אוקטובר 2023

Gavreto®
גברטו
Pralsetinib 100mg
Hard capsules

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על מספר עדכונים בעלון לרופא ובעלון לצרכן של התכשיר גברטו. בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויות הרשומות לתכשיר בישראל:

1.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC).

1.2 RET-Mutant Medullary Thyroid Cancer

GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.

1.3 RET Fusion-Positive Thyroid Cancer

GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

הסבר:
<u>טקסט עם קו תחתי</u> מציין טקסט שהוסף לעלון.
~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו ע"י משרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079 טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

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ב ב ר כ ה,

בתאור צפרי-חגג
מחלקת רישום

לילי אדר
רוקחת ממונה

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in ~~10~~12% of patients who received GAVRETO, including ~~2.7~~3.3% with Grade 3-4, and % with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD *[see Dosage and Administration (2.3)]*.

5.2 Hypertension

Hypertension occurred in ~~29~~35% of patients, including Grade 3 hypertension in ~~14~~18% of patients *[see Adverse Reactions (6.1)]*. Overall, % had their dose interrupted and ~~3.2~~4.8% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Serious hepatic adverse reactions occurred in ~~2.~~1.5% of patients treated with GAVRETO. Increased AST occurred in ~~69~~49% of patients, including Grade 3 or 4 in % and increased ALT occurred in ~~46~~37% of patients, including Grade 3 or 4 in ~~6~~4.8% *[see Adverse Reactions (6.1)]*. The median time to first onset for increased AST was 15 days (range: 5 days to ~~1~~2.5 years) and for increased ALT was ~~22~~ 24 days (range: 7 days to ~~1~~3.7 years).

Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity *[see Dosage and Administration (2.3)]*.

5.4 Hemorrhagic Events

Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in ~~2.5~~4.1% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage *[see Dosage and Administration (2.3)]*.

[…]

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Risk of Impaired Wound Healing *[see Warnings and Precautions (5.6)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438540 patients ~~with *RET* altered solid tumors, including with *RET* fusion-positive NSCLC (n = 220), and *RET* altered thyroid cancer (n=138),~~ in ARROW *[see Clinical Studies (14)]*. Among 438540 patients who received GAVRETO, 4771% were exposed for 6 months or longer and 2357% were exposed for greater than one year.

The most common adverse reactions (≥ 25%) were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, ~~musculoskeletal pain and diarrhea~~ edema, pyrexia, and cough. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased~~,~~ leukocytes, ~~calcium (corrected),~~ decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased calcium (corrected), decreased platelets, ~~and~~ increased alkaline phosphatase , increased potassium, decreased potassium and increased bilirubin.

RET Fusion-Positive Non-Small Cell Lung Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220281 patients with metastatic rearranged during transfection (*RET* fusion-positive) non-small cell lung cancer (NSCLC) in ARROW *[see Clinical Studies (14.1)]*. Among the 220281 patients who received GAVRETO, 4272% were exposed for 6 months or longer and 1956% were exposed for ~~greater than one~~ ≥1 year.

The median age was 60 years (range: 26 to 87 years); 5254% were female, 5046% were White, 4146% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 4565% of patients who received GAVRETO. The most frequent serious adverse ~~reaction~~reactions (in ≥ 2% of patients) ~~was~~were pneumonia, anemia, pneumonitis, pyrexia, sepsis, urinary tract infection, coronavirus infection, pleural effusion, dyspnea, musculoskeletal pain, pulmonary embolism, and

~~pyrexia~~seizure. Fatal adverse reactions occurred in ~~5~~7% of patients; fatal adverse reactions which occurred in > 1 patient included pneumonia (n = ~~3) and~~8), sepsis (n~~=2~~=3) and COVID (n=3).

Permanent discontinuation due to an adverse reaction occurred in ~~15~~20% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in ~~> 1 patient~~≥ 2% of patients included pneumonitis (~~1.8%),~~3.2%), and pneumonia (~~1.8%), and sepsis (1~~2.8%).

Dosage interruptions due to an adverse reaction occurred in ~~60~~73% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included ~~neutropenia~~anemia, pneumonia, pneumonitis, ~~anemia~~neutropenia, hypertension, ~~pneumonia,~~ increased blood creatine phosphokinase, fatigue, pyrexia~~,~~. increased aspartate aminotransferase (AST), increased ~~blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased~~ alanine aminotransferase (ALT), coronavirus infection, diarrhea, hypophosphatemia, musculoskeletal pain, thrombocytopenia, dyspnea, hemorrhage, leukopenia, lymphopenia, edema, sepsis, and ~~dyspnea~~vomiting.

Dose reductions due to adverse reactions occurred in ~~36~~51% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included anemia, neutropenia, ~~anemia,~~ pneumonitis, ~~neutrophil count decreased, fatigue,~~ increased blood creatine phosphokinase, leukopenia, hypertension, fatigue, pneumonia, and ~~leukopenia~~lymphopenia.

Table 4 summarizes the adverse reactions in ~~*RET* Fusion-Positive~~patients with NSCLC ~~Patients~~ in ARROW.

Table 4: Adverse Reactions (≥ 15%) in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Adverse ~~Reactions~~reaction	**GAVRETO N=~~220~~ = 281**	
	Grades 1~~-~~ - 4 (%)	**Grades 3~~-~~ or 4 (%)**
~~**General**~~		
~~Fatigue[1]~~	~~35~~	~~2.3*~~
~~Pyrexia~~	~~20~~	~~0~~
~~Edema[2]~~	~~20~~	~~0~~
Gastrointestinal disorders		
Constipation	~~35~~45	~~1*~~0.7
Diarrhea~~Diarrhea[3]~~	~~24~~30	~~3.~~2~~*~~.5
Nausea	19	0
Dry ~~Mouth~~mouth	~~16~~17	0
General Disorders and Administration Site Conditions		
Edema[1]	44	0
Fatigue[2]	42	2.5
Pyrexia	29	0.7
Musculoskeletal and Connective Tissue Disorders		

Musculoskeletal ~~Pain[4]~~pain[3]	~~32~~44	~~0~~2.5	
Increased Blood Creatine Phosphokinase	19	9	
Vascular			
~~Hypertension[5]~~Hypertension[4]	~~28~~38	~~14*~~18	
Respiratory, thoracic and mediastinal disorders			
~~Cough[6]~~Cough[5]	~~23~~36	0.~~5*~~4	
~~**Infections**~~Dyspnea	21	2.1	
Infection and Infestations			
Pneumonia[6]	24	13	
Urinary tract infection	16	3.6	
Metabolism and Nutrition Disorders			
Decreased appetite	18	1.1	
Nervous system disorders			
~~Pneumonia[7]~~Taste disorder[7]	17	~~8~~0	
Headache[8]	15	1.1	
Skin and subcutaneous tissue disorders			
Rash[9]	17	0	

[1] Includes the preferred terms: Edema, Swelling face, Peripheral swelling, Generalized oedema, Edema peripheral, Face edema, Periorbital edema, Eyelid edema, Swelling, Localized edema

[2] Includes the preferred terms: Fatigue, Asthenia

[3] Includes the preferred terms: Myalgia, Arthralgia, Pain in extremity, Neck pain, Musculoskeletal pain, Back pain, Musculoskeletal chest pain, Bone pain, Musculoskeletal stiffness

[4] Includes the preferred terms: hypertension, blood pressure increased

[5] Includes the preferred terms: Cough, Productive Cough, upper-airway cough syndrome

[6] Includes the preferred terms: Pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia cytomegaloviral, Atypical pneumonia, Lung infection, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia streptococcal, Pneumonia viral, Pneumonia pseudomonal

[7] Includes the preferred terms: Dysgeusia, Ageusia

[8] Includes the preferred terms: Headache, Tension Headache

[9] Includes the preferred terms: Rash, Rash maculo-papular, Dermatitis acneiform, Erythema, Rash generalized, Rash papular, Rash macular, Rash erythematous

~~[1] Fatigue includes fatigue, asthenia~~
~~[2] Edema includes edema peripheral, face edema, periorbital edema, eyelid edema, edema generalized, swelling~~

~~3~~

Clinically relevant adverse reactions occurring in < 15% of patients included pneumonitis (14%), vomiting (14%), abdominal pain (14%), and stomatitis (6%).

~~Diarrhea includes diarrhea, colitis, enteritis~~
~~[4] Musculoskeletal pain includes back pain, myalgia, arthralgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal stiffness, arthritis, spinal pain~~
~~[5] Hypertension includes hypertension, blood pressure increased~~
~~[6] Cough includes cough, productive cough, upper-airway cough syndrome~~
~~[7] Pneumonia includes pneumonia, atypical pneumonia, lung infection, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal~~
~~*Only includes a Grade 3 adverse reaction~~

Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=~~220~~281	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	~~74~~80	3.2~~.3~~
Increased ALT	~~49~~58	~~2.~~3.9
~~Increased alkaline phosphatase~~ Decreased albumin	~~42~~52	~~1.~~80
Decreased calcium (corrected)	~~39~~50	1.8
~~Decreased albumin~~	~~36~~	~~0~~
Decreased phosphate	~~35~~50	~~11~~17
Increased creatinine	~~33~~45	~~0.5~~1.4
Increased alkaline phosphatase	43	2.5
Decreased sodium	~~29~~42	~~7~~10
Decreased Potassium	27	4.6
Increased ~~potassium~~Potassium	~~26~~27	~~0.9~~1.8
Decreased Magnesium	25	0
Increased Bilirubin	20	1.8
Hematology		
Decreased ~~neutrophils~~leukocytes	~~61~~79	~~16~~11
Decreased hemoglobin	~~58~~78	~~9~~18
Decreased lymphocytes	~~56~~73	~~19~~32
Decreased neutrophils	70	21
Decreased platelets	~~27~~33	~~3.2~~5

~~Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 216 to 218 patients.~~

Clinically relevant laboratory abnormalities occurring in < 20% of patients who received GAVRETO included increased ~~phosphate (10%).~~ magnesium (14%).

RET-altered Thyroid Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with *RET*-altered Thyroid Cancer (including 19 patients with *RET* fusion-positive thyroid cancer) in ARROW *[see Clinical Studies (14.2, ~~14.3~~)]*. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥ 2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reaction occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included fatigue, pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting, pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue and thrombocytopenia.

Table 6 summarizes the adverse reactions occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 6: Adverse Reactions (≥ 15%) in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Adverse Reactions	**GAVRETO N=138**	
	Grades 1-4 (%)	**Grades 3-4 (%)**
Musculoskeletal		
Musculoskeletal Pain[1]	42	0.7*
Gastrointestinal		
Constipation	41	0.7*
Diarrhea[2]	34	5*
Abdominal Pain[3]	17	0.7*
Dry mouth	17	0
Stomatitis[4]	17	0.7*
Nausea	17	0.7*

Vascular		
Hypertension	40	21*
General		
Fatigue[5]	38	6*
Edema[6]	29	0
Pyrexia	22	2.2*
Respiratory		
Cough[7]	27	1.4*
Dyspnea[8]	22	2.2*
Nervous System		
~~Headache~~[7]Headache[9]	24	0
Peripheral ~~Neuropathy~~[8]Neuropathy[10]	20	0
~~Dizziness~~[9]Dizziness[11]	19	0.7*
~~Dysgeusia~~[10]Dysgeusia[12]	17	0
~~**Respiratory**~~		
~~Cough~~[11]	~~27~~	~~1.4*~~
~~Dyspnea~~[12]	~~22~~	~~2.2*~~
Skin and Subcutaneous		
Rash[13]	24	0
Metabolism and Nutrition		
Decreased Appetite	15	0

[1] Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain,
musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
[2] Diarrhea includes colitis, diarrhea
[3] Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
[4] Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
[5] Fatigue includes asthenia, fatigue
[6] Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
[7] Cough includes cough, productive cough, upper-airway cough syndrome
[8] Dyspnea includes dyspnea, dyspnea exertional
[9] Headache includes headache, migraine
[8]
[10] Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
[9][11] Dizziness includes dizziness, dizziness postural, vertigo
[10]
[12] Dysgeusia includes ageusia, dysgeusia
[11] ~~Cough includes cough, productive cough, upper-airway cough syndrome~~
[12] ~~Dyspnea includes dyspnea, dyspnea exertional~~
[13] Rash includes dermatitis, dermatitis acneiform, eczema, palmar-plantar, erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular
* Only includes a Grade 3 adverse reaction

Clinically relevant adverse reactions in < 15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

[…]

8.5 Geriatric Use

Of the 438540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 3031% were 65 years or ~~older.~~ and over, while 7% were 75 years and over.

No overall differences in pharmacokinetics (PK), safety or ~~efficacy~~effectiveness were observed ~~in comparison with~~between patients aged 65 years or older and younger patients.

[…]

14 CLINICAL STUDIES

14.1 Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of GAVRETO was evaluated in patients with *RET* fusion-positive metastatic NSCLC in a multicenter, non-randomized, open-label, multi-cohort clinical trial (ARROW, NCT03037385). The study enrolled, in separate cohorts, patients with metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Identification of a *RET* gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. Among the 114237 patients in the efficacy population(s) described in this section, samples from 5940% of patients were retrospectively tested with the ~~Life~~LIFE Technologies Corporation Oncomine Dx Target Test (ODxTT). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. Patients received GAVRETO 400 mg orally once daily until disease progression or unacceptable toxicity.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by a blinded independent central review (BICR) according to RECIST v1.1.

Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 87130 patients with *RET* fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy enrolled into a cohort of ARROW.

The median age was 6059 years (range: 2826 to 85); 4951% were female, 5340% were White, 3550% were Asian, 4.6% were Hispanic/Latino. ECOG performance status was 0-1 (9495%) or 2 (63.8%), 99% of patients had metastatic disease, and 4341% had either a history of or current CNS metastasis. Patients received a median of 2 prior systemic therapies (range 1–6); 4542% had prior anti-PD-1/PD-L1 therapy and 2527% had prior kinase inhibitors. A total of 5248% of the patients received prior radiation therapy. *RET* fusions were detected in 7780% of patients using NGS (4537% tumor samples; 2615% blood or plasma samples, 628% unknown), 2113% using FISH, and 2% using other methods. The most common *RET* fusion partners were KIF5B (7570%) and CCDC6 (1719%).

Efficacy results for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarized in Table 8.

Table 8: Efficacy Results in ARROW (Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

Efficacy Parameter	**GAVRETO** ~~(~~**N=~~87~~)130**
Overall Response Rate (ORR)[a] (95% CI)	~~57 (46, 68~~63 (54, 71)
Complete Response, %	~~5.7~~6
Partial Response, %	~~52~~57
Duration of Response (DOR)	~~(~~**N=~~50~~)82**
Median, months (95%CI)	~~NE (15.2~~38.8 (14.8, NE)
Patients with DOR ≥ ~~6~~12-months[b], %	~~80~~66

NE = not estimable
[a] Confirmed overall response rate assessed by BICR
[b] Based on observed duration of response

For the ~~39~~54 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 59% (95% CI: ~~42, 74~~45, 72) and the median DOR was ~~not reached~~22.3 months (95% CI: ~~11.3~~8.0, NE).

Among the ~~87~~130 patients with *RET*-fusion positive NSCLC, ~~8~~10 had measurable CNS metastases at baseline as assessed by BICR. No patients received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 47 of these ~~8~~10 patients including 2 patients with a CNS complete response; ~~75~~71% of responders had a DOR of ≥ 6 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in ~~27~~107 patients with treatment-naïve *RET* fusion-positive NSCLC with measurable disease enrolled into ARROW.

The median age was ~~65~~62 years (range 30 to 87); ~~52~~53% were female, ~~59~~49% were White, ~~33~~45% were Asian, and 42.8% were Hispanic or Latino. ECOG performance status was 0-1 for ~~96~~99% of the patients and ~~all~~98% of patients ~~(100%)~~ had metastatic disease; ~~37~~28% had either history of or current CNS metastasis. *RET* fusions were detected in ~~67~~68% of patients using NGS (~~41~~30% tumor samples; ~~22~~17% blood or plasma; 422% unknown) and ~~33~~19% using FISH. The most common *RET* fusion partners were *KIF5B* (~~70~~71%) and *CCDC6* (~~11~~18%).

Efficacy results for treatment-naïve *RET* fusion-positive NSCLC are summarized in Table 9.

Table 9: Efficacy Results for ARROW (Treatment-Naïve Metastatic *RET* Fusion-Positive NSCLC)

Efficacy Parameter	GAVRETO (N=27)107
Overall Response Rate (ORR)[a] (95% CI)	70 (50, 8678 (68, 85)
Complete Response, %	117
Partial Response, %	5971
Duration of Response (DOR)	(N=19)83
Median, months (95% CI)	13.4 (9.0 (6.3, NE4, 23.1)
Patients with DOR ≥ 612-months[b], %	5845

NE = not estimable

[a] Confirmed overall response rate assessed by BICR

[b] Based on observed duration of response

עדכונים מהותיים בעלון לצרכן

תופעות לוואי נוספות:

תופעות הלוואי השכיחות ביותר:

- עצירות
- לחץ דם גבוה
- עייפות
- כאבי שרירים ומפרקים
- עצירות
- שלשול
- עייפות
- ירידה בספירת דם של תאי דם לבנים, אדומים וטסיות
- ירידה ברמות הפוספט בדם
- ירידה ברמות הסידן בדם
- ירידה ברמות המלחים (נתרן) בדם
- נפיחות של הפנים, הזרועות, הרגליים, הידיים וכפות הרגליים (בצקת)
- חום
- שיעול
- תפקודי כבד לא תקינים בבדיקות דם

תוצאות בדיקות דם חריגות חמורות, השכיחות ביותר בטיפול עם גברטו:

- ירידה בספירת דם של תאי דם לבנים, תאי דם אדומים וטסיות
- ירידה ברמות פוספט, מלח (נתרן), סידן ואשלגן בדם
- תפקודי כבד לא תקינים בבדיקות דם
- עלייה ברמות אנזים הנקרא פוספטאזה בסיסית (alkaline phosphatase) בדם (בדיקה לבעיות כבד או עצמות)
- עליה ברמות אשלגן בדם

אלו לא כל תופעות הלוואי האפשריות של גברטו. **אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה או כאשר אתה סובל מתופעת לוואי שלא צוינה בעלון, עליך להתייעץ עם רופא.**