) and 42% (geometric mean ratio of 0.58 [90% CI: 0.26, 1.30]), respectively, in the presence of rabeprazole, the magnitude of the effect of the proton pump inhibitor was variable between patients.

Drug-Food Interactions

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase axitinib plasma concentrations and should be avoided.

INLYTA may be administered with or without food (see DOSAGE AND ADMINISTRATION). Administration of INLYTA with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*), is an inducer of CYP3A4/5, that may decrease axitinib plasma concentrations and should be avoided.

Drug-Laboratory Interactions

Interactions between INLYTA and laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

INLYTA as a single agent

The recommended oral starting dose of INLYTA is 5 mg twice daily (see CLINICAL TRIALS). INLYTA may be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY). INLYTA should be swallowed whole with a glass of water.

Dose increase or reduction is recommended based on individual safety and tolerability.

Patients who tolerate the INLYTA starting dose of 5 mg twice daily with no adverse reactions >Grade 2 (according Common Toxicity Adverse Event Criteria [CTCAE]) for two consecutive weeks, are normotensive, and are not receiving anti-hypertension medication, may have their dose increased to 7 mg twice daily. Subsequently, using the same criteria, patients who tolerate the INLYTA dose of 7 mg twice daily, may have their dose increased to a maximum of 10 mg twice daily.

Management of some adverse drug reactions may require temporary or permanent discontinuation and/or dose reduction of INLYTA therapy (see WARNINGS AND PRECAUTIONS). When dose reduction is necessary, the INLYTA dose may be reduced from 5 mg twice daily to 3 mg twice daily and further to 2 mg twice daily.

INLYTA in combination with Pembrolizumab

For the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) with no prior systemic therapy for metastatic RCC, the recommended dosing for INLYTA in combination with pembrolizumab is:

- Pembrolizumab – 200 mg administered as an intravenous infusion over 30 minutes once every 3 weeks until unacceptable toxicity, disease progression, or for up to 24 months or 35 doses, whichever is longer, in combination with;

- INLYTA – 5 mg orally twice daily (as described for INLYTA as single agent) until unacceptable toxicity or disease progression. As in KEYNOTE-426, when INLYTA is used in combination with Pembrolizumab, dose escalation may be considered for patients who tolerated the initial 5 mg INLYTA dose at intervals of six weeks or longer (i.e., at least 2 treatment cycles).

Refer to the pembrolizumab Product Monograph for recommended pembrolizumab dose information.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.

<u>Recommended Dose Modification for INLYTA used in combination with pembrolizumab</u>

In patients with RCC being treated with INLYTA in combination with pembrolizumab:

- If ALT or AST ≥ 3 times ULN but < 10 times ULN without concurrent total bilirubin ≥ 2

times ULN, withhold both pembrolizumab and INLYTA until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with INLYTA, consider dose reduction (as described for INLYTA as single agent).

- If ALT or AST ≥ 10 times ULN or >3 times ULN with concurrent total bilirubin ≥ 2 times ULN, permanently discontinue both pembrolizumab and INLYTA and consider corticosteroid therapy.

See manufacturer's Product Monograph for the coadministered product, pembrolizumab for toxicity management, dose adjustment guidelines for special populations, and contraindications.

When administering INLYTA in combination with pembrolizumab for the treatment of RCC, interrupt one or both as appropriate. No dose reductions are recommended for pembrolizumab. Withhold, dose reduce, or discontinue INLYTA.

Geriatric

No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.

Pediatric

Health Canada has not authorized an indication for pediatric use (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS, Special Populations).

Hepatic Impairment

No dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). Based on pharmacokinetic data, the starting dose of INLYTA should be decreased by approximately half in patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this patient population as an appropriate starting dose is unknown (see WARNINGS AND PRECAUTIONS, Hepatic Impairment, ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment

Axitinib has not been studied in patients with renal impairment. Caution should be exercised when administering INLYTA to patients with end-stage renal disease. No dose adjustments based on renal function are required in patients with mild to severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Strong CYP3A4/5 Inhibitors

Co-administration of INLYTA with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations and is not recommended (see DRUG INTERACTIONS).

Missed Dose

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no specific treatment for INLYTA overdose.

In the pivotal Phase 3 controlled clinical study with INLYTA for the treatment of patients with metastatic RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with INLYTA, patients who received starting doses of 10-mg twice daily or 20-mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, INLYTA should be withheld and supportive care instituted.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Axitinib was shown to inhibit tyrosine kinase VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. *In vitro*, axitinib has been shown to inhibit VEGF-mediated endothelial cell proliferation and survival. *In vivo*, axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibited metastases in many experimental models of cancer.

Pharmacodynamics

Electrocardiography

In a randomized, 2-way crossover study, 35 healthy subjects were administered a single oral 5 mg dose of INLYTA alone or on day 4 of a 7 day treatment with 400 mg/day ketoconazole. Axitinib at 5 mg was associated with a mean decrease in heart rate of 5 beats per minute. INLYTA did not result

in large mean changes in the QTc interval (> 20 msec) up to 3 hours post-dose, however smaller increases in the QTc interval (< 10 msec) cannot be ruled out.

Pharmacokinetics

Table 5. Axitinib Pharmacokinetic Parameter in Patients with Metastatic Renal Cell Carcinoma after Administration of 5 mg Axitinib Twice Daily for 15 Days (N=20)

	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	T_{max}[b] (hr)
Geometric mean (% CV)[a]	27.8 (79)	265 (77)	2.00 (1.0-2.5)

[a] % CV is the coefficient of variation around the arithmetic mean.
[b] T_{max} reported as median and range.

Absorption

Following administration of a single, oral 5 mg dose of axitinib, the median time to achieve peak concentrations ranged from 2.5 to 4.1 hours. Daily dosing results in approximately 1.4-fold accumulation as compared to administration of a single dose. Axitinib exhibits approximately linear steady-state pharmacokinetics at doses between 1 mg and 20 mg. The mean absolute bioavailability of axitinib following administration of a single, oral 5 mg dose of axitinib is 58%.

Administration of INLYTA with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting.

Distribution

Axitinib is highly bound (>99%) to human plasma proteins with preferential binding to albumin
and moderate binding to α_1-acid glycoprotein. In patients with metastatic RCC (n=20), at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) for clearance and apparent volume of distribution were 38 (80%) L/h and 160 (105%) L, respectively.

Metabolism

Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Excretion

The plasma half-life of axitinib ranges from 2.5 to 6.1 hours with steady state expected within 2 to 3 days of dosing.

Following oral administration of a 5-mg radioactive dose of axitinib, approximately 41% of the radioactivity was recovered in feces and 23% was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in feces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity. The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special Populations and Conditions

Age, Gender, and Race: Population pharmacokinetic analyses from patients with metastatic cancer (including metastatic RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Pediatrics (< 18 years): The safety and efficacy of INLYTA in pediatric patients have not been established. (See INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS, Special Populations and Conditions).

Hepatic Impairment: *In vitro* and *in vivo* data indicate that axitinib is primarily metabolized by the liver. Compared to subjects with normal hepatic function, systemic exposure following a single dose of INLYTA was similar in patients with mild hepatic impairment (Child-Pugh class A) and approximately 2-fold higher in patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, Special Populations).

Renal Impairment: INLYTA has not been studied in patients with renal impairment. Population pharmacokinetic analysis (based on pre-existing renal function) was carried out in 590 healthy volunteers and patients, including five with severe renal impairment (15 mL/min ≤CLcr <29 mL/min), 64 with moderate renal impairment (30 mL/min ≤CLcr <59 mL/min), and 139 with mild renal impairment (60 mL/min ≤CLcr <89 mL/min). Mild to severe renal impairment did not have meaningful effects on the pharmacokinetics of axitinib. Data from only one patient with end-stage renal disease are available.

STORAGE AND STABILITY

Store at a controlled room temperature of 25°C; excursions permitted to 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INLYTA tablets are supplied as follows:

- 1 mg: red, film-coated, oval tablets debossed with "Pfizer" on one side and "1 XNB" on the other and containing 1 mg of axitinib
- 3 mg: red film-coated, round tablets, debossed with "Pfizer" on one side and "3 XNB" on the other side and containing 3 mg of axitinib.
- 5 mg: red, film-coated, triangular tablets debossed with "Pfizer" on one side and "5 XNB" on the other and containing 5 mg of axitinib.
- 7 mg: red film-coated, diamond-shaped tablets, debossed with "Pfizer" on one side and "7 XNB" on the other side and containing 7 mg of axitinib.

Both tablets contain the following excipients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry II red as inactive ingredients. The Opadry II red film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

INLYTA 1 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.

INLYTA 3 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.

INLYTA 5 mg tablets are presented as follows:

- bottles of 60
- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.

INLYTA 7 mg tablets are presented as follows:

- bottles of 60

- foil/foil blister packs containing 28 ([14 tabs/blister] x [2 blisters]), or 56 ([14 tabs/blister] x [4 blisters]) tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

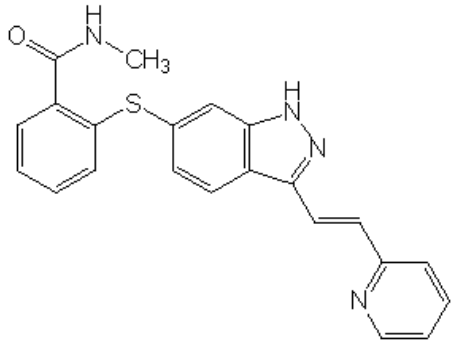
Proper name: Axitinib

Chemical name: *N*-methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl] benzamide

Molecular formula: $C_{22}H_{18}N_4OS$

Molecular mass: 386.47 Daltons

Structural formula:



Physicochemical properties: Axitinib is a white to light-yellow powder with a pKa of 4.8. The solubility of axitinib in aqueous media over the range pH 1.1 to pH 7.8 is in excess of 0.2 µg/mL. The partition coefficient (n-octanol/water) is 3.5.

CLINICAL TRIALS

INLYTA for the Treatment of Patients with Metastatic RCC of Clear Cell Histology after Failure of Prior Systemic Therapy with either a Cytokine or the VEGFR-TKI, Sunitinib

The safety and efficacy of INLYTA were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients (N=723) with metastatic RCC whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomized (1:1) to receive INLYTA (n=361) or sorafenib (n=362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QoL).

Study demographics and trial design

Table 6 presents the patient demographics in the INLYTA Phase 3 clinical study.

Of the 723 patients enrolled in this study, 389 patients (54%) had received 1 prior sunitinib-based therapy, 251 patients (35%) had received 1 prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8%) had received 1 prior bevacizumab-based therapy, and 24 patients (3%) had received 1 prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the INLYTA and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

Table 6. Summary of Patient Demographics in Phase 3 Trial of INLYTA (Intent to Treat Population)

Characteristic		INLYTA N=361 n (%)	Sorafenib N=362 n (%)
Age (years)	<65	238 (66)	238 (66)
	≥65	123 (34)	124 (34)
Gender	Male	265 (73)	258 (71)
	Female	96 (27)	104 (29)
Race	White	278 (77)	269 (74)
	Asian	77 (21)	81 (22)
	Black	1 (<1)	4 (1)
	Other	5 (1)	8 (2)
ECOG performance status	ECOG 0	195 (54)	200 (55)
	ECOG 1	165 (45)	160 (44)
	ECOG >1	1 (<1)	0 (0)
Geographic region	North America	88 (24)	98 (27)
	Europe	187 (52)	170 (47)
	Asia	73 (20)	79 (22)
	Other	13 (4)	15 (4)
MSKCC risk group	Favorable	100 (28)	101 (28)
	Intermediate	134 (37)	130 (36)
	Poor	118 (33)	120 (33)
	NA	9 (2)	11 (3)
Prior Treatment	Sunitinib-containing regimen	192 (53)	195 (54)
	Cytokine-containing regimen	126 (35)	125 (35)
	Bevacizumab-containing regimen	31 (9)	29 (8)
	Temsirolimus-containing regimen	12 (3)	13 (4)

ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan-Kettering Cancer Center

Study results

The average daily dose of INLYTA was approximately 5 mg twice daily. There was a statistically significant advantage for INLYTA over sorafenib for the primary endpoint of PFS (see Table 7 and Figures 1 to 3). The magnitude of the increase in median PFS in the axitinib arm as compared to the sorafenib arm varied in subgroups stratified by prior treatment. The subgroups of patients who failed prior therapy with temsirolimus or bevacizumab were too small for a reliable assessment of efficacy data. There was no statistically significant difference in OS between the two treatment arms.

Table 7. Efficacy Results by Independent Assessment

Endpoint/Study Population	INLYTA	Sorafenib	HR (95% CI)	P-value
PFS [a,b]				
Overall ITT	N= 361	N = 362		
Median, months (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	0.67 (0.54, 0.81)	<0.0001[c]
Sunitinib-refractory subgroup	N=194	N=195		
Median, months (95% CI)	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)	0.74 (0.57, 0.96)	0.0215[d]
Cytokine-refractory subgroup	N=126	N=125		
Median, months (95% CI)	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)	0.46 (0.32, 0.68)	<0.0001[d]
OS				
Overall ITT	N=361	N=362		
Median, months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
Sunitinib-refractory subgroup	N=194	N=195		
Median, months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
Cytokine-refractory subgroup	N=126	N=125		
Median, months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS

CI: Confidence interval; CR: Complete response; HR: Hazard ratio (INLYTA/sorafenib); ITT: Intent to treat; NE: Not estimable; NS: not statistically significant; OS: overall survival; PFS: Progression-free survival; PR: Partial response

[a] Time from randomization to progression or death due to any cause, whichever occurs first.

[b] Assessed by independent radiology review according to RECIST.

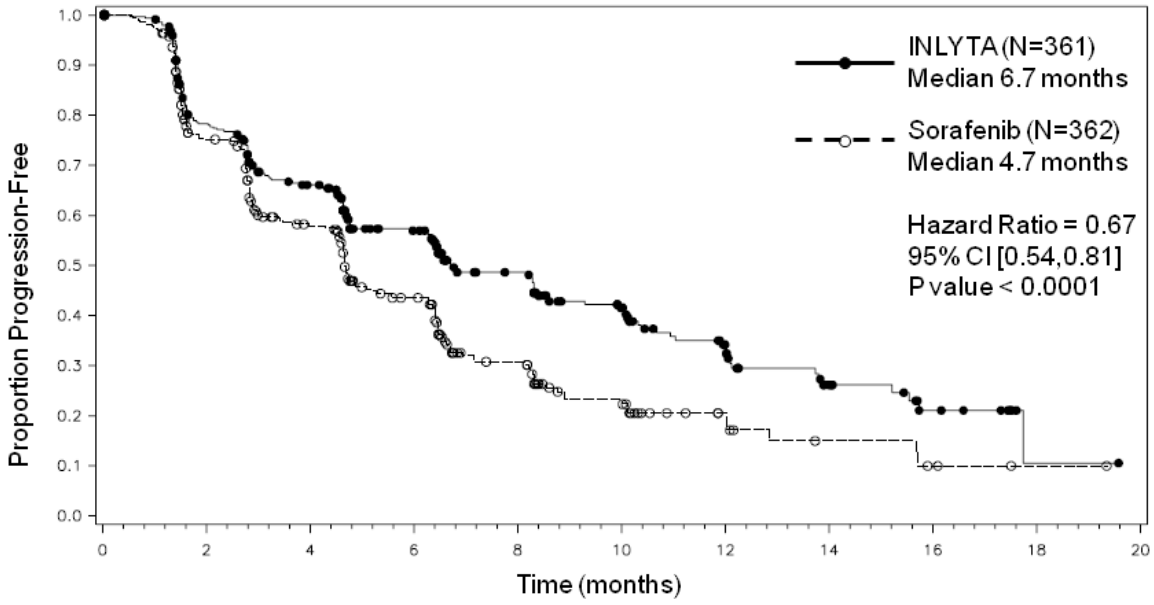
[c] Two-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the two-sided p-value is <0.023). One-sided p-value is <0.0001 from a log-rank test of treatment stratified by ECOG performance status and prior therapy (comparison is considered statistically significant if the one-sided p-value is <0.023).

[d] Two-sided p-value from a log-rank test of treatment stratified by ECOG performance status. One-sided p-values for sunitinib and cytokine-refractory subgroups are p=0.0107 and p<0.0001, respectively, from a log-rank test of treatment stratified by ECOG performance status.

The objective response rate (ORR) was assessed by an independent radiology review according to RECIST criteria. Overall, 19.4% [95% CI: 15.4%, 23.9%] of patients in the axitinib treatment arm and 9.4% [95% CI: 6.6%, 12.9%] of patients in the sorafenib arm achieved a confirmed ORR. The risk ratio (RR) was 2.06 [95% CI: 1.41, 3.00], with a two-sided p-value of 0.0001*. In the sunitinib-refractory subgroup, ORR was confirmed in 11.3% [95% CI: 7.2%, 16.7%] of patients in the axitinib arm and in 7.7% [95% CI: 4.4%, 12.4%] of patients in the sorafenib arm (RR of 1.48 [95% CI: 0.79, 2.75), two-sided p-value of 0.2169**). In the cytokine-refractory subgroup, the ORR was confirmed in 32.5% [95% CI: 24.5%, 41.5%] of patients in the axitinib arm and in 13.6% [95% CI: 8.1%, 20.9%] of patients in the sorafenib arm (RR of 2.39 [95% CI: 1.43, 3.99], two-sided p-value of 0.0004***).

*One-sided p-value = 0.0001; **One-sided p-value = 0.1085; ***One-sided p-value = 0.0002.

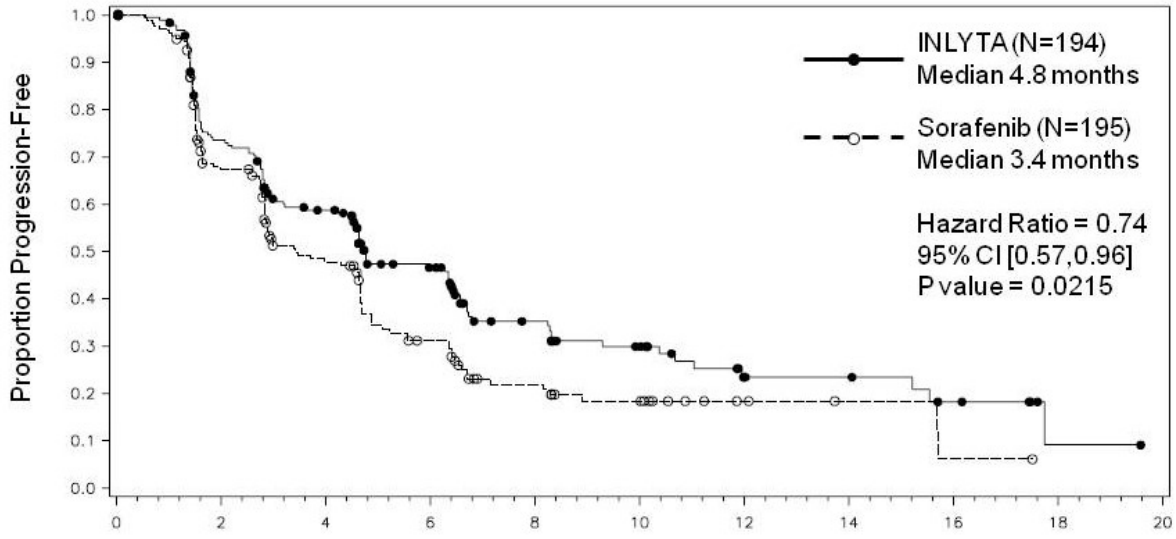
Figure 1. Kaplan-Meier Curve for Progression Free Survival by Independent Assessment for Overall Patient Population



Number of Subjects At Risk

INLYTA:	361	256	202	145	96	64	38	20	10	1	0
Sorafenib:	362	224	157	100	51	28	12	6	3	1	0

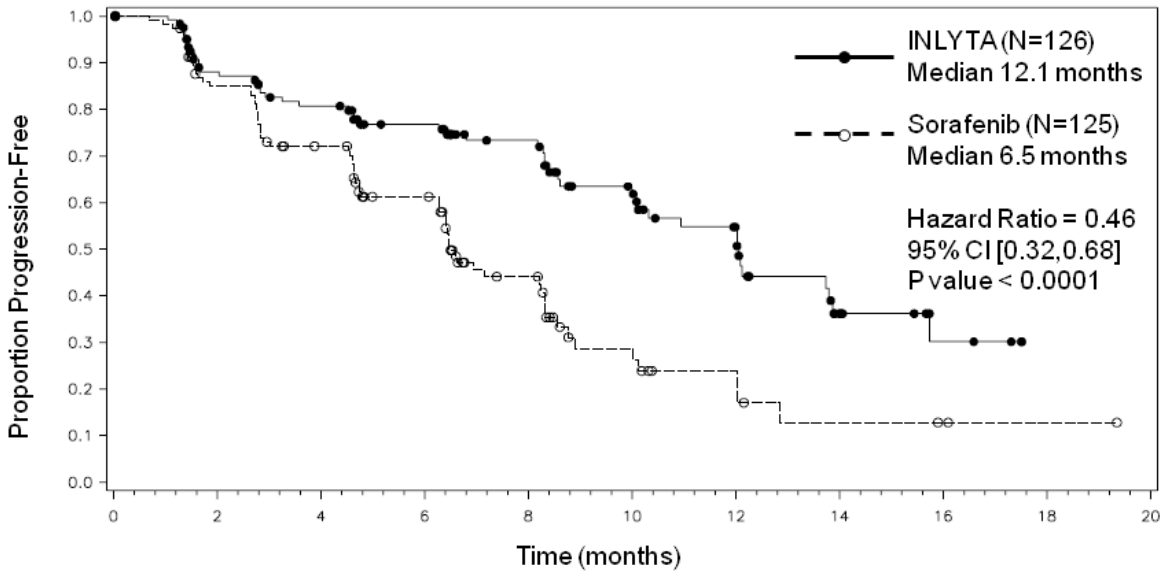
Figure 2. Kaplan-Meier Curve for Progression Free Survival by Independent Assessment for Prior Sunitinib Subgroup



Number of Subjects At Risk

INLYTA:	194	132	97	60	34	24	11	10	6	1	0
Sorafenib:	195	104	67	37	20	13	5	3	1	0	0

Figure 3. Kaplan-Meier Curve for Progression Free Survival by Independent Assessment for Prior Cytokine Subgroup



Number of Subjects At Risk											
INLYTA:	126	98	86	73	55	38	27	10	4	0	0
Sorafenib:	125	93	75	57	28	12	7	3	2	1	0

The efficacy of INLYTA was independent of the following demographic and baseline disease characteristics: age, gender, race, geographic region, MSKCC status and ECOG status.

In the pivotal study, the QoL assessments were based on self-reported global scores from protocol-specified questionnaires, EuroQoL EQ-5D and FKSI-15. Analysis compared patients on therapy in both arms. Although the assessments showed no statistically significant difference between treatment with axitinib or sorafenib, INLYTA demonstrated a 17% decrease in risk compared to sorafenib for the pre-specified time to deterioration (TTD) composite endpoint, defined as the time to the first occurrence of death, progression or meaningful deterioration in QoL based on the FKSI-15 questionnaire (HR = 0.83 [95% CI: 0.70, 0.98]; 2-sided p-value = 0.0282[§]).

[§]One-sided p-value = 0.0141.

INLYTA, in Combination with Pembrolizumab, for the Treatment of Adult Patients with Advanced or Metastatic RCC Naïve to Treatment

Study demographics and trial design

The efficacy of pembrolizumab in combination with axitinib was investigated in a randomized, multicenter, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced or metastatic RCC with clear cell component, regardless of PD-L1 tumour status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The trial excluded patients with autoimmune disease or a medical condition that required systemic immunosuppression within the last 2 years. Patients were randomized (1:1) to receive either pembrolizumab 200 mg once every 3 weeks in combination with axitinib 5 mg twice daily or sunitinib 50 mg once daily for 4 weeks and then off treatment for 2 weeks. Randomization was stratified by risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus "Rest of the World").

Treatment with pembrolizumab and axitinib continued until RECIST 1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for pembrolizumab, for up to 24 months or 35 administrations, whichever was longer. Administration of pembrolizumab and axitinib was permitted beyond RECIST 1.1-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year. Assessment of tumour status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter.

Among the 861 patients in KEYNOTE-426 (432 patients in the pembrolizumab combination arm and 429 in the sunitinib arm), baseline characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 99.9% had a Karnofsky Performance Score (KPS) of ≥ 70%; and patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

Study Results

The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). Secondary efficacy outcome measures were objective response rate (ORR) and response duration, as assessed by BICR using RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The median follow-up time for the pembrolizumab combination arm was 13.2 months (range: 0.1 – 21.5 months). Table 8 summarizes key efficacy measures at the pre-specified first interim analysis. OS and PFS benefits were observed in the Intent To Treat population and regardless of PD-L1 expression level.

Table 8: Efficacy Results for Patients with Advanced and Metastatic RCC in KEYNOTE-426

Endpoint	Pembrolizumab with axitinib n=432	Sunitinib n=429
Primary Efficacy Outcome Measure OS[a]		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	0.00005	
Primary Efficacy Outcome Measure PFS[a]		
Number of patients with event (%)	183 (42%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value†	0.00012	
Secondary Efficacy Outcome Measure ORR[a]		
Overall response rate‡ (95% CI)	59% (54, 64)	36% (31, 40)
Complete response	6%	2%
Partial response	53%	34%
p-Value§	<0.0001	

[a] The initial one-sided type 1 error rate level for OS, PFS, ORR were 0.023, 0.002, and 0.025 respectively. The corresponding p-value bounds at the interim analysis for OS and PFS were 0.0001 and 0.0013, respectively. For ORR, the corresponding p-value bound after alpha reallocation from PFS and OS following pre-specified multiplicity adjustment was 0.025.

* Based on the stratified Cox proportional hazard model

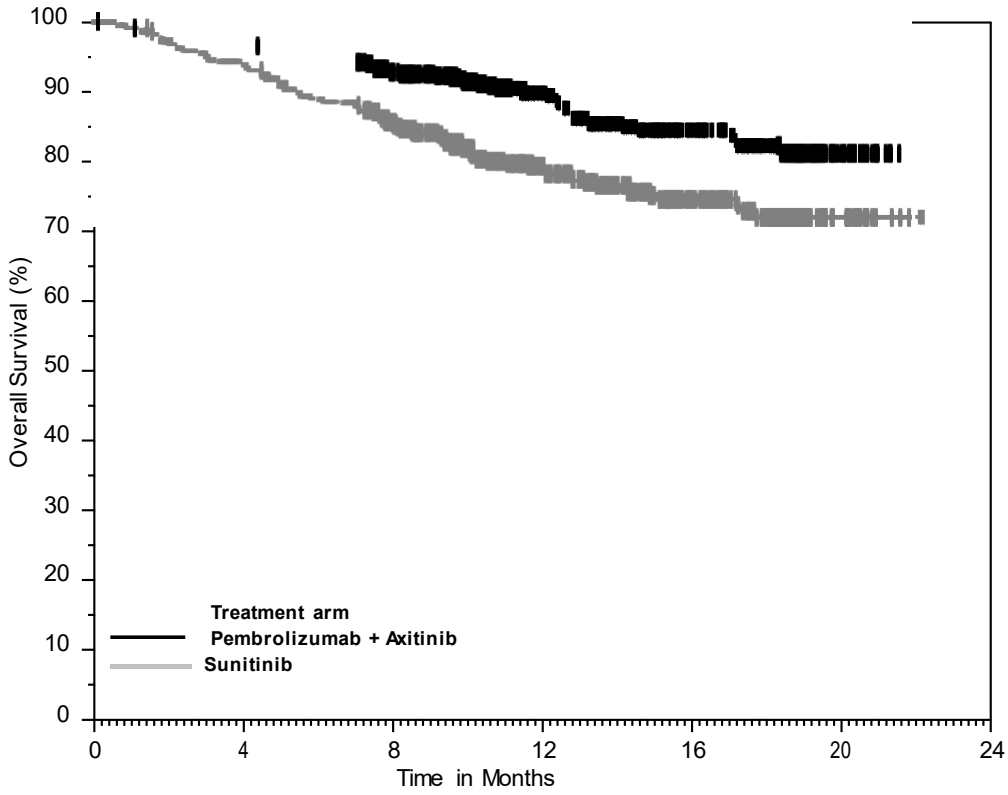
† Based on stratified log-rank test.

‡ Based on patients with a best overall response as confirmed complete or partial response

§ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

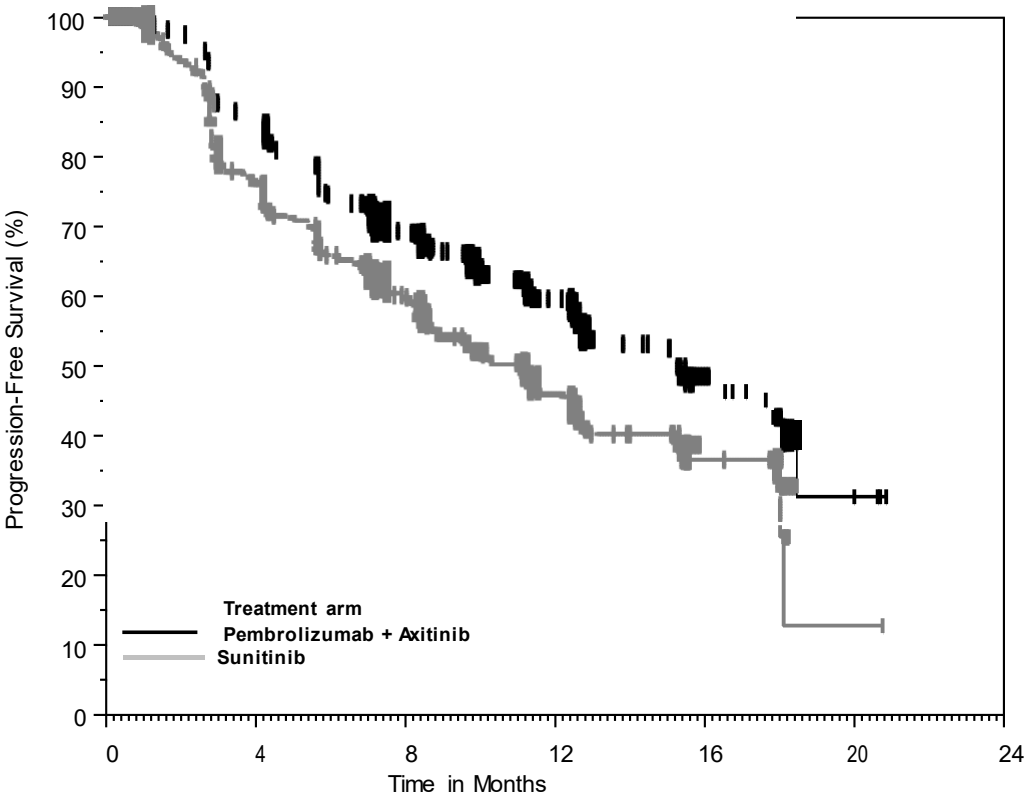
NA = not available

Figure 4: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



Number at Risk							
Pembrolizumab + Axitinib:	432	417	378	256	136	18	0
Sunitinib:	429	401	341	211	110	20	0

Figure 5: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



Number at Risk							
Pembrolizumab + Axitinib:	432	357	251	140	42	3	0
Sunitinib:	429	302	193	89	29	1	0

DETAILED PHARMACOLOGY

Also refer to PART I, ACTION AND CLINICAL PHARMACOLOGY.

Nonclinical Pharmacology

Safety Pharmacology

In safety pharmacology studies, there were no axitinib-related respiratory or cardiovascular effects in mice, rats or dogs following the administration of single oral doses of up to 30 mg/kg in mice and dogs and 500 mg/kg in rats. Hemodynamic changes (decreased blood pressure and temporally-related decreases and increases in heart rate relative to vehicle) were observed in the

mouse at 30 mg/kg/day following repeat-dose administration (approximately 35 times the human clinical exposure based on AUC at the recommended human starting dose).

In a human ether-à-go-go-related gene (hERG) potassium channel assay, 7% inhibition was observed at 3 μM, the highest evaluable concentration. The IC_{50} value for hERG current inhibition by axitinib is considered >3 μM, providing a safety margin ≥8000-fold the human clinical exposure based on Cmax at the recommended human starting dose.

TOXICOLOGY

The nonclinical toxicologic profile of axitinib has been extensively investigated, as shown in Table 9.

Table 9. Key Responses in Toxicology Studies with Axitinib

Single-Dose Toxicity						
Species/ Strain	**Duration**	**Dose[a] (mg/kg/day)**	**Key Response(s)**	**NOAEL** (mg/kg/day)	**LOAEL** (mg/kg/day)	**Safety Margin[b]**
Mouse/ CD-1	1 day	2000[c]	None observed	2000	>2000	NC
Dog/ Beagle	1 day	2000[c]	Fecal changes (nonformed, mucoid, discolored)	2000	>2000	19.1
Repeat-Dose Toxicity						
Species/ Strain	**Duration**	**Dose[a] (mg/kg/day)**	**Key Response(s)**	**NOAEL** (mg/kg/day)	**LOAEL** (mg/kg/day)	**Safety Margin[b]**
Mouse/ CD-1	14 days	50	Decreased body weight gain	250 (M)/ 50 (F)	500 (M)/ 250 (F)	351.2 (M)/ 23.5 (F)
		250	Decreased reticulocytes and thymus weights			
		500	Mortality; decreased red blood cell parameters; decreased testis/epididymis weights			
Mouse/ CD-1	28 days	10	None observed	10	30	1.4
		30	Increased MCH, MCV, reticulocytes; thickened growth plate			
		250	Testicular atrophy/degeneration; absence of corpora lutea.			
Mouse/ CD-1	13 or 26 weeks[d]	10	Incisor tooth odontopathy; decreased corpora lutea	<10	10	<1.5
		30	Decreased red blood cells; hyperplasia, inflammation of cecal mucosa			
		100	Mortality; hypospermia in the testes; thickened growth plate; uterine atrophy			

NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level (defined as the dose immediately above the NOAEL dose); NC = Not calculated; M = Male; F = Female; MCH = Mean corpuscular hemoglobin; MCV = Mean corpuscular volume.

[a] Total daily dose; twice daily (BID) dose delivered approximately 6 hours apart, unless otherwise indicated.

[b] Safety margin calculated as [total $AUC_{NOAEL, NOEL}$ /total AUC of 265 ng•h/mL at the recommended human dose of 5 mg BID]; AUC exposures in animals were obtained near termination unless otherwise noted.

[c] Single dose administration followed by a 14-day observation period.

[d] Study included a 4-week recovery period following 13 weeks of dosing.

Table 9. Key Responses in Toxicology Studies with Axitinib (cont'd)

Repeat-Dose Toxicity (cont'd)

Species/ Strain	Duration	Dose[a] (mg/kg/day)	Key Response(s)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Safety Margin[b]
Dog/ Beagle	14 days	25/50[e]	Decreased body weight; oral mucosal erythema.	25/50	50/100	12.5[f]
		50/100[e]	Dark areas on the intestinal mucosa, rectum, stomach			
		150/300[e]	Mortality; decreased reticulocytes			
Dog/ Beagle	28 days	10	Abnormal feces (discolored); delayed sexual maturity, absence of corpora lutea or small follicles	<10	10	<0.3
		30	Decreased reticulocytes; inflammation/ulceration of oral mucosa and tongue; gastrointestinal hemorrhage, inflammation, fibrinoid necrosis of vessels; thickened growth plate; pancreatic zymogen granule depletion with acinar cell proliferation or increased acinar cell apoptosis			
		100	Mortality; bone marrow hypocellularity; multinucleated giant cells in testes			
Dog/ Beagle	13 or 26 weeks[d]	6	Abnormal feces (nonformed, mucoid, liquid, discolored)	6	10	0.5
		10	Mortality; bone marrow erythroid hypocellularity; arteriolar fibrinoid necrosis with inflammation in the stomach; pancreatic zymogen granule depletion			
Dog/ Beagle	39 weeks[g]	1 (M)	Increased incidence of fecal abnormalities	1 (M)/ 6 (F)	3 (M)/ >6 (F)	0.02 (M)/ 0.6 (F)
		3 (M)	Decreased testis weights, testicular degeneration/atrophy and syncytial cells; epididymal luminal cellular debris			
		6 (M)	Epididymal hypospermia			
		6 (F)	Increased incidence of fecal abnormalities			

NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level (defined as the dose immediately above the NOAEL); M = Male; F = Female.

[a] Total daily dose; twice daily (BID) dose delivered approximately 6 hours apart, unless otherwise indicated.

[b] Safety margin calculated as [total $AUC_{NOAEL,\ NOEL}$ /total AUC of 265 ng•h/mL at the recommended human dose of 5 mg BID]; AUC exposures in animals were obtained near termination unless otherwise noted.

[d] Study included a 4-week recovery period following 13 weeks of dosing.

[e] X/Y where X = the dose delivered from Day 1 through the first dose of Day 9 and Y = the dose delivered from the second dose of Day 9 until the end of the treatment period on Day 14.

[f] Safety margin calculated based on Day 1 AUC exposure values in animals.

[g] Study included an 8-week recovery period following 39 weeks of dosing.

Table 9. Key Responses in Toxicology Studies with Axitinib (cont'd)

Reproductive and Developmental Toxicity

Male Reproduction and Fertility

Species/ Strain	Duration	Dose[a] (mg/kg/day)	Key Response(s)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Safety Margin[b]
Mouse/ CD-1	≥70 days	10	Reduced sperm density	<10	10	<3.6
		30	Reduced sperm density (statistically significant)			
		100	Reduced sperm count, reduced testes weights			

Female Reproduction and Fertility

Species/ Strain	Duration	Dose[a] (mg/kg/day)	Key Response(s)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Safety Margin[b]
Mouse/ CD-1	≥15 days	30	Decreased fertility and embryonic viability	<30	30	<10.8

Embryo-fetal Development

Species/ Strain	Duration	Dose[a] (mg/kg/day)	Key Response(s)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Safety Margin[b]
Mouse/ CD-1	DG6 to 17	1	Reversible delays in ossification within historical control range	1[h]	3[h]	0.1
		3	Cleft palate, common variations in skeletal ossification			

NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level (defined as the dose immediately above the NOAEL); DG = Day of gestation.

[a] Total daily dose; twice daily (BID) dose delivered approximately 6 hours apart, unless otherwise indicated.

[b] Safety margin calculated as [total $AUC_{NOAEL, NOEL}$ /total AUC of 265 ng•h/mL at the recommended human dose of 5 mg BID]; AUC exposures in animals were obtained near termination unless otherwise noted.

[h] Based on developmental not maternal effects.

Single Dose Toxicity

Axitinib was well-tolerated following single-dose administration in the mouse and dog at dosages up to 2000 mg/kg, as evidenced by the lack of any adverse effects during a 14-day observation period.

Repeat Dose Toxicity

The primary toxicities following repeat-dose administration were observed in the gastrointestinal, hematopoietic, musculoskeletal (physeal dysplasia and dental caries), and reproductive organs of the mouse and dog, where the axitinib effect on vascular beds was often reflected (see Table 6). Gastrointestinal toxicities (hemorrhage, inflammation, fibrinoid necrosis of vessels) in the dog were accompanied clinically by increased incidences of abnormal fecal excretions, though increases in fecal abnormalities were also observed in the dog without accompanying microscopic findings. Gastrointestinal effects in the mouse were characterized by mucosal hyperplasia and inflammation in the cecum and colon following 6 months of dosing. Hematopoietic effects primarily reflected an effect on the erythron, and were observed in studies of ≥14 days duration in the mouse and dog. Physeal dysplasia was observed in immature mice and dogs given axitinib for at least 1 month, and dental caries were observed in mice treated for more than 1 month. Male reproductive organ effects were identified in the testes/epididymis

(decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms) in mice and dogs. Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy. Partial to full reversibility was demonstrated for the gastrointestinal, hematopoietic, musculoskeletal, and reproductive toxicities observed following 13 or 39 weeks of dosing. Safety margins associated with the primary toxicities were identified in the therapeutic or sub-therapeutic range.

Reproductive and Developmental Toxicities

Male and Female Reproduction and Fertility

Axitinib has the potential to impair reproductive function and fertility in humans. Axitinib did not affect mating or fertility in male mice at any dose tested following at least 70 days of treatment with axitinib. However, reduced testicular weights, sperm density and count were noted following at least 70 days of treatment. In female mice, reduced fertility and embryonic viability were observed at all doses tested following at least 15 days of treatment with axitinib. As shown in Table 6, the no observed adverse effect level (NOAEL) for these findings was not identified.

Embryo-fetal Development
Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate and common variations in skeletal ossification at sub-therapeutic exposures (see Table 6).

Carcinogenicity

Carcinogenicity studies have not been performed with axitinib.

Genotoxicity
Axitinib was tested using a series of genetic toxicology assays consisting of *in vitro* bacterial reverse mutation (Ames), human lymphocyte chromosome aberration, and *in vivo* mouse bone marrow micronucleus assays. Axitinib was not mutagenic or clastogenic in these assays; however, axitinib was shown to be an aneugen in the *in vivo* mouse bone marrow micronucleus test at AUC exposures >18350 ng·h/mL.

REFERENCES

1. Baffert F, Le T, Sennino B, Thurston G, Kuo CJ, Hu-Lowe D, McDonald DM. Cellular changes in normal blood capillaries undergoing regression after inhibition of VEGF signaling. Am J Physiol Heart Circ Physiol 2006; 290(2): H547–559.

2. Hu-Lowe DD, Zou HY, Grazzini ML, Hallin ME, Wickman GR, Rewolinski DA, et al. Nonclinical anti-angiogenesis and anti-tumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res 2008; 14(22):7272–7283.

3. Liu G, Rugo HS, Wilding G, McShane TM, Evelhoch JL, Ng C, et al. Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: results from a phase I study. J Clin Oncol 2005; 23: 5464–5473.

4. Mancuso MR, Davis R, Norberg SM, O'Brien S, Sennino B, Nakahara T, et al. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. J Clin Invest 2006; 116(10): 2610–2621.

5. Rini BI, Escudier B, Tomczak P, Kaprin A, Hutson TE, Szczylik C, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomized phase 3 trial. Lancet 2011; 378 (9807): 1931-1939.

6. Rini BI, Wilding G, Hudes G, Stadler WM, Kim S, Tarazi J, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 4462-4468.

7. Rixe O, Bukowski RM, Michaelson MD, Wilding G, Hudes GR, Bolte O, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol 2007; 8(11): 975–984.

8. Rugo HS, Herbst RS, Liu G, Park JW, Kies MS, Steinfeldt HM, et al. Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. J Clin Oncol. 2005; 23(24): 5474-5483.

PART III: CONSUMER INFORMATION

PRINLYTA®
(axitinib tablets)

This leaflet is part III of a three-part "Product Monograph" published when INLYTA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INLYTA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

INLYTA is used in the treatment of adult patients with metastatic (the spread of cancer to other parts of the body) kidney cancer (Renal Cell Carcinoma or RCC) who have had other treatments.

INLYTA is used with another drug called pembrolizumab to treat adults with kidney cancer (Renal Cell Carcinoma or RCC). It is used when the kidney cancer has spread to other parts of the body and has not been treated before.

What it does:

INLYTA specifically targets the activity of certain enzymes called tyrosine kinases that play a major role in transmitting the chemical signals required for critical cellular processes. INLYTA prevents growth of blood vessels from surrounding tissue to a solid tumour, and prevents the growth of cancer cells.

When it should not be used:

Do not take INLYTA:

- If you are allergic (hypersensitive) to axitinib or any of the other ingredients of INLYTA, listed under "**What the nonmedicinal ingredients are:**"

What the medicinal ingredient is:

axitinib

What the nonmedicinal ingredients are:

The nonmedicinal ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and Opadry® II Red. The Opadry® II Red film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

What dosage forms it comes in:

INLYTA is available as oral tablets containing 1 mg, 3mg, 5 mg, or 7 mg of axitinib.

INLYTA 5 mg tablets are film-coated, triangular shaped tablets debossed with "Pfizer" on one side and "5 XNB" on the other side.

INLYTA 1 mg tablets are film-coated, oval shaped tablets debossed with "Pfizer" on one side and "1 XNB" on the other side.
INLYTA 3 mg tablets are film-coated, round shaped tablets debossed with "Pfizer" on one side and "3 XNB" on the other side.

INLYTA 7 mg tablets are film-coated, diamond shaped tablets debossed with "Pfizer" on one side and "7 XNB" on the other side.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

INLYTA should be prescribed and managed by a doctor experienced in the use of cancer drugs.

INLYTA has not been studied in patients with severely reduced liver function (severe hepatic impairment).

Possible serious side effects with INLYTA include:

- high blood pressure and high blood pressure crisis
- blood clots in the vein or the artery
- bleeding (in the brain, respiratory and gastrointestinal tract)
- gastrointestinal perforation (a tear in the stomach or intestine wall) that may result in death
- reversible posterior leukoencephalopathy syndrome, symptoms include headache, confusion, seizures, and visual loss.
- heart problems that may lead to death.

BEFORE you use INLYTA talk to your doctor or pharmacist:

- If you have high blood pressure and its complications, including separation of the layers of the arterial wall (Artery Dissection).
- If you have thyroid gland problems.
- If you have had a recent problem with blood clots in your veins or arteries (types of blood vessels) including stroke, heart attack, embolism, or thrombosis.
- If you have bleeding problems.
- If you have an unhealed wound following surgery or if you have surgery scheduled.
- If you have liver or kidney problems.
- If you have any gastrointestinal disorders.
- If you have any neurological disorders.
- If you have heart problems.
- If you are pregnant or planning to become pregnant. INLYTA may affect male and female fertility.
- If you are breast-feeding or planning to breast-feed. It is not known if INLYTA passes into your breast milk. You and your doctor should decide if you will take INLYTA or breast-feed. You should not do both.
- If you have a rare hereditary problem of lactose intolerance.

Use in children (under 18 years):
INLYTA is not recommended for use in children since it has not been studied in children under 18 years of age.

Contraception:

- INLYTA may cause birth defects.
- Women should not get pregnant and should not plan to get pregnant during treatment with INLYTA.
- Men and women should use effective birth control during treatment with INLYTA. Talk with your doctor about effective birth control methods.
- Call your doctor right away if you become pregnant during treatment with INLYTA.

INTERACTIONS WITH THIS MEDICATION

Taking other medicines:
Tell your doctor if you are taking other drugs, including prescription and non-prescription, vitamins, and herbal products. INLYTA and certain other medicines can interact with each other and cause serious side effects.

Especially tell your doctor if you take:

- Dexamethasone (a steroid).
- Medicine for: asthma, tuberculosis (TB), seizures (epilepsy), bacterial infections (antibiotics), fungal infections (antifungals), depression, or HIV (AIDS).
- Herbal medicines (such as St. John's wort).
- Antacids, such as rabeprazole, which should be avoided 2 hours before and 2 hours after taking INLYTA.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine. Do not take other medicines with INLYTA until you have talked with your doctor.

Also, do not drink grapefruit juice or eat grapefruit as they may change the amount of INLYTA in your body.

PROPER USE OF THIS MEDICATION

Usual dose:

- Take INLYTA exactly as prescribed by your doctor.
- Usual Starting Dose: 5 mg taken by mouth twice a day with or without food.
- Maximum dose: 10 mg twice daily.
- Swallow the tablet whole with a glass of water.

- Do not drink grapefruit juice or eat grapefruit as they may change the amount of INLYTA in your body.
- You may take INLYTA alone or with pembrolizumab. If you take INLYTA with pembrolizumab, it is important that you read the Patient Medication Information for pembrolizumab. To find this information:
  - Go online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
  - Contact your healthcare professional.

Overdose:

If you think you may have accidentally taken too many INLYTA tablets, immediately contact your doctor, or poison control centre, or go to the emergency room of the nearest hospital even if there are no symptoms.

Missed Dose:
If you vomit or miss a dose of INLYTA, don't take an additional dose. Take the next dose at the usual time. Call your doctor right away if you take too much INLYTA.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

INLYTA may cause the following serious side effects:

- High blood pressure
- Decreased thyroid function (hypothyroidism)
- Increased bleeding problem
- Blood clot in the veins, arteries, or lungs
- Tear in the intestinal wall (perforation of the bowel)

Very common side effects (these are likely to affect more than or equal to 1 in every 10 people):

- decreased thyroid gland function (hypothyroidism) with symptoms such as fatigue, constipation, dry skin, weight gain
- diarrhea (frequent or loose bowel movements)
- nausea
- vomiting
- constipation
- soreness of the mouth, tongue, or throat
- abdominal pain
- upset stomach
- tiredness or feeling weak
- hoarseness (disorder of the voice)
- decreased appetite
- decreased weight
- joint pain
- pain in extremity
- headache
- taste disturbance
- protein in urine
- cough
- breathlessness
- rash, redness, itching or peeling of your skin (hand-foot syndrome)
- dry skin
- itchy skin
- hair loss
- redness of skin
- high blood pressure
- bleeding problems (nosebleed, blood in urine, rectal bleeding, coughing up blood)

Common side effects (these are likely to affect more than or equal to 1 but less than 10 in every 100 people):

- dizziness
- upper stomach pain
- muscle pain
- dehydration
- decreased amount of red blood cells in the blood
- hemorrhoids
- ringing in the ears
- increase in lipase (an enzyme from the pancreas)
- blood clot in the lung
- formation of blood clot in deep vein
- some vascular disorders of the retina
- increased red blood cells in the blood
- transient stroke-like episodes
- increased thyroid gland function (hyperthyroidism) with symptoms such as rapid weight loss, sweating, faster heartbeat
- excess bilirubin in blood with symptoms such as yellow coloring of the skin
- painful tongue
- kidney failure
- heart problems

Uncommon side effects (these are likely to affect more than or equal to 0.1 but less than 1 in every 100 people):

- severe and rapid increase in blood pressure (hypertensive crisis)
- loss of monocular vision (retinal artery occlusion)
- a neurological disorder called reversible posterior leukoencephalopathy syndrome with symptoms such as headache, seizures, lethargy, confusion, blindness and other visual disturbances

The most common side effects when INLYTA is given in combination with pembrolizumab are:

- diarrhea;
- nausea;
- inflammation of the moist, inner lining of the body, like the mouth, nose, lungs, stomach;
- feeling unusually tired or weak;
- fatigue;
- increase in liver enzyme levels;
- decreased appetite;
- joint pain;
- protein in urine;
- voice change;
- itching;
- rash;
- high blood pressure.

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the side effects with INLYTA. Ask your doctor or pharmacist for more information.

INLYTA can cause abnormal exam, blood and urine test results. Your doctor will do some tests before, during and after your treatment. The doctor will interpret the results. They will tell you if there are any abnormalities in your tests that might need treatment.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
high blood pressure		√	
bleeding problems (nosebleed, blood in urine, rectal bleeding, coughing up blood)		√	
Hyperthyroidism (high thyroid hormone): anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly feelings of having rapid, fluttering or pounding heart		√	
Palmar-plantar erythrodysaesthesia syndrome (also called Hand-Foot syndrome): red or swollen palms, thick calluses and blisters of the hands and soles of the feet, tingling or burning, tightness of the skin		√	
Common			
Heart problems (cardiomyopathy) with symptoms such as shortness of breath, fatigue, and swollen feet, ankles, legs and abdomen		√	
Uncommon			
decreased thyroid gland function (hypothyroidism) with symptoms such as fatigue, constipation, dry skin, weight gain		√	
problem with blood clots in your veins or arteries (types of blood vessels)		√	
perforation of the bowel (tear in your intestinal wall)		√	

***Myasthenia gravis:** muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing		√	
***Myocarditis (inflammation of the heart muscle and lining around the heart):** abnormal heartbeat, chest pain that may resemble a heart attack, fatigue, fever and other signs of infection including headache, muscle aches, sore throat, diarrhea, or rashes, joint pain or swelling, leg swelling, shortness of breath		√	
***Flesh-Eating Disease** (bacterial infection of the skin): A red, warm, or swollen area of skin that spreads quickly. Severe pain, including pain beyond the area of the skin that is red, warm, or swollen. Fever.		√	
***Pneumonitis (inflammation of the lung tissue):** shortness of breath, cough, fatigue, loss of appetite, unintentional weight loss		√	
Very rare			
Artery Dissection (sudden severe pain in the back, chest or abdomen)		√	
Artery Aneurysm (a bulge in the wall of any artery including in the chest, arms, legs, heart, and brain): symptoms will differ by the site. They can be cough, coughing up blood. Strong pain high in your neck or in your back when you didn't hurt yourself. Problems swallowing. Hoarse voice. Unusual pulsing in your chest or abdomen.		√	

***Serious Side Effects linked to the use of INLYTA with pembrolizumab.**

This is not a complete list of side effects. For any unexpected effects while taking INLYTA, contact your doctor or pharmacist.

HOW TO STORE IT

- Store INLYTA tablets at a controlled room temperature of 25°C (excursions permitted to 15 - 30°C).
- Store in the original package.
- Do not use after the expiry date (EXP) shown on the outer pack and label.
- Do not use any pack that is damaged or shows signs of tampering.
- Keep INLYTA, and all other medicines, out of the reach and sight of children.
- As with all medicines, INLYTA should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of the medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.pfizer.ca or can be obtained by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada ULC.

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