

Supplementary Online Content

Bird ST, Tian F, Flowers N, et al. Idelalisib for treatment of relapsed follicular lymphoma and chronic lymphocytic leukemia: a comparison of treatment outcomes in clinical trial participants vs Medicare beneficiaries [published online December 19, 2019]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.3994

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Baseline characteristics for Medicare beneficiaries receiving off-label IDEL for CLL and IDEL+R for FL, in reference to other study cohorts

	FOLLICULAR LYMPHOMA			CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R	IDEL+R		IDEL
Characteristic, %	Study 101-09	Medicare	Medicare	Study 312-0116 ¹	Medicare	Medicare
	<i>n</i> = 26	<i>n</i> = 305	<i>n</i> = 51	<i>n</i> = 89	<i>n</i> = 294	<i>n</i> = 250
Age						
65-74	69.2	45.2	45.1	64.0	47.6	39.2
≥75	30.8	54.8	54.9	36.0	52.4	60.8
Sex						
Female	46.2	54.8	58.8	33.7	37.8	44.4
Race						
White	88.6	93.1	90.2	91.0	89.1	87.6
Asian	3.8	1.0	---	---	---	0.8
Black	---	2.6	5.8	3.4	8.2	7.2
Other	7.6	3.3	4.0	5.6	2.7	4.4
Region						
United States	50.0	100	100	70.8	100	100.0
Charlson Score						
2	73.1	34.1	29.4	34.8	30.6	28.0
3	15.4	14.1	15.7	41.6	17.7	18.4
4	7.7	12.8	13.7	15.7	15.6	15.2
≥5	3.8	39.0	41.2	7.9	36.1	38.4
Baseline Comorbidity²						
Cardiac	34.6	63.6	56.9	30.7	71.4	78.0
Endocrine	23.1	63.0	64.7	34.1	59.9	71.2
Gastrointestinal	46.2	81.6	82.4	68.2	77.6	83.6
Hepatobiliary	3.8	26.2	33.3	4.5	23.8	26.8

Characteristic, %	FOLLICULAR LYMPHOMA			CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R	IDEL+R		IDEL
	Study 101-09 <i>n</i> = 26	Medicare <i>n</i> = 305	Medicare <i>n</i> = 51	Study 312-0116 ¹ <i>n</i> = 89	Medicare <i>n</i> = 294	Medicare <i>n</i> = 250
Baseline Comorbidity²						
Immune system	26.9	41.3	35.3	19.3	55.8	59.6
Infections and infestations	38.5	70.8	72.5	53.4	81.0	84.4
Metabolism and nutrition	42.3	78.0	86.3	56.8	85.7	87.6
Musculoskeletal and connective tissue	53.8	82.3	94.1	56.8	84.7	90.4
Nervous system	19.2	47.5	56.9	40.9	44.2	56.8
Psychiatric	30.8	35.7	37.3	39.8	30.3	34.4
Renal and urinary disorders	11.5	64.6	58.8	55.7	63.9	73.2
Respiratory, thoracic, and mediastinal	23.1	76.1	80.4	56.8	81.3	88.8
Skin and subcutaneous tissue	23.1	62.3	68.6	23.9	75.2	74.4
Vascular	57.7	86.6	76.5	62.5	88.8	89.6
Prior Therapy: Groups						
Antibody - CD52	---	---	---	15.9	0.3	---
Antibody - CD20	100	59.7	58.8	98.9	45.2	37.6
Radiotherapeutic anti-CD20	15.4	4.6	2.0	1.1	---	---
DNA-crosslinker - alkylator	100	33.1	37.3	94.3	22.8	23.6
DNA-crosslinker - platinum based	26.9	3.9	7.8	1.1	0.7	0.8
Proteasome inhibitor	15.4	0.7	2.0	1.1	---	2.0
Purine Analog	11.5	2.0	2.0	60.2	2.7	3.6
Cereblon inhibitor	3.8	8.5	3.9	17.0	0.7	1.2
Topoisomerase inhibitor	69.2	10.8	15.7	17.0	1.4	3.2
Antimetabolite	19.2	4.6	7.8	1.1	1.0	1.2
Microtubule Antagonist	76.9	13.4	19.6	30.7	2.0	5.2
Other Therapy ³	3.8	---	---	3.4	---	---

¹ Renamed Study 312-0117 for the long-term follow-up extension phase

² Baseline comorbidity defined using the System Organ Class from the Medical Dictionary for Regulatory Activities (MedDRA)

³ Other Therapy includes: BCL-inhibitor, Tyrosine Kinase Inhibitor, HDAC inhibitor, mTOR inhibitor, CD19-directed T cell engager

eTable 2: Rates of serious and fatal infections by anatomical location per 100 person-years by study cohort

	FOLLICULAR LYMPHOMA				CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R		IDEL+R		IDEL
	Study 101-09	Medicare	Study 313-0124	Medicare	Study 312-0116	Medicare	Medicare
Fatal Infections							
Total	18.6	27.6	7.5	5.8	9.8	18.4	46.1
Bloodstream Infection	---	12.0	2.5	2.9	3.8	11.3	23.8
CNS Infection	---	0.6	---	---	0.8	---	---
Endocarditis	---	---	---	---	---	---	---
Gastrointestinal Infection	---	0.6	---	---	0.8	---	2.5
Genitourinary Infection	---	4.2	---	---	---	0.5	5.8
Respiratory Infection	12.5	9.6	2.5	2.9	4.5	5.6	13.2
Soft Tissue Infection	---	0.6	---	---	---	0.5	0.8
Viral Infection	6.2	---	---	---	---	---	---
Other Infection	---	---	2.5	---	---	0.5	---
Serious Infections							
Total	67.1	78.7	65.1	103.8	81.6	80.1	118.2
Bloodstream Infection	---	31.1	10.4	35.7	19.2	36.9	47.4
CNS Infection	---	0.6	---	---	1.5	0.9	---
Endocarditis	---	---	---	---		0.9	1.6
Gastrointestinal Infection	---	7.8	13.0	21.0	4.6	7.6	12.5
Genitourinary Infection	6.3	24.1	10.3	35.0	4.0	14.8	38.5
Respiratory Infection	48.9	43.8	26.6	55.6	39.8	47.6	69.6
Soft Tissue Infection	6.3	5.4	2.5	12.2	4.8	7.7	9.2
Viral Infection	19.1	4.2	7.7	---	3.1	4.8	2.5
Other Infection	6.3	4.2	15.7	5.9	19.5	6.2	5.9

Rows may sum to more than the totals or subtotals because patients may have had more than one type of infection. A patient could only contribute one event to each row. Rates for serious infections included time from IDEL initiation until the first serious infection. PY = person-years, IDEL=idelalisib, IDEL+R = idelalisib with rituximab

eTable 3: Serious and fatal infection counts by infection type among all subjects and beneficiaries

	FOLLICULAR LYMPHOMA				CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R		IDEL+R		IDEL
Infection Type, # (%)	Study 101-09 <i>n</i> = 26	Medicare <i>n</i> = 305	Study 313-0124 <i>n</i> = 62	Medicare <i>n</i> = 51	Study 312-0116 <i>n</i> = 89	Medicare <i>n</i> = 294	Medicare <i>n</i> = 250
Fatal Infections							
<i>Total</i>	3 (11.5)	46 (15.1)	3 (4.8)	2 (3.9)	13 (14.6)	39 (13.3)	57 (22.8)
Bloodstream Infection	---	20 (6.6)	1 (1.6)	1 (2.0)	5 (5.6)	23 (7.8)	29 (11.6)
Soft Tissue Infection	---	1 (0.3)	---	---	---	2 (0.7)	1 (0.4)
CNS Infection	---	1 (0.3)	---	---	1 (1.1)	---	---
Endocarditis	---	---	---	---	---	---	---
Gastrointestinal Infection	---	1 (0.3)	---	---	1 (1.1)	---	3 (1.2)
Genitourinary Infection	---	7 (2.3)	---	---	---	1 (0.3)	8 (3.2)
Respiratory Infection	2 (7.7)	16 (5.2)	1 (1.6)	1 (2.0)	6 (6.7)	12 (4.4)	16 (6.4)
Viral Infection	1 (3.8)	---	---	---	---	---	---
Other Infection	---	---	1 (1.6)	---	---	1 (0.3)	---
Serious Infections							
<i>Total</i>	8 (30.8)	121 (39.7)	22 (35.5)	26 (51.0)	57 (64.0)	142 (48.3)	119 (47.6)
Bloodstream Infection		50 (16.4)	4 (6.5)	11 (21.6)	22 (24.7)	73 (24.8)	55 (22.0)
Soft Tissue Infection	1 (3.8)	10 (3.3)	1 (1.6)	4 (7.8)	6 (6.7)	18 (6.1)	11 (4.4)
CNS Infection	---	1 (0.3)	---	---	2 (2.2)	2 (0.7)	---
Endocarditis	---	---	---	---	---	2 (0.7)	2 (0.8)
Gastrointestinal Infection	---	14 (4.6)	5 (8.1)	7 (13.7)	6 (6.7)	16 (5.4)	15 (6.0)
Genitourinary Infection	1 (3.8)	41 (13.4)	4 (6.5)	11 (21.6)	5 (5.6)	33 (11.2)	48 (19.2)
Respiratory Infection	6 (23.1)	70 (23.0)	10 (16.1)	16 (31.4)	37 (41.6)	93 (31.6)	76 (30.4)
Viral Infection	3 (11.5)	10 (3.3)	3 (4.8)	---	4 (4.5)	13 (4.4)	4 (1.6)
Other Infection	1 (3.8)	7 (2.3)	6 (9.7)	2 (3.9)	22 (24.7)	14 (4.8)	8 (3.2)

	FOLLICULAR LYMPHOMA				CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R		IDEL+R		IDEL
Infection Type, # (%)	Study 101-09	Medicare	Study 313-0124	Medicare	Study 312-0116	Medicare	Medicare
	<i>n = 26</i>	<i>n = 305</i>	<i>n = 62</i>	<i>n = 51</i>	<i>n = 89</i>	<i>n = 294</i>	<i>n = 250</i>
Bloodstream Infection							
<i>Total</i>	---	50 (16.4)	4 (6.5)	11 (21.6)	22 (24.7)	73 (24.8)	55 (22.0)
<i>Total w/septic shock</i>	---	18 (5.9)	---	3 (5.9)	6 (6.7)	15 (5.1)	20 (8.0)
CNS Infection	---	---	---	---	1 (1.1)	1 (0.3)	---
Soft Tissue Infection	---	---	---	1 (2.0)	3 (3.4)	4 (1.4)	2 (0.8)
Central Venous Catheter	---	3 (1.8)	---	---	---	2 (0.7)	2 (0.8)
Endocarditis	---	---	---	---	---	1 (0.3)	2 (0.8)
Gastrointestinal Infection	---	2 (1.2)	---	3 (5.9)	1 (1.1)	3 (1.0)	5 (2.0)
Genitourinary Infection	---	10 (3.3)	---	5 (9.8)	2 (2.2)	9 (3.1)	6 (2.4)
Respiratory Infection	---	28 (9.2)	1 (1.6)	2 (3.9)	5 (5.6)	40 (13.6)	37 (14.8)
Viral Infection	---	---	---	---	---	1 (0.3)	---
Other Infection	---	---	---	1 (2.0)	---	5 (1.7)	2 (0.8)
Not Specified	---	14 (4.6)	3 (4.8)	2 (3.9)	13 (14.6)	17 (5.8)	9 (3.6)
Soft Tissue Infection					---		
<i>Total</i>	1 (3.8)	10 (3.3)	1 (1.6)	4 (7.8)	6 (6.7)	18 (6.1)	11 (4.4)
Cellulitis	1 (3.8)	5 (1.6)	1 (1.6)	3 (5.9)	5 (5.6)	15 (5.1)	10 (4.0)
Other	---	5 (1.6)	---	1 (2.0)	1 (1.1)	3 (1.0)	1 (0.4)
CNS Infection							
<i>Total</i>	---	1 (0.3)	---	---	2 (2.2)	2 (0.7)	---
Meningitis	---	---	---	---	---	2 (0.7)	---
Other	---	1 (0.3)	---	---	2 (2.2)	---	---

	FOLLICULAR LYMPHOMA				CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R		IDEL+R		IDEL
Infection Type, # (%)	Study 101-09	Medicare	Study 313-0124	Medicare	Study 312-0116	Medicare	Medicare
	<i>n = 26</i>	<i>n = 305</i>	<i>n = 62</i>	<i>n = 51</i>	<i>n = 89</i>	<i>n = 294</i>	<i>n = 250</i>
CNS Infection							
<i>Total</i>	---	1 (0.3)	---	---	2 (2.2)	2 (0.7)	---
Meningitis	---	---	---	---	---	2 (0.7)	---
Other	---	1 (0.3)	---	---	2 (2.2)	---	---
Endocarditis							
<i>Total</i>	---	---	---	---	---	2 (0.7)	2 (0.8)
Gastrointestinal Infection							
<i>Total</i>	---	14 (4.6)	5 (8.1)	7 (13.7)	6 (6.7)	16 (5.4)	15 (6.0)
Enterocolitis w/c.diff	---	8 (2.6)	---	4 (7.8)	1 (1.1)	8 (2.7)	11 (4.4)
Gastroenteritis	---	1 (0.3)	5 (8.1)	1 (2.0)	3 (3.4)	2 (0.7)	3 (1.2)
Other GI Infection	---	6 (2.0)	---	3 (5.9)	2 (2.2)	6 (2.0)	2 (0.8)
Genitourinary Infection							
<i>Total</i>	1 (3.8)	41 (13.4)	4 (6.5)	11 (21.6)	5 (5.6)	33 (11.2)	48 (19.2)
Pyelonephritis	---	4 (1.3)	---	---	---	4 (1.4)	---
GU Device, implant, Graft	---	1 (0.3)	---	---	---	1 (0.3)	---
Urinary Tract Infection	1 (3.8)	39 (12.8)	4 (6.5)	11 (21.6)	4 (4.5)	31 (10.5)	48 (19.2)
Other GU Infection	---	---	---	---	1 (1.1)	---	---
Respiratory Infection							
<i>Total</i>	6 (23.1)	70 (23.0)	10 (16.1)	16 (31.4)	37 (41.6)	93 (31.6)	76 (30.4)
Upper Respiratory	---	5 (1.6)	---	2 (3.9)	7 (7.9)	11 (3.7)	5 (2.0)
Lower Respiratory	6 (23.1)	67 (22.0)	10 (16.1)	15 (29.4)	35 (39.3)	88 (29.9)	74 (29.6)
Pneumonia	4 (15.4)	61 (20.0)	10 (16.1)	14 (27.5)	25 (28.1)	78 (26.5)	69 (27.6)
Location Not Specified	---	---	---	---	1 (1.1)	---	---

	FOLLICULAR LYMPHOMA				CHRONIC LYMPHOCYTIC LEUKEMIA		
	IDEL		IDEL+R		IDEL+R		IDEL
Infection Type, # (%)	Study 101-09	Medicare	Study 313-0124	Medicare	Study 312-0116	Medicare	Medicare
	<i>n = 26</i>	<i>n = 305</i>	<i>n = 62</i>	<i>n = 51</i>	<i>n = 89</i>	<i>n = 294</i>	<i>n = 250</i>
Viral Infection							
<i>Total</i>	3 (11.5)	10 (3.3)	3 (4.8)	---	4 (4.5)	13 (4.4)	4 (1.6)
CMV	1 (3.8)	1 (0.3)	1 (1.6)	---	1 (1.1)	2 (0.7)	---
Herpes Zoster	2 (7.7)	5 (1.6)	1 (1.6)	---	1 (1.1)	4 (1.4)	3 (1.2)
Influenza	---	4 (1.3)	1 (1.6)	---	---	7 (2.4)	1 (0.4)
Other Virus	---	---	---	---	2 (2.2)	---	---
Other Infection							
<i>Total</i>	1 (3.8)	7 (2.3)	6 (9.7)	2 (3.9)	22 (24.7)	14 (4.8)	8 (3.2)
Devices, implants, grafts	---	---	---	---	---	5 (1.7)	---
Pathogen only specified	---	1 (0.3)	---	1 (2.0)	---	3 (1.0)	3 (1.2)
Location not specified	---	---	---	---	3 (3.4)	---	---
Other Infection	1 (3.8)	6 (2.0)	6 (9.7)	1 (2.0)	20 (22.5)	7 (2.4)	5 (2.0)

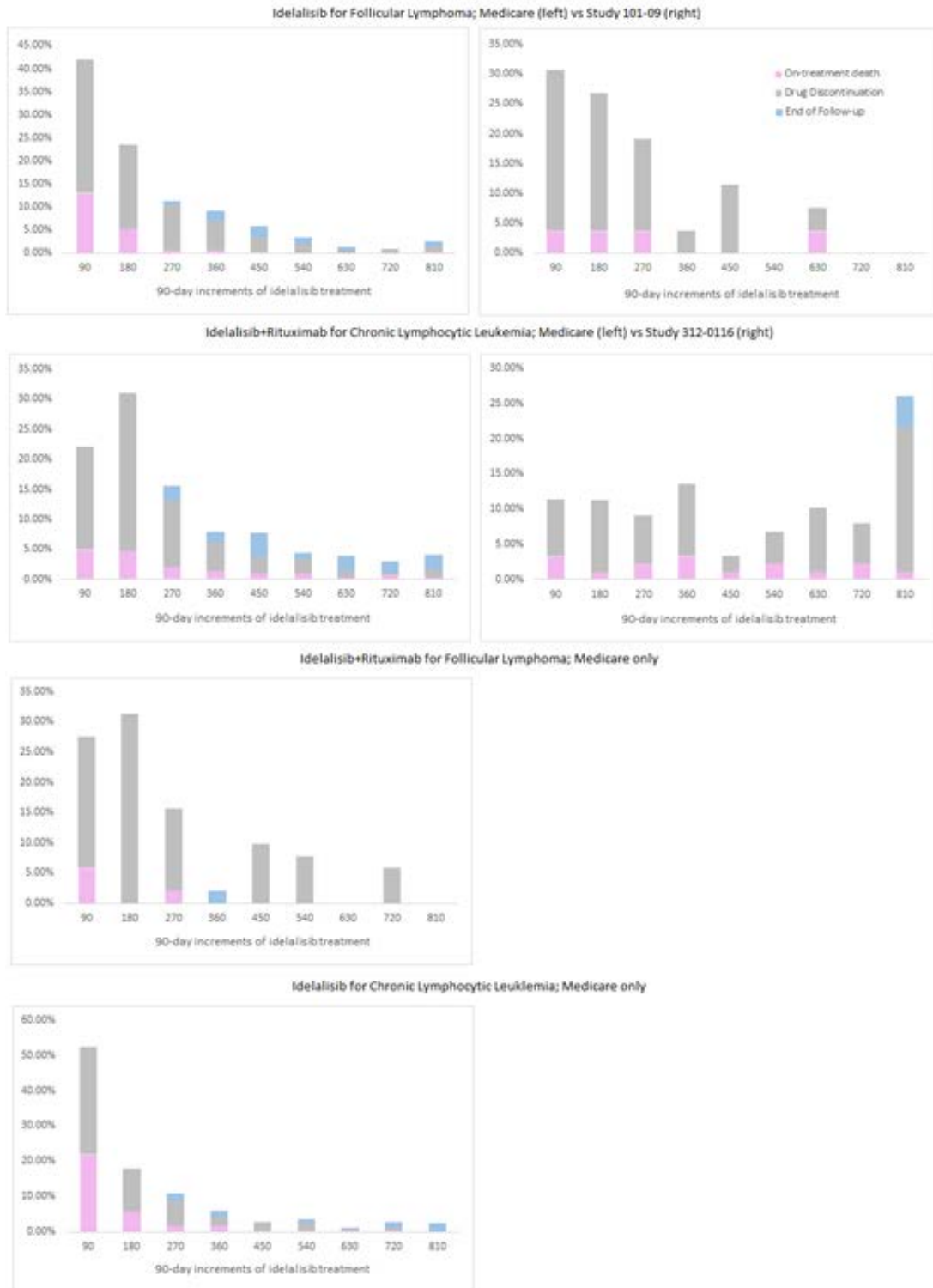
Rows may sum to more than the totals or subtotals because patients may have had more than one type of infection.

eTable 4: Infectious organisms present in Medicare beneficiaries during inpatient stays or coded with receipt of an antibiotic

Pathogen	Number	Percent
	<i>n = 900</i>	<i>100%</i>
Candida	58	6.4
Escherichia coli	44	4.9
Clostridium difficile	30	3.3
Streptococcus	25	2.8
Gram-negative	23	2.6
Other Viral	23	2.6
Pseudomonas	22	2.4
Herpes Zoster	16	1.8
MRSA	16	1.8
Influenza	13	1.4
Enterococcus	11	1.2
Pneumocystis jirovecii	10	1.1
Staphylococcus	10	1.1
Klebsiella pneumoniae	7	0.8
MSSA	7	0.8
Aspergillosis	4	0.4
Cytomegalovirus	4	0.4
Rhinovirus	4	0.4
Anaerobes	3	0.3
Respiratory Syncytial Virus	3	0.3
Cryptococcosis	2	0.2
Legionella	2	0.2
Listeria	1	0.1
Mycoplasma	1	0.1
Pneumococcus	1	0.1
Salmonella	1	0.1

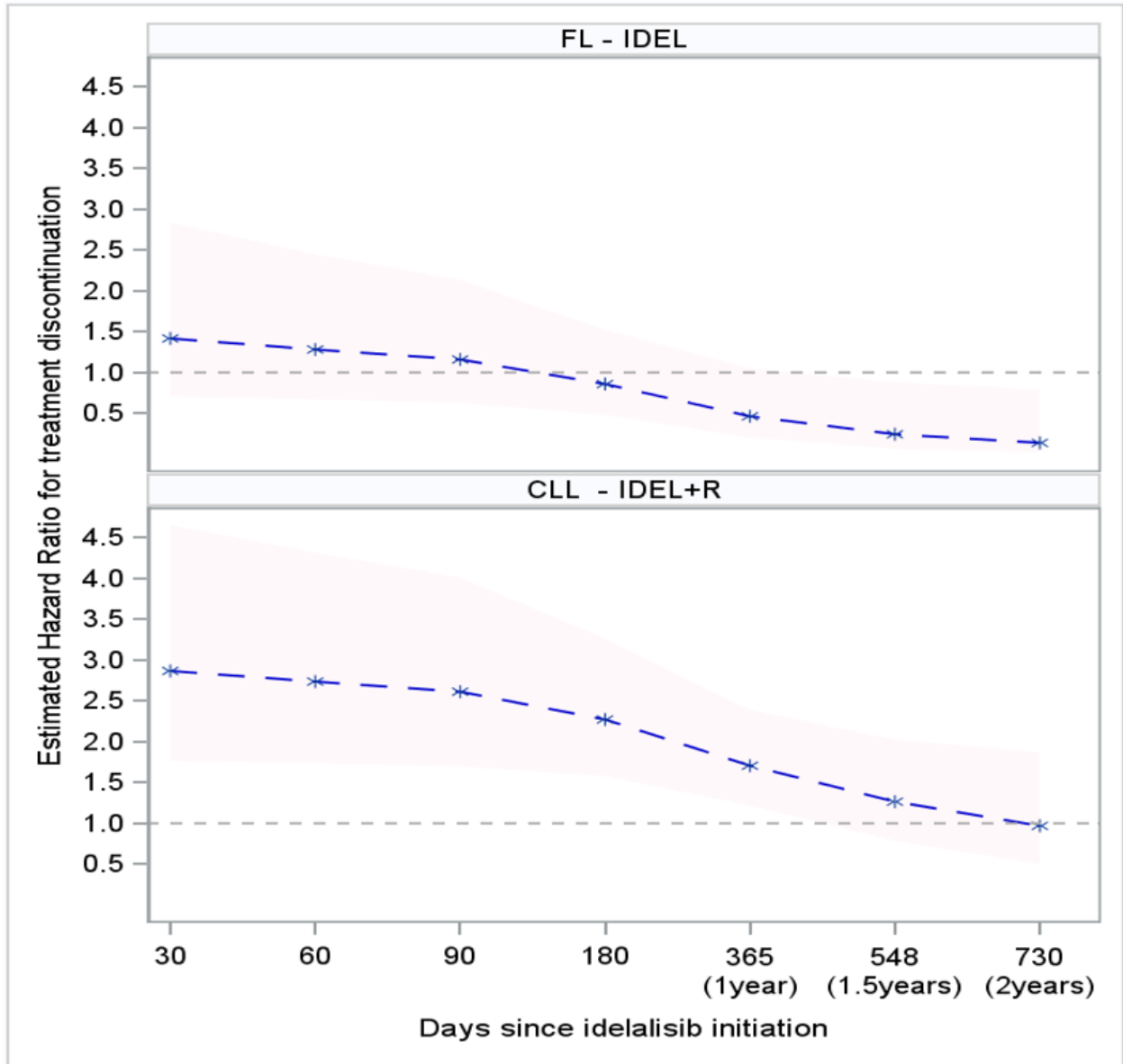
MRSA = Methicillin-resistant staphylococcus aureus; MSSA = methicillin susceptible staphylococcus aureus.

eFigure1: Reasons for censoring in time to treatment discontinuation analysis by 90-day therapy increment among Medicare beneficiaries and trial subjects by study cohort



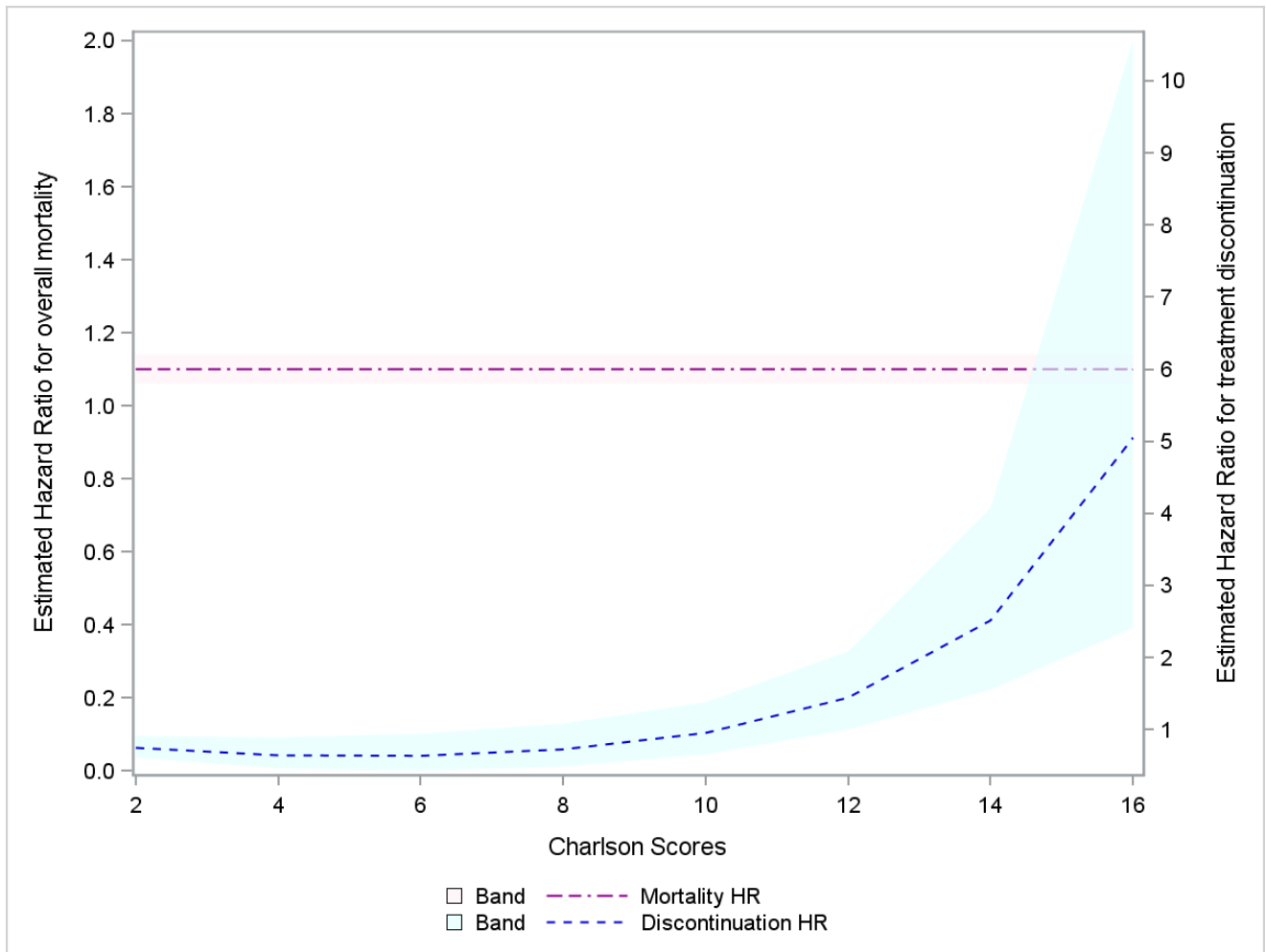
Medicare beneficiaries had higher rates of early mortality and treatment discontinuation than clinical trial subjects.

eFigure 2. Estimated hazard ratio for treatment discontinuation over time, Medicare vs. clinical Trial



This figure depicts the change the Hazard Ratio for treatment discontinuation, by time since idelalisib initiation, when comparing Medicare beneficiaries versus clinical trial subjects. Horizontal dashed line represents a HR of 1.0.

eFigure 3: Hazard ratio for treatment discontinuation and mortality among clinical trial patients and Medicare beneficiaries with each 1-Unit increase in Charlson score



This figure depicts the impact of each 1-unit increase in Charlson score on the outcomes of treatment discontinuation and mortality. Multiple variable definitions for Charlson score were evaluated based on model fit, including Akaike Information Criterion, tests of linearity, and plots of log Hazard Ratio (HR). Charlson score had best model fit for the overall mortality outcome in 1-unit increments, while the best fit for the treatment discontinuation model was both a linear and quadratic term. As shown in the above graph, the HR for mortality is constant with each 1-unit increase in Charlson Score (HR 1.10, 95%CI 1.06-1.14). A higher Charlson score predicts a more (than linearly expected) increase in the HR for treatment discontinuation.

eFigure 4: Rates of serious infections by study cohort for ≤6 versus >6 months of idelalisib treatment

