Journal of Translational Science

Research Article

ISSN: 2059-268X

Dabrafenib plus trametinib in elderly patients (>75 years) with BRAF V600E mutated metastatic non-small-cell lung cancer: A multicenter retrospective experience from real-life

Maione P[1*], De Marinis F[2], Romano G[3], Spitaleri G[2], Galetta D[4], Morabito A[5], Rocco D[6], Tiseo M[7,8], Vitiello F[6], Palumbo G[5], Muto M[9] and Gridelli C[1]

[1]Division of Medical Oncology, S.G. Moscati Hospital, Avellino, Italy

[2]Division of Thoracic Oncology, IEO, European Institute of Oncology, IRCCS, Milan Italy

[3]U.O. Oncologia, P.O. Vito Fazzi Lecce Italy

[4]SSD Oncologia Medica Patologia Toracica, IRCCS Oncologico Giovanni Paolo II, Bari, Italy

[5]Thoracic Medical Oncology, Istituto Nazionale Tumori, IRCCS "Fondazione G. Pascale", Napoli, Italy

[6]U.O.C. di Pneumologia Oncologica, A.O.R.N. dei Colli Plesso-Monaldi, Napoli, Italy

[7]Department of Medicine and Surgery, University of Parma, Parma, Italy

[8]Medical Oncology Unit, University Hospital of Parma, Parma, Italy

[9]U.O.C. Radiotherapy, S.G. Moscati Hospital, Avellino, Italy

Abstract

Dabrafenib is a BRAF kinase inhibitor selective for the BRAF V600 mutation, while trametinib is a potent mitogen-activated kinase (MEK) inhibitor. A three-arm, non-randomised phase 2 study in patients with BRAF V600E mutated metastatic NSCLC has demonstrated significant clinical acitivity for dabrafenib plus trametinib combination therapy, leading the NCCN and ESMO guidelines to recommend the use of these targeted agents as first-line therapy before chemotherapy and immunotherapy in this molecular subgroup of patients with BRAF V600E mutated advanced NSCLC. Despite excellent antitumor activity, the incidence of grade 3-4 events and the rate of discontinuation are not negligible in this patient population, and mainly the optimal management of elderly patients aged more than 75 years remains challenging. Here we present our retrospective treatment series from clinical practice in this special patient population focusing mainly on the feasibility of this combination treatment. A relevant disease control rate was confirmed in our series with eight partial responses and three stable diseases reported (one patient was not evaluable for response). Grade 3 toxicities were reported in 4/12 patients and in 7/12 patients dose reduction due to relevant toxicities was required. Treatment was interrupted because of toxicity, temporary in 10/12 patients and definitively in 2/12 patients. The great majority of the grade 2-3 adverse events occurred in the first two months of treatment. Our data from real life, although retrospective and limited at 12 patients, seem to suggest that preventive dose-reduction and strict clinical monitoring in the first month of treatment, may limit life threatening events and early permanent or long discontinuation in order to avoid subsequent under-treatment of this patient population.

Introduction

Non-small cell lung cancer (NSCLC) constitutes more than 80% of all lung cancers [1]. Several oncogenic driver gene mutations or rearrangements (EGFR, BRAF, ALK, ROS1, NTRK, RET, KRAS, HER2, and MET) have been well characterized and subsequent targeted therapies against these molecular abnormalities have been developed with brilliant therapeutic outcomes for NSCLC patients [2-5]. Specifically, activating BRAF mutations, occur in about 1–5% of lung adenocarcinomas, with V600E mutations, the one with major therapeutic implication, accounting for about the half of these cases [6].

Activating BRAF mutations are generally mutually exclusive from other more common oncogenic drivers as EGFR mutations or ALK rearrangements [7], and the presence of BRAF V600E mutation seems to be associated with poor therapeutic outcomes for patients treated with platinum-based chemotherapy [8,9]. Interesting retrospective data exist on the efficacy of immune checkpoint inhibitors in patients with BRAF-mutant NSCLC, as first and second-line treatment [10]. Thus, this patient population cannot be excluded from immunotherapy, expecially if their tumors express PDL-1 > 50%, as patients with different forms of oncogene addicted NSCLC. The efficacy of immunotherapy in BRAF-mutant NSCLC might be explained with the high prevalence of smokers and the frequent association with increased tumor mutational burden [11].

The molecular mechanism behind the oncogenic potential of BRAF V600E mutations is the constitutive activation of the mitogen-activated

Correspondence to: Paolo Maione, Division of Medical Oncology, S.G.Moscati Hospital, Contrada Amoretta – 83100 - Avellino, Italy, E-mail: pmaione@libero.it

Keywords: *dabrafenib, trametinib, elderly patients, NSCLC, BRAFV600E mutation, safety*

Received: June 12, 2022; **Accepted:** June 19, 2022; **Published:** June 21, 2022

protein kinase (MAPK) pathway [12]. Antitumor activity has been reported with dabrafenib, a BRAF kinase inhibitor selective for the BRAF V600 mutation, as monotherapy, but the combination with the potent mitogen-activated kinase (MEK) inhibitor trametinib, producing a dual MAPK pathway inhibition, has produced enhanced outcomes in terms of response rate and clinical benefit [12-14]. A three-arm, non-randomised phase 2 study in patients with BRAF V600E mutant metastatic NSCLC started in 2011, and primary results of this trial (NCT01336634) were first reported in April 2016. The overall response rate (ORR) in patients who received dabrafenib monotherapy (cohort A) was 33% (95% CI, 23%–45%), progression-free survival (PFS) was 5.5 months and duration of response (DOR) was 9.6 months as per investigator assessment [15]. Pretreated (cohort B) and treatment-naïve (cohort C) patients with BRAF V600E-mutant metastatic NSCLC received dabrafenib 150 mg twice daily and trametinib 2 mg once daily. In pretreated and treatment-naïve patients who received dabrafenib plus trametinib combination therapy (cohorts B and C), the ORR was 63.2% (95% CI, 49.3%–75.6%) and 64% (95% CI, 46– 79), and the median PFS was 9.7 and 10.9 months, respectively. The median overall survival (OS) was not reported in pretreated patients and was immature in treatment-naïve patients [13].

Recently, Planchard et al, reported updated ORR, PFS, DOR, OS, and safety with a minimum follow-up of 5 years in pretreated and treatment-naïve patients with BRAF V600E-mutant metastatic NSCLC receiving dabrafenib plus trametinib [16]. At data cut-off, for cohorts B (57 patients) and C (36 patients), the median follow-up was 16.6 (range, 0.5–78.5) and 16.3 (range, 0.4–80) months, ORR (95% CI) was 68.4% (54.8–80.1) and 63.9% (46.2–79.2), median PFS (95% CI) was 10.2 (6.9– 16.7) and 10.8 (7.0–14.5) months, and median OS (95% CI) was 18.2 (14.3–28.6) and 17.3 (12.3–40.2) months, respectively. The 4- and 5-year survival rates were 26% and 19% in pretreated patients and 34% and 22% in treatment-naïve patients, respectively. As a consequence, the NCCN and ESMO guidelines recommend the use of targeted agents as first-line therapy before chemotherapy and immunotherapy in patients with advanced NSCLC with an oncogenic driver including dabrafenib plus trametinib in BRAF V600E mutated NSCLC [1,17]. However, unfortunately, around half of BRAF mutant NSCLC patient remain orphan of a specific targeted therapy [12].

Although the toxicity profile of the combination of dabrafenib and trametinb was reported by authors of the above described trial as manageable [13-15], in clinical practice physicians describe difficulties in managing adverse events in some special populations, mainly elderly patients aged more than 75 years, expecially if also they have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 2 and/or with relevant comorbidities. In fact, the safety profile of this combination cannot be defined particularly suitable to elderly patients as other targeted therapies (i.e. EGFR and ALK/ROS1 inhibitors), with an incidence of grade 3-4 events and a rate of discontinuation not negligible. In the above described phae II trial regardless of the age dose reductions were frequent, 48% for dabrafenib and 32% for trametinib, although the majority of the patients needed only one dose reduction. Also dose interruption constituted a widely used approach, 77% for dabrafenib with 46% of these patients with three or more dose interruptions, and 77% for trametinib of which 30% with three or more dose interruptions. The most frequent adverse events were pyrexia (56%), nausea (51%), vomiting (41%), dry skin (39%), oedema peripheral (38%) and diarrhoea (37%). The most frequent adverse events of grade ≥3 occurring in ≥5% of patients were hypertension, hyponatraemia, neutropenia, pyrexia, dyspnoea, anaemia, and increased alanine aminotransferase [16]. In our knowledge there is poor information about tolerability and dose management in the elderly population.

In this article we describe our retrospective case series from clinical practice of 12 elderly advanced NSCLC patients aged more than 75 years, harboring BRAF V600E mutations and treated with dabrafenib and trametinib combination, with a special focus on the toxicities reported and on approaches used to face them in terms of permanent discontinuation, dose interruption and dose reduction.

Methods

Patients were identified at seven participating institutions all from Italy. All patients were 75 years old or older, diagnosed with advanced NSCLC with BRAF V600E mutation identified by local molecular profiling (e.g., DNA-based next-generation sequencing or polymerase chain reaction). Patients have received dabrafenib plus trametinib irrespective of treatment lines at the doses of: dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The main topics of this retrospective experience from real life were safety, in terms of grade 2-3 or more adverse events, and toxicity management, in terms of dose reductions and temporary or definitive interruptions. As secondary focus, disease control rate (partial/complete responses and disease stabilizations) was also reported. Patient demography, prior treatments, PD-L1 expression and eventually concomitant other gene alterations were also collected. Due to the little size of the sample, we have performed descriptive statistical analyses.

Results

Data collected in seven centers from 12 V600EBRAF mutated advanced NSCLC patients, aged >75 years and treated with dabrafenib plus trametinib combination, were retrospectively reviewed. Nine patients were treatment-naive and three pretreated (two with one previous line, one with two previous lines). The age range was 76-85, PS was 0-1 in ten patients and 2 in two patients. The presence of comorbidities was large in this series of patients, as often described in elderly smokers patients, in particular the presence of cardiovascular diseases as hypertension and chronic ischemic cardiopathy. In six patients two comorbidities were recorded, three patients had three or more comorbidities, two patients had one comorbidity, and only one patient had no comorbidities. Polipharmacy was obviously widely represented in these patients, and the inclusion of dabrafenib and trametinib in the every-day drug prescription, constituted a problem in terms of communication and patient compliance. PDL-1 expression was > 50% in four patients, <1% in five patients, and 1-49% in three patients. Other target mutations or rearrangements were reported only in one patient (a p.Arg912Leu RET mutation) (Table 1).

Table 1. Characteristics of patients

Patients (N=12)	
Median age (range)	(76-85)
Sex (Male/female)	8/4
Smokers (Never/former/current)	1/7/4
PS (0-1/ 2)	10/2
Comorbidities:	
None	1
1-2	8
≥ 3	3
Prior treatments	
None	9
1	2
2	1
PD-L1 expression	
< 1%	5
1-49%	3
≥ 50%	4
Concomitant other gene alterations	
p.Arg912Leu RET mutation	1

Table 2. Antitumor activity

Partial Response	Stable Disease	Treatment duration <3 months	Treatment duration >6 months	Treatment duration > 10 months
8/12 patients	3/12 patients	1/12 patients	5/12patients	6/12 patients

Eleven patients were evaluable for antitumor activity, and we reported eight partial responses (PR) and three stable diseases (SD). One patient was not evaluable for response because he died 1 month after the beginning of treatment for causes not related to treatment and to neoplastic disease. Treatment duration was < 3 months in only one patient (treatment interrupted for causes different from cancer and treatment toxicity), while was > 6 months in all the other 11 patients and >10 months in 6/11 patients (Table 2).

All patients were evaluable for toxicity. Treatment was started at standard doses in 11/12 patients. The single patient approached from the beginning with dose reduction had a PS=2. Grade 3 toxicities were reported in 4/12 patients (1 anemia, 1 pyrexia, 1 pyrexia plus anemia plus cutaneous reaction, 1 neutropenia). Grade 2 toxicities were reported in 6/12 patients and included neutropenia, thrombocytopenia, pyrexia, asthenia, cystitis. Only in 2/12 patients were reported only grade 1 adverse events. The great majority of the grade 2-3 adverse events occurred in the first two months of treatment and in all these patients treatment interruption was required. In 7/12 patients dose reduction due to relevant toxicities was required. In two patients treatment was definitively interrupted because of toxicity. In the single PS 2 patient not approached with dose reduction from the beginning, grade 3 toxicities were reported with early treatment interruption (Tables 3,4).

In our experience the entity of dose reduction has varied from dabrafenib 75 mg once daily or 75 mg twice daily or 150 mg in the morning and 75 mg in the evening depending on the severity of the toxicities reported. Trametinib has been reduced to three-times per week administration or to monday-friday administration.

Discussion

Combination treatment with dabrafenib plus trametinib offers the best option of improving quality of life, tumor shrinkage and survival prolongation to patients with metastatic NSCLC harboring BRAF V600E mutation. These outcomes are comparable to other targeted therapies administered in the treatment of different oncogene addicted NSCLC. However, the safety profile of this combination therapy, although manageable in the young and fit population, presents some features that can become critical when treating very old and/or frail patients. BRAF mutations do not seem to be related to age and, unlikely to NSCLC harbouring fusion genes, patients with BRAF mutated NSCLC are older with a median age ranging from 63 to 71.5 years old [18,14].

Our retrospective data, although limited at 12 patients, seem to suggest that preventive dose-reduction and strict clinical monitoring in the first month of treatment, may limit life threatening events and early permanent or long discontinuation in order to avoid subsequent undertreatment of this patient population. In the pretreated population of the trial conducted by Planchard et al. [15], adverse events led to permanent discontinuation in 12% of patients, dose interruption or delay in 61% and dose reduction in 35%. The most frequent adverse event was confirmed to be pyrexia (56%). Only 58% of patients received at least 80% of the planned dose of dabrafenib while 75% of patients received at least 80% of the planned dose of trametinib. Even if no data according age has been reported it can be supposed that the majority of lost doses should have been occurred in elderly patients, expecially if also PS 2 and/or with major comorbidities. However, although 19/93 patients treated within cohorts B and C of this trial were elderly aged more than 75 years, the safety profile has not been reported separately for this special population. Moreover only 6/93 patients had a PS 2 (12%). In a recently reported large retrospective analysis, in 1076 melanoma and NSCLC (only 72 NSCLC cases) patients enrolled in three registration trials, pyrexia was confirmed to be the most common and challenging adverse event that physicians have to face when administering such combination [19]. About 60% of the patients developed pyrexia, in 5.7% of the analysed population grade 3/4 pyrexia was reported and 15.6% developed a protocol-defined serious pyrexia event. As in our retrospective experience, pyrexia occurred early in the majority of the cases, and became less frequent with the prosecution of the treatment. The approach used to face this adverse event was mainly temporary dose interruption of both dabrafenib and trametinib, but the median time needed to re-start treatment has not been reported and also the dose-reduction as management strategy has not been discussed. Also Chalmers et al recently focused on the topic of safety management of dabrafenib and trametinib by thoracic oncologists [20]. In fact, this combination constitutes a new approach in NSCLC treatment, with a peculiar toxicity profile and moreover unfamiliar to thoracic oncologist. In the 93 patients with previously untreated or treated metastatic BRAF V600E-positive NSCLC treated with dabrafenib plus trametinib in the BRF113928 trial, 57% were treated for >6 months and 29% were treated for ≥1 year. Pyrexia, fatigue, nausea, and dry skin were the most common events overall but a variety of adverse events occurred with different incidence and included cutaneous, ocular, and hemorrhagic conditions [21,22]. In a recently reported case of an elderly patient with BRAF V600E-mutated NSCLC, who received dabrafenib plus trametinib treatment, although a marked response was obtained, the patient was unable to continue to receive combination treatment because he developed important hypoalbuminemia and peripheral edema and was subsequently switched to supportive care [23]. This case report is the demonstration that administering the combination at standard doses from the beginning, is a risk in the very old patient or in elderly frail patients. The risk of toxic death or irreversible toxicity is really low, but it can be high the risk of slow recover from toxicity with a subsequent undertreatment of cancer disease.

In our opinion, the use of dabrafenib plus trametinib in elderly patients is to be considered much more challenging for the physician than the administration of last generation EGFR or ALK/ROS inhibitors, these ones characterized by an excellent safety profile to be defined drugs particularly suitable for special populations as PS2 and elderly patients. Specifically designed prospective clinical trials on the feasibility of the combination of dabrafenib and trametinib in these patients populations have not been conducted and also retrospective

Table 3. Main adverse events reported

Event	G2 N (%)	G3 N (%)
Anemia	-	2 (16%)
Neutropenia	2 (16%)	1 (8%)
Thrombocytopenia	1 (8%)	-
Pyrexia	1 (8%)	2 (16%)
Skin reaction	-	1 (8%)
Asthenia	1 (8%)	-
Cystitis	1 (8%)	-

Table 4. Grade 2-3 toxicity rate and toxicity management

Grade 2 toxicities	Grade 3 toxicities	Temporary interruption	Definitive interruption	Dose reduction
6/12 patients (50%)	4/12 patients (33%)	10/12 patients	2/12 patients	7/12 patients

analyses are not available from the literature. In our retrospective series, the antitumoral activity of the regimen was confirmed in elderly patients aged more than 75. However early relevant toxicities that produced treatment interruption, negative impact in terms of quality of life and early restart at reduced dose, were reported in the majority of patients that started treatment at standard doses. In our opinion, in elderly patients aged more than 75 years, expecially if with PS 2 and or with relevant comorbidities, treatment with dabrafenib plus trametinib could be started with dose reduction, and eventually continued at standard doses after 1 month of treatment without grade 2 toxicities occurring. A possible scheme of dose reduction from the start of treatment might be dabrafenib 75 mg twice daily or 150 mg in the morning and 75 mg in the evening according to patients characteristics. Trametinib may be reduced to three-times per week administration or to monday-friday administration depending on PS and comorbidities. In fit elderly patients (PS0-1 and no relevant comorbidities), treatment could be started at standard dose. Moreover, in all elderly patients, weekly blood examination and bimonthly clinical examination at hospital for early recognition of adverse events are strongly recommended, especially in the first two months of treatment.

Conclusion

In conclusion, there are limited retrospective clinical data about special patient populations as elderly and poor PS patients with BRAF mutant NSCLC. The combination of targeted agents dabrafenib trametinib constitute an opportunity of survival benefit, but specific approaches in terms of schedules, dose reductions and interruptions are needed to avoid an excess of toxicity with a negative impact on quality of life and definitive treatment discontinuation.

Conflicts of interest

Paolo Maione. Speakers' or consultants' fee from Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, MSD, Sanofi, Amgen, Roche, Eli-Lilly, Pfizer.

Cesare Gridelli. Consulting or advisory role or speaker bureau member at Amgen, Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GSK, Karyopharm, Menarini, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda.

Filippo De Marinis. Fee for advisory board member from Novartis.

Alessandro Morabito. Speakers bureaus: AstraZeneca, BMS, MSD, Novartis, Roche, Boehringer, Pfizer, Lilly. Advisory board: MSD, Boehringer, Takeda

Marcello Tiseo. Speakers' and consultants' fee from Astra-Zeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre, Amgen, Merck, Sanofi and received institutional research grants from Astra-Zeneca, Boehringer Ingelheim.

Giampiero Romano, Domenico Galetta, Danilo Rocco, Gianluca Spitaleri, Giuliano Palumbo, Fabiana Vitiello and Matteo Muto have no conflicts of interest to declare.

References

1. National Comprehensive Cancer Network (2020) Non-Small Cell Lung Cancer (Version 6.2020).
2. Zappa C, Mousa SA (2016) Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res* 5: 288-300. [Crossref]
3. Dagogo-Jack I, Lennerz JK (2020) Personalized Diagnostic Workflows: The Next Wave of Precision Medicine in NSCLC. *Journal of Thoracic Oncology* 15: 888-890. [Crossref]
4. Arbour KC, Riely GJ (2019) Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. *JAMA* 322: 764-774. [Crossref]
5. Tsang ES, Shen Y, Chooback N (2019) Clinical outcomes after whole-genome sequencing in patients with metastatic non-small-cell lung cancer. *Cold Spring Harb Mol Case Stud* 5: a002659.
6. O'Leary CG, Andelkovic V, Ladwa R (2019) Targeting BRAF mutations in non-small cell lung cancer. *Transl Lung Cancer Res* 8: 1119-1124.
7. Leonetti A, Facchinetti F, Rossi G (2018) BRAF in non-small cell lung cancer (NSCLC): Pickaxing another brick in the wall. *Cancer Treat Rev* 66: 82-94. [Crossref]
8. Cardarella S, Ogino A, Nishino M (2013) Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clinical cancer research: an official journal of the American Association for Cancer Research* 19: 4532-4540. [Crossref]
9. Marchetti A, Felicioni L, Malatesta S (2011) Clinical Features and Outcome of Patients With Non– Small-Cell Lung Cancer Harboring BRAF Mutations. *Journal of Clinical Oncology* 29: 3574-3579.
10. Tabbò F, Pisano C, Mazieres J (2022) How far we have come targeting BRAF-mutant non small cell lung cancer (NSCLC). *Cancer Treatment Reviews* 103: 102335. [Crossref]
11. Offin M, Pak T, Mondaca S (2019) Molecular characteristics, immunophenotype, and immune checkpoint inhibitor response in BRAF non-V600 mutant lung cancers. *J Thorac Oncol* P1.04-39.
12. Santarpia L, Lippman SM, El-Naggar AK (2012) Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. *Expert Opinion on Therapeutic Targets* 16: 103-119. [Crossref]
13. Planchard D, Besse B, Groen HJM (2016) Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *The Lancet Oncology* 17: 984-993.
14. Planchard D, Smit EF, Groen HJM (2017) Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *The Lancet Oncology* 18: 1307-1316.
15. Planchard D, Kim TM, Mazieres J (2016) Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *The Lancet Oncology* 17: 642-650.
16. Planchard D, Besse B, Groen H (2020) Updated overall survival (OS) and genomic analysis from a single-arm phase II study of dabrafenib (D) + trametinib (T) in patients (pts) with BRAF V600E mutant (Mut) metastatic non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology* 38 (15_suppl): 9593-9593.
17. Planchard D, Popat S, Kerr K (2018) Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 29: 192-237. [Crossref]
18. Cui G, Liu D, Li W (2017) A meta-analysis of the association between BRAF mutation and non small cell lung cancer. *Medicine* 96: 1-7.
19. Schadendorf D, Robert C, Dummer R (2021) Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in BRAF-mutant cancers. *European Journal of Cancer* 153: 234-241. [Crossref]
20. Chalmers A, Cannon L, Akerley W (2019) Adverse Event Management in Patients with BRAF V600E-Mutant Non-Small Cell Lung Cancer Treated with Dabrafenib plus Trametinib. *The Oncologist* 24: 963-972.
21. Tafinlar (dabrafenib) [package insert]. *East Hanover, NJ: Novartis Pharmaceuticals Corporation;* 2018.
22. Odogwu L, Mathieu L, Blumenthal G (2018) FDA Approval Summary: Dabrafenib and Trametinib for the Treatment of Metastatic Non-Small Cell Lung Cancers Harboring BRAF V600E Mutations. *The Oncologist* 23: 740-745. [Crossref]
23. Dotsu Y, Fukuda M, Honda N (2020) Dabrafenib and trametinib therapy in an elderly patient with non-small cell lung cancer harboring the BRAF V600E mutation. *Thoracic Cancer*