

Running head: CLINICOPATHOLOGICAL FEATURES OF COLITIS

Supplementary Table 1: Characteristics of total cohort (n=118)

Characteristics	Colitis (n=118) N(%)	No colitis (n=1343) N(%)	p-value
Age, median	62 (30-92)	66 (16-101)	0.02
Gender			
Male	80 (66.2)	960 (65.7)	0.99
Female	41 (33.8)	501 (34.3)	
Type of Treatment			
Ipilimumab only	3 (6.5)	43 (93.5)	<.0001
Anti PD-1 (Nivolumab/Pembrolizumab)	35 (3.5)	965 (96.5)	
Combination therapy (Ipilimumab/Anti PD1)	80 (14.5)	473 (85.5)	
Endoscopy and Histopathology available	67 (56.8)	-	

CLINICOPATHOLOGICAL FEATURES OF COLITIS

2

Supplementary Table 2: Characteristics of Patients with Colitis

Characteristics	Overall (n=115)*	PD1 (n=35)	IPI+PD1 (n=80)	P-value
Age, years - median (range)	62 (30-92)	66 (37-92)	62 (30-78)	0.02
Sex, n (%)				
Female	40 (35)	11 (31)	29 (36)	0.62
Male	75 (65)	24 (69)	51 (64)	
Autoimmune disease history, n (%)				
No	102 (89)	33 (94)	69 (86)	0.21
Yes	13 (11)	2 (6)	11 (14)	
ECOG				
0	92 (80)	30 (86)	62 (78)	0.31
≥1	23 (20)	5 (14)	18 (22)	
AJCC v8 staging, n (%)				
Resected stage III [†]	17 (15)	9 (26)	8 (10)	0.01
Unresected stage IIIC	3 (2)	2 (6)	1 (1)	
Stage IV	95 (83)	24 (69)	71 (89)	
Other irAEs, n (%)				
Rash	50 (44)	12 (34)	38 (48)	0.19
Vitiligo	23 (20)	7 (20)	16 (20)	1.00
Pneumonitis	12 (10)	2 (6)	10 (13)	0.27
Nephritis	4 (4)	0 (0)	4 (5)	0.18
Hypophysitis	12 (10)	2 (6)	10 (13)	0.27
Thyroid disorders	22 (20)	1 (3)	21 (27)	< 0.01
Hepatitis	21 (19)	4 (13)	17 (22)	0.26

2

CLINICOPATHOLOGICAL FEATURES OF COLITIS

3

Objective response, n (%) ^{¶¶}				
CR/PR/SD**	53 (54)	14 (54)	39 (54)	0.99
PD	45 (46)	12 (46)	33 (46)	

*Excludes 3 patients with ipilimumab only.

**CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

[¶] Received treatment as adjuvant and neo-adjuvant immunotherapy

^{¶¶} Only in advanced melanoma(stage IIIC/IV melanoma) patients

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response;

PD, disease progression

3

CLINICOPATHOLOGICAL FEATURES OF COLITIS

4

Supplementary Table 3: Endoscopic and histopathologic features of colitis in IPI+PD1 and PD1 treated patients

Endoscopic and histopathologic characteristics	Overall (n=64)*	PD1 (n=20)	IPI+ PD1 (n=44)	P-value
Degree of Inflammation, n(%)				
Absent	17 (26.6)	6 (30.0)	11 (25.0)	0.56
Mild	22 (34.4)	8 (40.0)	14 (31.8)	
Moderate	23 (35.9)	5 (25.0)	18 (40.9)	
Severe	2 (3.1)	1 (5.0)	1 (2.3)	
Pattern of Inflammation, n(%)				
Absent	17 (26.6)	5 (25.0)	15 (34.1)	0.60
Diffuse	19 (29.7)	4 (20.0)	12 (27.3)	
Patchy	17 (26.6)	7 (35.0)	10 (22.7)	
Confluent	11 (17.2)	4 (20.0)	7 (15.9)	
Congestion, n(%)				
Absent	24 (37.5)	9 (45.0)	14 (32.6)	0.34
Present	40 (53.1)	11 (55.0)	29 (67.4)	
Erythema , n(%)				
Absent	30 (46.9)	11(55.0)	19 (43.2)	0.38
Present	34 (53.1)	9(45.0)	25 (56.8)	
Ulceration, n(%)				
Absent	48 (75.0)	15 (75.0)	33 (75.0)	1.0
Few	7 (10.9)	2 (10.0)	5 (11.4)	
Multiple	9 (14.1)	3 (15.0)	6 (13.6)	
Mucopurulent exudate				
Absent	45 (70.3)	15 (75.0)	25 (56.8)	0.70

4

CLINICOPATHOLOGICAL FEATURES OF COLITIS

5

Mild	16 (25.0)	5 (10.0)	11 (25.0)	
Severe	3 (14.1)	0 (0.0)	3 (6.8)	
Crypt architecture, n(%)				
Normal	39 (60.9)	12 (60.0)	27 (61.4)	0.59
Mild architectural change	17 (26.6)	7 (35.0)	10 (22.7)	
Moderate diffuse/multifocal Abnormalities	4 (6.3)	0 (0.0)	4 (9.1)	
Severe diffuse/multifocal abnormalities	4 (6.3)	1 (5.0)	3 (6.8)	
Mucin depletion, n(%)				
Absent	34 (53.1)	15 (75.0)	19 (43.2)	0.08
Indefinite	7 (26.6)	0 (0.0)	7 (15.9)	
Minimal	18 (28.1)	4 (20.0)	14 (31.8)	
Marked	5 (7.8)	1 (5.0)	4 (9.1)	
Chronic inflammatory infiltrate, n (%)				
No increase	9 (14.1)	4 (20.0)	5 (11.4)	0.42
Mild/equivocal increase	27 (42.2)	10 (50.0)	17 (38.6)	
Moderate increase	25 (39.1)	6 (30.0)	19 (43.2)	
Marked increase	3 (4.7)	0 (0.0)	3 (6.8)	
Pattern of inflammatory infiltrate, n (%)				
Absent	9 (14.1)	4 (20.0)	5 (11.4)	0.52
Focal	17 (26.6)	6 (30.0)	11 (25.0)	
Diffuse	38 (59.4)	10 (50.0)	28 (63.6)	
Lamina propria eosinophils, n (%)				
No increase	62 (96.9)	19 (95.0)	43 (97.7)	0.53
Mild/equivocal increase	2 (3.1)	1 (5.0)	1 (2.3)	

5

CLINICOPATHOLOGICAL FEATURES OF COLITIS

6

Lamina propria neutrophils , n (%)				
No increase	17 (26.6)	8 (40.0)	9 (20.5)	0.08
Mild/equivocal increase	24 (37.5)	9 (45.0)	15 (34.1)	
Moderate increase	19 (29.7)	2 (10.0)	17 (38.6)	
Marked Increase	4 (6.3)	1 (4.0)	3 (6.8)	
Apoptotic cells in epithelium, n (%)				
Absent	44 (68.8)	12 (60.0)	32 (72.7)	0.37
Occasional(<2 apoptotic bodies/10 crypts)	12 (18.8)	5 (25.0)	7 (15.9)	
Borderline (3-6 apoptotic bodies/10 crypts)	7 (10.9)	2 (10.0)	5 (11.4)	
Prominent (>7 apoptotic bodies/10 crypts)	1 (1.6)	1 (5.0)	0 (0.0)	
Erosion in epithelium, n (%)				
Absent	51 (79.7)	19 (95.0)	32 (72.7)	0.05
Present	13 (20.3)	1 (5.0)	12 (27.3)	

6

CLINICOPATHOLOGICAL FEATURES OF COLITIS

7

Supplementary Table 4: Features of Steroid-sensitive, Infliximab-sensitive and Infliximab-refractory groups

Characteristics	Overall (n=64)	Steroid Sensitive (n=24)	Infliximab Sensitive (n=31)	Infliximab Refractory (n=9)	P value
Endoscopic features					
Type of Endoscopy, n (%)					
Colonoscopy	29 (45.3)	13 (54.2)	11 (35.5)	5 (55.6)	0.30
Sigmoidoscopy	35 (54.7)	11 (45.8)	20 (64.5)	4 (44.4)	
Vascularity, n(%)					
Normal	27 (42.2)	13 (54.2)	12 (38.7)	2 (22.2)	0.39
Partially absent	17 (26.6)	6 (25.0)	9 (29.0)	2 (22.2)	
Totally absent	20 (31.3)	5 (20.8)	10 (32.0)	5 (55.6)	
Congestion (oedema)					
Absent	24 (37.5)	11 (45.8)	11 (35.5)	2 (22.2)	0.44
Present	40 (62.5)	13 (54.2)	20 (64.5)	7 (77.8)	
Erythema					
Absent	30 (46.9)	14 (58.3)	14 (45.2)	2 (22.2)	0.19
Present	34 (53.1)	10 (41.7)	17 (54.8)	7 (77.8)	
Ulcer					
Absent	48 (75.0)	19 (79.2)	25 (80.6)	4 (44.4)	0.07
Few	7 (10.9)	3 (12.5)	1 (3.2)	3 (33.3)	
Multiple	9 (14.1)	2 (8.3)	5 (16.1)	2 (22.2)	
Histopathologic features					
Crypt architectural changes, n(%)					
Absent	39 (60.9)	16 (66.7)	19 (61.3)	4 (44.4)	0.73

7

CLINICOPATHOLOGICAL FEATURES OF COLITIS

8

Mild	17 (26.6)	6 (25.0)	7 (22.6)	4 (44.4)	
Moderate	4 (6.3)	1 (4.2)	3 (9.7)	0 (0.0)	
Severe	4 (6.3)	1 (4.2)	2 (6.5)	1 (11.1)	
Mucin depletion,n(%)					
Absent	34 (53.1)	17 (70.8)	13 (41.9)	4 (44.4)	0.19
Indefinite	7 (10.9)	2 (8.3)	4 (12.9)	1 (11.1)	
Minimal	18 (28.1)	5(20.8)	9 (29.0)	4 (44.4)	
Marked	5 (7.8)	0 (0.0)	5 (16.1)	0 (0.0)	
Pattern of inflammatory infiltrate					
Absent	9 (14.1)	5 (20.8)	3 (9.7)	1 (11.1)	0.56
Focal	17 (26.6)	5 (20.8)	8 (25.8)	4 (44.4)	
Diffuse	38 (59.4)	14 (58.3)	20 (64.5)	4 (44.4)	
Lamina propria eosinophils, n (%)					
No increase	62 (96.9)	23 (95.8)	30 (96.8)	9 (100)	1.00
Mild/equivocal increase	2 (3.1)	1 (4.2)	1 (3.2)	0 (0.0)	
Apoptotic cells in epithelium, n (%)					
Absent	44 (68.0)	18 (75.8)	22 (71.0)	4 (44.4)	0.15
Occasional(<2 apoptotic bodies/10 crypts)	12 (18.8)	5 (20.8)	4 (12.9)	3 (33.3)	
Borderline (3-6 apoptotic bodies/10 crypts)	7 (10.9)	1 (4.2)	5 (16.1)	1 (11.1)	
Prominent (>7 apoptotic bodies/10 crypts)	1 (1.6)	0 (0.0)	0 (0.0)	1 (11.1)	
Location of intraepithelial lymphocytosis, n (%)					
Absent	43 (67.2)	15 (62.5)	21 (67.7)	7 (77.8)	0.39
Crypt predominant	12 (18.8)	4 (16.7)	7 (22.6)	2 (22.2)	
Crypt and superficial	9 (14.1)	5 (20.8)	3 (9.7)	0 (0.0)	
Intraepithelial lymphocytosis grade					

8

CLINICOPATHOLOGICAL FEATURES OF COLITIS

9

Absent	43 (67.2)	17 (65.4)	21 (67.7)	7 (77.8)	0.65
Borderline 10-20/100HPF	13 (20.3)	4 (15.4)	7 (22.6)	2 (22.2)	
Severe >20/100 HPF	8(12.5)	5 (19.2)	3 (9.7)	0 (0.0)	
Ulceration					0.13
Absent	62 (96.9)	23 (95.8)	22 (71.0)	8 (88.9)	
Present	2 (3.1)	1 (4.2)	9 (29.0)	1 (11.1)	

9