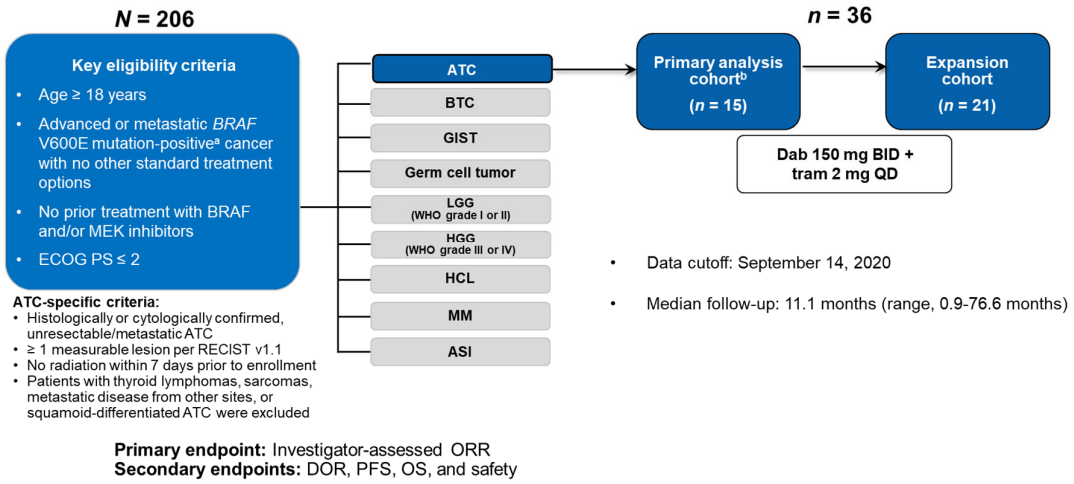
Supplementary Material (online only)

Supplement to: Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in patients with *BRAF* V600E–mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study.

Supplementary Figure S1. ROAR study design



ASI, adenocarcinoma of the small intestine; ATC, anaplastic thyroid cancer; BID, twice daily; BTC, biliary tract cancer; dab, dabrafenib; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumor; HCL, hairy cell leukemia; HGG, high-grade glioma; LGG, low-grade glioma; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ROAR, Rare Oncology Agnostic Research; tram, trametinib; WHO, World Health Organization.

[a] Per local assessment, with retrospective confirmation by central review via the THxID-BRAF kit (bioMérieux, Durham, NC).

[b] In November 2015, the primary analysis cohort was closed early for efficacy, and an expansion cohort was opened.

Supplementary Table S1. Serious adverse events

Serious AEs, *n* (%)[a]	**(*n* = 36)** **Any Grade**
Any	20 (56)
Pneumonia	8 (22)
Pleural effusion	3 (8)
Urinary tract infection	2 (6)
Acute kidney injury	2 (6)
Neutrophil count decreased	2 (6)
Hematochezia	2 (6)
Leukopenia	2 (6)
Pyrexia	1 (3)
Sepsis	1 (3)
Dehydration	1 (3)
Fatigue	1 (3)
Pulmonary embolism	1 (3)
Anemia	1 (3)
Ejection fraction decreased	1 (3)
Femoral neck fracture	1 (3)
Hematuria	1 (3)
Hypotension	1 (3)
Neutropenia	1 (3)
Wound infection	1 (3)
Aortic thrombosis	1 (3)
Autoimmune hemolytic anemia	1 (3)
Bladder transitional cell carcinoma	1 (3)
Cardiac ventricular thrombosis	1 (3)
Clavicle fracture	1 (3)
Clostridium difficile infection	1 (3)
Diverticulitis	1 (3)
Dizziness	1 (3)
Dysphagia	1 (3)
Dyspnea	1 (3)
Facial nerve disorder	1 (3)
Hallucination	1 (3)
Hyperglycemic hyperosmolar nonketotic syndrome	1 (3)
Hyponatremia	1 (3)
Esophageal stenosis	1 (3)
Paralysis recurrent laryngeal nerve	1 (3)
Pelvic infection	1 (3)
Pneumonia aspiration	1 (3)
Pneumonia necrotizing	1 (3)
Pulmonary hematoma	1 (3)
Rhabdomyolysis	1 (3)
Rib fracture	1 (3)
Staphylococcal infection	1 (3)
Stress cardiomyopathy	1 (3)
Syncope	1 (3)

AE, adverse event; ATC, anaplastic thyroid cancer.

[a] All-cause serious AEs of any grade that occurred in the ATC cohort.

Supplementary Table S2. Dabrafenib and trametinib dose intensity and exposure

Category	(*n* = 36)	
	Dabrafenib	**Trametinib**
Duration of exposure, median (range), months	7.0 (1-63)	7.0 (1-63)
Patient status, *n* (%)		
Treatment ongoing	2 (6)	2 (6)
Discontinued	34 (94)	34 (94)
Progressive disease	22 (61)	22 (61)
Adverse event	6 (17)	6 (17)
Patient withdrawal	6 (17)	6 (17)
Daily dose, mean (SD), mg[a]	252.7 (56.59)	1.7 (0.35)
Patients with dose reduction, *n* (%)	28 (78)	11 (31)
No. of dose reductions, *n* (%)		
1	4 (11)	7 (19)
2	6 (17)	2 (6)
≥ 3	18 (50)	2 (6)
Dose reductions, *n*	167	19
Reasons for dose reduction, *n* (%)		
Adverse events	39 (23)	12 (63)
Patient nonadherence	89 (53)	6 (32)
Other	39 (23)	1 (5)
Patients with dose interruption, *n* (%)	28 (78)	27 (75)
No. of dose interruptions, *n* (%)		
1	10 (28)	7 (19)
2	3 (8)	6 (17)
≥ 3	15 (42)	14 (39)
Dose interruptions, *n*	106	129
Reasons for dose interruption, *n* (%)		
Adverse events	71 (67)	56 (43)
Patient noncompliance	22 (21)	48 (37)
Other	13 (12)	25 (19)

[a] Periods of dose interruption (zero doses between periods of nonzero doses) are counted in the calculation of average daily dose.

Supplementary Table S3. Adverse events leading to treatment discontinuation or dose modification

AEs, *n* (%)[a]	(*n* = 36) Any Grade
Leading to discontinuation	6 (17)
Dyspnea	2 (6)
Pleural effusion	2 (6)
Nausea	1 (3)
Ejection fraction decreased	1 (3)
Pneumonia	1 (3)
Acute kidney injury	1 (3)
Aspiration	1 (3)
Conjunctivitis	1 (3)
Diverticulitis	1 (3)
Peripheral edema	1 (3)
Esophageal stenosis	1 (3)
Paralysis recurrent laryngeal nerve	1 (3)
Pericardial effusion	1 (3)
Pneumonia necrotizing	1 (3)
Rhabdomyolysis	1 (3)
Leading to dose interruption	18 (50)
Pyrexia	5 (14)
Pneumonia	3 (8)
Chills	2 (6)
AST increased	2 (6)
Ejection fraction decreased	2 (6)
Neutrophil count decreased	2 (6)
Leukopenia	2 (6)
Nausea	1 (3)
Fatigue	1 (3)
Neutropenia	1 (3)
ALT increased	1 (3)
Rash maculopapular	1 (3)
Vision blurred	1 (3)
Anemia	1 (3)
Urinary tract infection	1 (3)
Asthenia	1 (3)
Atrial fibrillation	1 (3)
Blood AP increased	1 (3)
Pulmonary embolism	1 (3)
Wound infection	1 (3)
Back pain	1 (3)
Clavicle fracture	1 (3)
Dizziness	1 (3)
Facial nerve disorder	1 (3)
Femoral neck fracture	1 (3)
Hallucination	1 (3)
Hyperglycemic hyperosmolar nonketotic syndrome	1 (3)
Hypotension	1 (3)
Oral candidiasis	1 (3)
Pelvic infection	1 (3)
Pleural effusion	1 (3)
Pneumonia aspiration	1 (3)

Pulmonary hematoma	1 (3)
Rib fracture	1 (3)
Skin lesion	1 (3)
Syncope	1 (3)
Weight decreased	1 (3)
Leading to dose reduction	17 (47)
Pyrexia	6 (17)
Fatigue	2 (6)
Neutrophil count decreased	2 (6)
Ejection fraction decreased	2 (6)
Pneumonia	2 (6)
Pneumonitis	2 (6)
WBC count decreased	2 (6)
Chills	1 (3)
Headache	1 (3)
Peripheral edema	1 (3)
ALT increased	1 (3)
Neutropenia	1 (3)
Pruritus	1 (3)
Blood creatinine increased	1 (3)
Dermatitis acneiform	1 (3)
Fungal infection	1 (3)
Cystitis	1 (3)
Dyspepsia	1 (3)
Erythema	1 (3)
Hyponatremia	1 (3)
Pleural effusion	1 (3)
Proteinuria	1 (3)

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; ATC, anaplastic thyroid cancer; WBC, white blood cell.

[a] All-cause AEs of any grade leading to dose interruptions, dose reductions, or discontinuations of any drug in the ATC cohort.

Supplementary Table S4. Time to adverse event–related discontinuation of study treatment

Patient	Study Time to Dabrafenib Discontinuation, months	Study Time to Trametinib Discontinuation, months
1	43.2	22.0
2	5.3	2.1
3	1.8	1.8
4	1.4	1.4
5	6.4	6.4
6	5.2	5.2