CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 2 Study to Evaluate Safety and Anti-tumor Activity of Avelumab in Combination With Talazoparib in Patients With BRCA or ATM Mutant Tumors

Study Number: B9991032

Regulatory Agency or Public Disclosure Identifier Number:

US IND: 133,902, EudraCT: 2018-000345-39, NCT03565991

Study Phase: 2

Name of Study Intervention: Avelumab

Trade Name: BAVENCIO®

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Final CSR (LPLV Date) Version 1.0	21 June 2023

Number of Study Center(s) and Investigator(s):

A total of 202 participants were enrolled at 42 centers in 9 countries.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Hyman David Michael, Zelnak Amelia B., Bauer Todd Michael, et al. JAVELIN BRCA/ATM: A phase 2 trial of avelumab (anti–PD-L1) plus talazoparib (PARP inhibitor) in patients with advanced solid tumors with a BRCA1/2 or ATM defect Journal of Clinical Oncology 2019;37 15_ Suppl:TPS2660.

Schram AM, Colombo N, Arrowsmith E, et al. Avelumab Plus Talazoparib in Patients With BRCA1/2- or ATM-Altered Advanced Solid Tumors: Results From JAVELIN BRCA/ATM, an Open-Label, Multicenter, Phase 2b, Tumor-Agnostic Trial. JAMA Oncology 2023;9(1):29-39.

CLINICAL STUDY REPORT SYNOPSIS

Study Period:

First Participant First Visit (FPFV): 18 June 2018

Last Participant Last Visit (LPLV): 03 February 2023

This study was terminated.

Rationale:

This was a Phase 2 study to assess the safety and efficacy of the avelumab plus talazoparib combination in up to approximately 200 patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or somatic breast cancer susceptibility gene (BRCA)1, BRCA2, or ataxia telangiectasia mutated (ATM) gene defect, as determined by local assessment and classification. Patients with these gene defects have limited therapeutic options after their disease has progressed on standard of care (SOC) chemotherapy.

Avelumab is a human immunoglobulin (IgG)1 monoclonal antibody (mAb) directed against programmed death ligand 1 (PD-L1). Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint pathway.

Talazoparib is a potent, orally bioavailable poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor, which is cytotoxic to human cancer cell lines harboring gene mutations that compromise DNA repair, an effect referred to as synthetic lethality, by inhibiting PARP catalytic activity and trapping PARP protein on DNA, thereby preventing DNA repair, replication, and transcription.

It was anticipated that patients with tumors harboring defects in the BRCA1, BRCA2, or ATM gene would likely benefit from treatment with the combination of avelumab plus talazoparib, independent of their tumor type, and that the combination might produce additive or synergistic anti-tumor activity relative to each drug used as a single agent.

Objectives and Endpoints:

Type	Objective	Endpoints
Primary		

CLINICAL STUDY REPORT SYNOPSIS

Type	Objective	Endpoints
Efficacy	To evaluate objective response rate (ORR) of avelumab in combination with talazoparib, in participants with locally advanced or metastatic solid tumors harboring BRCA1, BRCA2 or ATM defect.	Confirmed objective response (OR) in participants with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by blinded independent central review (BICR), using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) and, in participants with metastatic castration resistant prostate cancer (mCRPC), RECIST v1.1 and Prostate Cancer Working Group 3 (PCWG3) (bone).
Secondary		
Safety	To assess the overall safety and tolerability of avelumab in combination with talazoparib.	• Adverse events (AEs) as characterized by type, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.4.03), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing.
Pharmacokinetics (PK)	To characterize the PK of avelumab and talazoparib when given in combination.	PK parameters including: pre-dose/trough concentrations (C_{trough}) for avelumab and talazoparib, post-dose concentrations for talazoparib, and maximum concentration (C_{max}) for avelumab.
Immunogenicity	To evaluate the immunogenicity of avelumab when given in combination with talazoparib.	Avelumab anti-drug antibody (ADA) levels and neutralizing antibody (NAb) against avelumab.

CLINICAL STUDY REPORT SYNOPSIS

Type	Objective	Endpoints
Efficacy	To assess other measures of the anti-tumor activity of avelumab in combination with talazoparib.	• Confirmed OR as assessed by the investigator, using RECIST v1.1 and, in participants with mCRPC, RECIST v1.1 and PCWG3. • Time to event endpoints: Endpoints as assessed by BICR and as assessed by the investigator, using RECIST v1.1 and in participants with mCRPC, RECIST v1.1 and PCWG3, including time to response (TTR), duration of response (DoR), and progression free survival (PFS). Additional time-to-event endpoints include overall survival (OS) for all participants and time to prostate specific antigen (PSA) progression (≥25% increase) for mCRPC participants. • PSA response ≥50% decrease and circulating tumor cell (CTC) count conversion for participants with mCRPC. • Cancer antigen 125 (CA-125) response ≥50% decrease for participants with ovarian cancer.

CLINICAL STUDY REPORT SYNOPSIS

Type	Objective	Endpoints
Biomarker	• To assess the correlation of anti-tumor activity of avelumab in combination with talazoparib with PD-L1 expression in baseline tumor tissue.	• PD-L1 expression level in baseline tumor tissue.
	• To assess the correlation of anti-tumor activity and emergence of resistance with defects in a panel of key oncogenes, including BRCA1/2 and ATM, and tumor mutational burden (TMB) in circulating tumor DNA (ctDNA) and tumor tissue at baseline, during treatment and at the end of treatment.	• Presence of defects in a panel of key oncogenes, including BRCA 1/2 and ATM, and TMB in ctDNA and tumor tissue at baseline, during treatment, and at the end of treatment.
[redacted]	[redacted]	[redacted]

CLINICAL STUDY REPORT SYNOPSIS

Type	Objective	Endpoints
[redacted]	[redacted]	• [redacted]

CLINICAL STUDY REPORT SYNOPSIS

Methodology:

This was a Phase 2, open-label, multi-center, non-randomized study of avelumab in combination with talazoparib in adult participants with locally advanced or metastatic solid tumors with a pathogenic or likely pathogenic germline or loss-of-function somatic BRCA1 or BRCA2, or ATM gene defect, as determined by local assessment and classification, who have received at least 1 line of SOC treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. Two cohorts were enrolled in parallel:

- Cohort 1 was to enroll up to approximately 150 participants with locally advanced or metastatic solid tumors with one or more defects in the BRCA1 or BRCA2 genes;
- Cohort 2 was to enroll up to approximately 50 participants with locally advanced or metastatic solid tumors with one or more defects in the ATM gene.

  Note: in the event that a participant had concomitant defects in more than 1 of the three genes (BRCA1 or BRCA2 or ATM), they were to be enrolled in Cohort 1.

Number of Participants (planned and analyzed):

Planned: Up to approximately 150 participants were to be enrolled in Cohort 1 and 50 participants in Cohort 2. Thus, a total of approximately 200 participants were to be enrolled.

Analyzed: A total of 200 out of 202 enrolled participants received at least 1 dose of study drug; 159 in Cohort 1 and 41 in Cohort 2.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants with tumors harboring defects in the BRCA1, BRCA2, or ATM gene. Participants had to have measurable disease by RECIST v1.1 (non-measurable disease was only allowed in participants with mCRPC).

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

All participants were assigned to receive a fixed dose of avelumab 800 mg every 2 weeks (Q2W) intravenously and oral talazoparib at 1 mg once daily (QD) or 0.75 mg QD for participants with moderate renal impairment at baseline.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1708519	17-003337	1 mg	Capsules
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1G003	16-003176	200 mg	Solution
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1707899	17-003251	1 mg	Capsules
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1H001/2	18-000308	200 mg	Solution
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1810119	18-002600	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1800870	18-000623	1 mg	Capsules
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1J004	18-003041	200 mg	Solution
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1807947	18-001962	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1813425	18-004049	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1912494	19-003198	1 mg	Capsules
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1J008	19-000790	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1J005	19-000003	200 mg	Solution
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1813431	18-004057	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1905903	19-002206	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1708520	17-003337	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1800874	18-000627	1 mg	Capsules
Talazoparib 1 mg Bottle 30 ct. (MDV3800 Capsules)	1807950	18-001965	1 mg	Capsules

Duration of Study Intervention:

Treatment with avelumab and talazoparib would continue until disease progression was confirmed by the investigator (except where treatment was allowed beyond progression), participant refusal, unacceptable toxicity, or until the study was terminated by the sponsor, whichever occurred first.

CLINICAL STUDY REPORT SYNOPSIS

Summary of Results:

Demographic and Other Baseline Characteristics:

There were 108 (67.9%) females and 51 (32.1%) males in Cohort 1. The median (range) age was 57 years (26, 84). One hundred and ten (69.2%) participants were under 65 years. The majority of participants (117 [73.6%]) were White.

There were 24 (58.5%) females and 17 (41.5%) males in Cohort 2. The median (range) age was 61 years (32, 89). Twenty-five (61.0%) participants were under 65 years and 2 (4.9%) participants were over 85 years. The majority of participants (37 [90.2%]) were White.

Various solid tumors were enrolled in this study. In Cohort 1, the most common (≥5% of participants) enrolled tumor types were HR+ HER2- BC (16.4%), CRPC (16.4%), ovarian cancer (germ cell tumors excluded) (16.4%), TNBC (15.7%), pancreatic cancer (islet cell and carcinoid tumors excluded) (10.1%), colorectal cancer (5.0%) and cholangiocarcinoma (5.0%). In Cohort 2, the most common (≥5% of participants) enrolled tumor types were colorectal cancer (22.0%), HR+ HER2- BC (14.6%), CRPC (12.2%), pancreatic cancer (islet cell and carcinoid tumors excluded) (12.2%), ovarian cancer (7.3%), and endometrial cancer (7.3%).

Exposure:

In Cohort 1, the median duration of treatment with avelumab was 22.9 weeks with a median of 10 infusions. The median duration of treatment with talazoparib was 23.1 weeks.

In Cohort 2, the median duration of treatment with avelumab was 16 weeks with a median of 8 infusions. The median duration of treatment with talazoparib was 16.4 weeks.

Efficacy Results:

The confirmed ORR based on BICR assessment was:

- 27.7% (95% confidence interval [CI]: 20.9%, 35.3%) in Cohort 1, with 11 participants achieving complete response (CR) and 33 participants achieving partial response (PR).
- 7.3% (95% CI: 1.5%, 19.9%) in Cohort 2, with 3 participants achieving PR.

The confirmed ORR based on investigator assessment was:

- 34.6% (95% CI: 27.2%, 42.5%) in Cohort 1, with 8 participants achieving CR and 47 participants achieving PR.
- 14.6% (95% CI: 5.6%, 29.2%) in Cohort 2, with 6 participants achieving PR.

The agreement rate between BICR and investigator assessments of objective response was 88.1% and 87.8% in Cohorts 1 and 2, respectively.

CLINICAL STUDY REPORT SYNOPSIS

Based on BICR assessment, the posterior probabilities of ORR ≥40% (prespecified target) were 0.059 and <0.001 for Cohorts 1 and 2, respectively.

In Cohort 1, for the 127 participants with measurable disease at baseline, the ORR based on BICR assessment was 33.1% (95% CI: 25.0%, 42.0%). One hundred and twenty-two participants had BRCA-dependent tumor types (defined as breast, ovarian, prostate, and pancreatic cancers, and uterine leiomyosarcoma) and 37 participants had non-BRCA-dependent cancer types. Responses were more frequent in participants with BRCA-dependent tumor types (ORR: 33.6% [95% CI: 25.3%, 42.7%]) compared with non-BRCA-dependent tumor types (ORR: 8.1% [95% CI: 1.7%, 21.9%]). For the 51 participants with BC, the ORR was 51.0% (95% CI: 36.6%, 65.2%).

In Cohort 1, the ORR was numerically higher for participants with germline vs somatic tumor BRCA1/2 alterations: 31.0% (18 participants, 95% CI: 19.5%, 44.5%) vs 10.0% (1 participant, 95% CI: 0.3%, 44.5%), respectively.

Based on BICR assessment,

- In Cohort 1, the median DoR was 12.5 months (95% CI: 7.5, NE).
- In Cohort 2, the DoR was 6.7 months for the only responder with subsequent progression.

For participants who had an OR as assessed by BICR, the median TTR was 1.8 months (range: 1.5, 12.1) for Cohort 1. In Cohort 2, the median TTR for the 3 responders was 5.5 months (range: 1.6, 16.8).

Based on investigator assessment,

- In Cohort 1, the median DoR was 8.8 months (95% CI: 7.5, 10.7).
- In Cohort 2, the median DoR was 7.1 months (95% CI: 5.5, 9.7).

For participants who had an OR as assessed by investigator, the median TTR was 1.8 months (range: 1.5, 18.4) for Cohort 1. In Cohort 2, median TTR was 4.0 months (range: 1.9, 14.0).

Median PFS based on BICR assessment was 3.7 months (95% CI: 3.1, 5.4) in Cohort 1 and 3.5 months (95% CI: 1.8, 5.5) in Cohort 2.

Median PFS based on investigator assessment was 5.3 months (95% CI: 3.7, 5.6) in Cohort 1 and 3.7 months (95% CI: 2.1, 7.4) in Cohort 2.

Median OS was 11.9 months (95% CI: 10.1, 13.7) in Cohort 1 and 16.4 months (95% CI: 12.8, 21.9) in Cohort 2.

CLINICAL STUDY REPORT SYNOPSIS

Safety Results:

Overall, 136 (68.0%) participants experienced Grade ≥3 all-causality treatment-emergent adverse events (TEAEs) and 102 (51.0%) participants experienced Grade ≥3 treatment-related TEAEs. Serious TEAEs were reported in 57 (28.5%) participants and were treatment-related in 16 (8.0%) participants. The overall rate of all-causality and treatment-related TEAEs leading to discontinuations of either avelumab or talazoparib was low (<5%). Immune-related adverse events (irAEs) were reported in 27 (13.5%) participants and infusion-related reactions (IRRs) were reported in 42 (21.0%) participants. There were no treatment-related TEAEs leading to death.

Overall, the most frequently reported TEAEs (≥30% of participants) were anaemia (50.0%), nausea (47.0%) and fatigue (34.5%). The most frequently reported Grade ≥3 TEAEs (≥5% of participants) were anaemia (36.5%), platelet count decreased (8.0%), thrombocytopenia (8.0%), neutropenia (7.5%), fatigue (6.0%) and disease progression (5.0%).

Overall, the most frequently reported treatment-related TEAEs (≥20% of participants) were anaemia (45.5%), nausea (32.5%), and fatigue (24.0%). The most frequently reported Grade ≥3 treatment-related TEAEs (≥5% of participants) were anaemia (34.5%), thrombocytopenia (8.0%), platelet count decreased (7.5%), and neutropenia (7.0%).

A total of 152 (76.0%) participants died. The most frequently reported cause of death was disease progression (121 participants [60.5%]). No deaths were attributed to study treatment toxicity.

A total of 16 (8.0%) participants had TEAEs leading to death. The most frequently reported TEAEs leading to death was disease progression (10 participants [5.0%]). All other TEAEs leading to death were reported in single participant.

A total of 57 (28.5%) participants had serious adverse events (SAEs). The most frequently reported SAEs (≥2% of participants) were disease progression (10 participants [5.0%]), anaemia (6 participants [3.0%]) and pneumonia (5 participants [2.5%]). A total of 16 (8.0%) participants had treatment-related SAEs. The most frequently reported treatment-related SAE (≥2% of participants) was anaemia (6 participants [3.0%]).

A total of 8 (4.0%) participants had TEAEs leading to discontinuation of avelumab only, including 7 (3.5%) with treatment-related events; 4 (2.0%) participants had TEAEs leading to discontinuation of talazoparib only with all being treatment-related. The most frequent TEAE leading to discontinuation of avelumab only was arthralgia in 2 participants (1.0%) and the most frequent TEAE leading to discontinuation of talazoparib only was anaemia in 2 participants (1.0%).

A total of 7 (3.5%) participants had TEAEs leading to permanent discontinuation of all study drugs. The most frequently reported TEAE leading to permanent discontinuation of all study drugs was intestinal obstruction (2 participants [1.0%]). No other TEAEs leading to discontinuation was reported in more than 1 participant. One participant had a

CLINICAL STUDY REPORT SYNOPSIS

treatment-related TEAE leading to discontinuation of all study drugs (drug-induced liver injury).

A total of 27 (13.5%) participants had AEs classified as irAEs, including 6 (3.0%) with Grade ≥3 irAEs. The most frequently reported irAE (≥ 5%) by Cluster was Immune-related Thyroid disorders (15 participants [7.5%]). The most frequently reported Grade ≥3 irAE (≥2%) by Cluster was Immune-related Hepatitis (4 participants [2.0%]).

Serious irAEs were reported in 4 participants (2.0%). The serious irAEs included alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, immune-mediated hepatitis, drug-induced liver injury, hepatic enzyme increased and myositis. None of the serious irAEs were reported in more than 2 participants.

A total of 42 (21.0%) participants had IRRs. One participant had Grade 3 IRR; no other participants had Grade ≥3 IRRs. One participant in Cohort 1 had a serious IRR. There were no Grade 5 IRRs.

Pharmacokinetic Results:

Avelumab:

Mean and median avelumab C_{trough} (0 H) and C_{max} (1 H) concentrations were consistent with previously reported C_{trough} and C_{max} concentrations following avelumab 10 mg/kg Q2W monotherapy. The avelumab exposure for 800 mg flat dose in this study was less variable than the body weight-based dosing regimen of 10 mg/kg Q2W. Serum trough concentrations of avelumab appeared to be at steady state at Cycle 3 and beyond.

Talazoparib:

The geometric mean of C_{trough} at Cycle 3 Day 1 was 3.31 ng/mL with a 95% CI of (2.36, 4.65) ng/mL which is within the range of historical data for talazoparib C_{trough} at steady state for 1 mg QD dosing (3.53 ng/mL). The pre-dose and post-dose concentrations of talazoparib were similar between the 1 mg (normal/mild renal impairment) and 0.75 mg (moderate renal impairment) dose groups.

Immunogenicity Results:

Of the 199 participants with at least 1 valid ADA result at any time point, 192 (96.5%) were ADA never-positive. Of the 7 (3.5%) ADA ever-positive participants, 6 were baseline ADA positive, and only 1 participant had a treatment-induced transient ADA response. No participant experienced a treatment-boosted ADA response. ADA never-positive rate was 96.2% and 97.5% for Cohort 1 (BRCA1/2 defect) and Cohort 2 (ATM defect), respectively.

Due to the low observed immunogenicity rate, NAb analysis was not conducted.

CLINICAL STUDY REPORT SYNOPSIS

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Conclusions:

Efficacy:

- Various solid tumors were enrolled in this study. In Cohort 1 (BRCA1/2 defect), the most common (≥5% of participants) enrolled tumor types were HR+ HER2- BC (16.4%), CRPC (16.4%), ovarian cancer (germ cell tumors excluded) (16.4%), TNBC (15.7%), pancreatic cancer (islet cell and carcinoid tumors excluded) (10.1%), colorectal cancer (5.0%) and cholangiocarcinoma (5.0%). In Cohort 2 (ATM defect), the most common (≥5% of participants) enrolled tumor types were colorectal cancer (22.0%), HR+ HER2- BC (14.6%), CRPC (12.2%), pancreatic cancer (islet cell and carcinoid tumors excluded) (12.2%), ovarian cancer (7.3%), and endometrial cancer (7.3%).

- In Cohort 1 (BRCA1/2 defect), the ORR was 27.7% (95% CI: 20.9%, 35.3%) based on BICR assessment and 34.6% (95% CI: 27.2%, 42.5%) based on investigator assessment. Antitumor activity for the combination therapy was mainly observed in BRCA-dependent tumor types (ie, breast, ovarian, prostate, pancreatic cancers and uterine leiomyosarcoma) (ORR: 33.6% [95% CI: 25.3%, 42.7%] vs ORR in non-BRCA-dependent tumor types: 8.1% [95% CI: 1.7%, 21.9%], which was

CLINICAL STUDY REPORT SYNOPSIS

comparable with that reported for PARP inhibitor monotherapy). The median DoR was 12.5 months (95% CI: 7.5, NE) based on BICR assessment and 8.8 months (95% CI: 7.5, 10.7) based on investigator assessment.

- In Cohort 2 (ATM defect), the ORR was 7.3% (95% CI: 1.5%, 19.9%) based on BICR assessment and 14.6% (95% CI: 5.6%, 29.2%) based on investigator assessment. Overall, participants enrolled in the ATM cohort had limited clinical benefit from the treatment with the avelumab plus talazoparib combination. Because of the low clinical activity, enrollment of Cohort 2 was closed after 41 participants were treated. The DoR was 6.7 months based on BICR assessment for the only evaluable responder and the median DoR was 7.1 months (95% CI: 5.5, 9.7) based on investigator assessment.

- Neither Cohort 1 nor Cohort 2 met the prespecified target ORR of 40%, indicating that a pan-cancer tumor-agnostic approach with this combination is not an optimal clinical strategy.

Safety:

- The safety profile of avelumab at 800 mg Q2W in combination with talazoparib 1 mg QD was consistent with the known safety profile of each drug with no new safety signals observed for avelumab or talazoparib. The toxicities were generally manageable with low rate (<5%) of any study drug discontinuation.

- The incidence of Grade ≥3 irAEs and serious irAEs was generally low (3.0% and 2.0%, respectively). There were no Grade 5 irAEs.

PK and Immunogenicity:

- There was no evidence of any PK drug-drug interaction between talazoparib and avelumab, and avelumab treatment-emergent ADA incidence in presence of talazoparib was low.

Biomarkers:

- In Cohort 1, the ORR was numerically higher for participants with germline vs somatic tumor BRCA1/2 alterations.

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