INESTABILIDAD MICROSATELITAL, puesta al día en relación a KEYNOTE-177

Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study

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Córdoba, 09 de Junio 2020

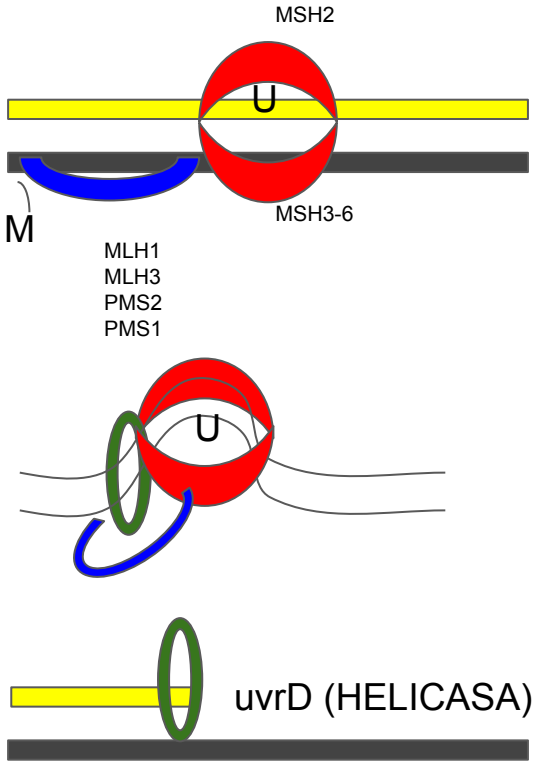
Methyl mismatch repair system

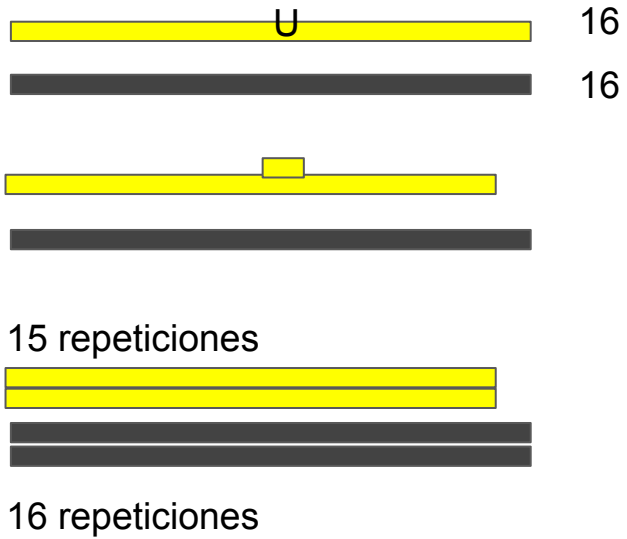
Mut proteins
Mut-S
Mut-L
Mut-H

Deamination
C - U
A - hypoxanthine

Methylation

“GATC” (DAM)





1. **Los microsatélites son secuencias cortas de ácido desoxirribonucleico (ADN), repetidas en tándem a lo largo del genoma. En el genoma humano hay más de medio millón de microsatélites**

2. **La inestabilidad de microsatélites (IMS) se define como una disminución o un aumento en la longitud de los microsatélites en el ADN tumoral, en comparación con el ADN normal correspondiente.**

3. **Las mutaciones en los genes del sistema de reparación de apareamiento erróneos o mismatch repair (MMR) impiden que los errores de replicación cometidos por el ADN polimerasa sean reparados, lo que permite la aparición de un fenotipo mutador y, por ende, una elevada tasa de mutación celular, y da origen a la IMS**

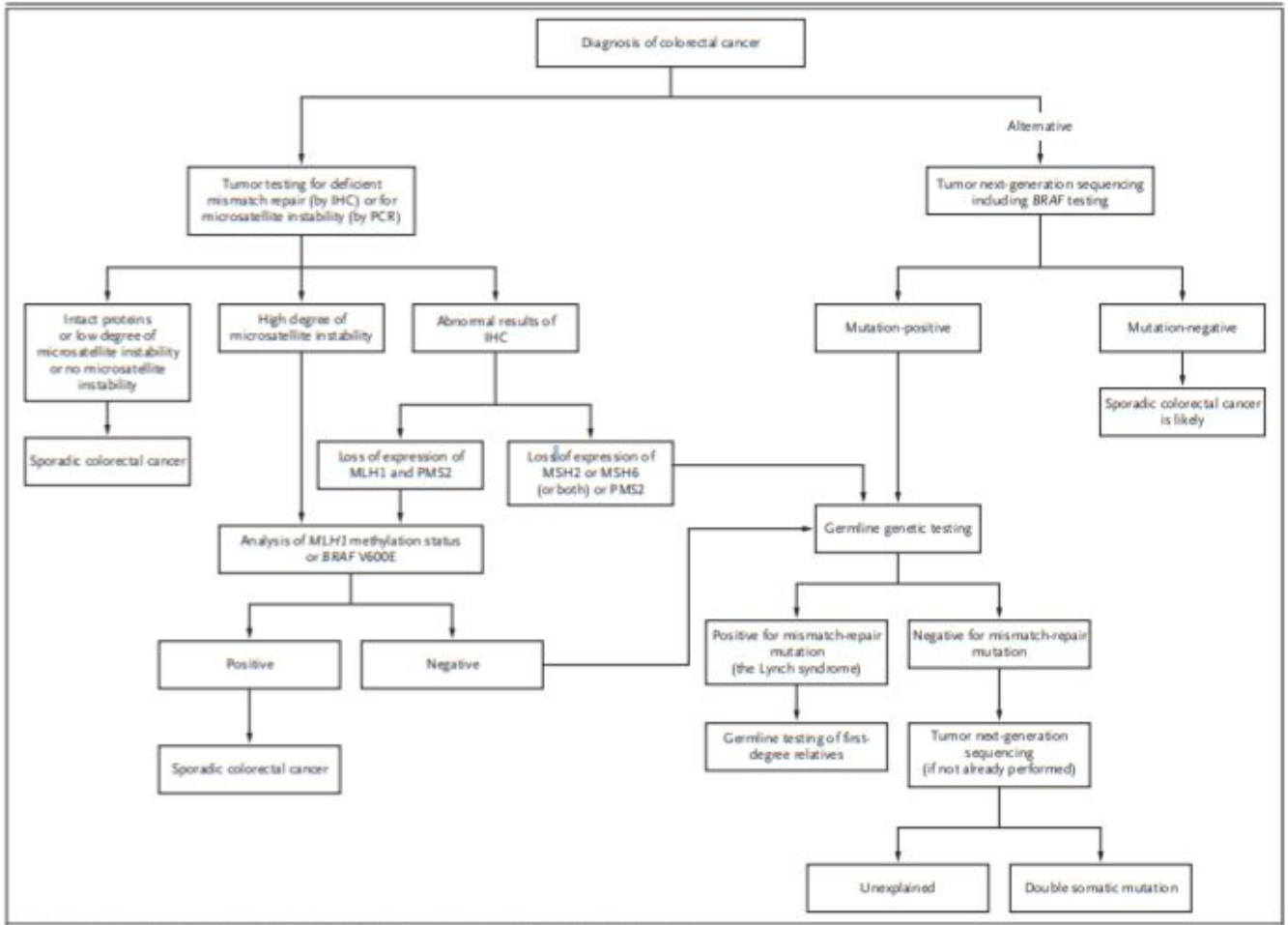
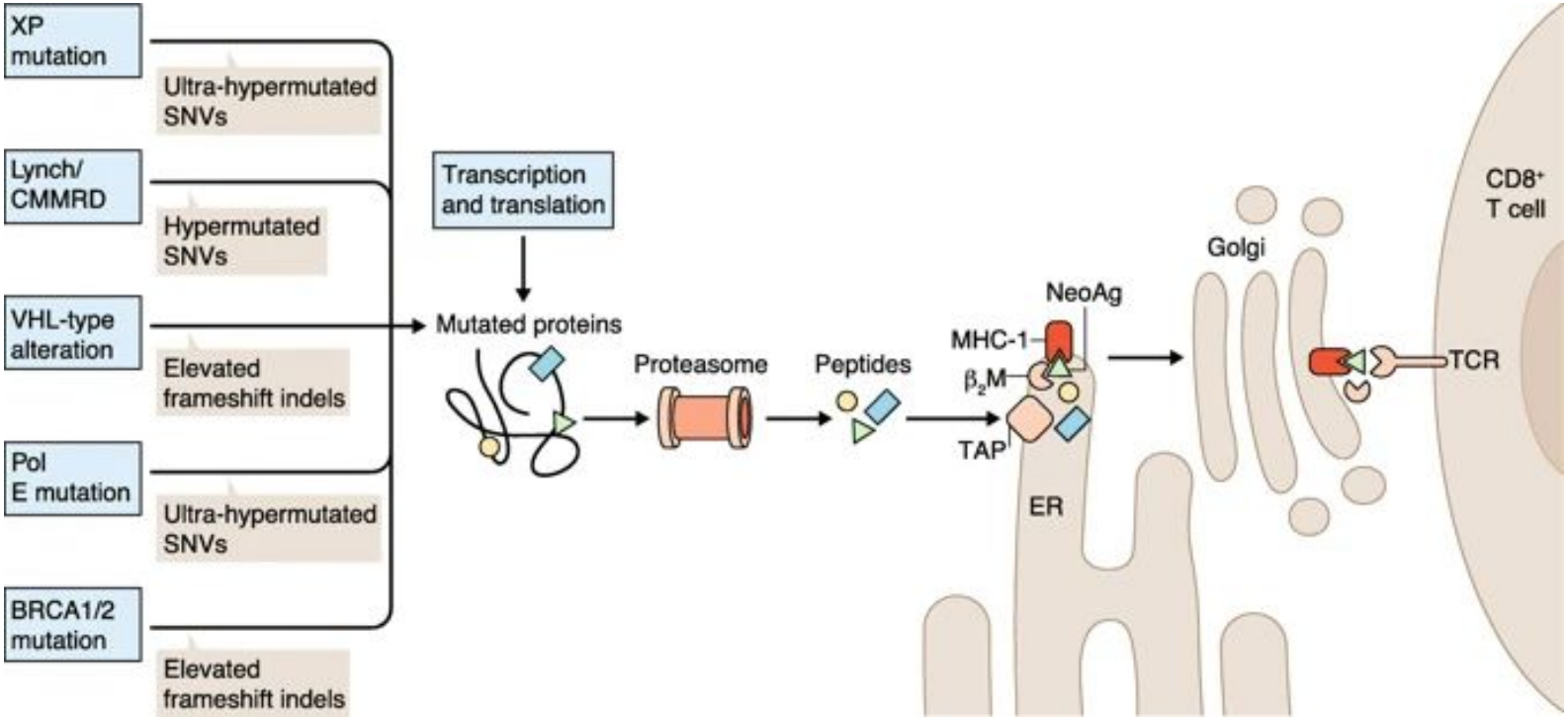
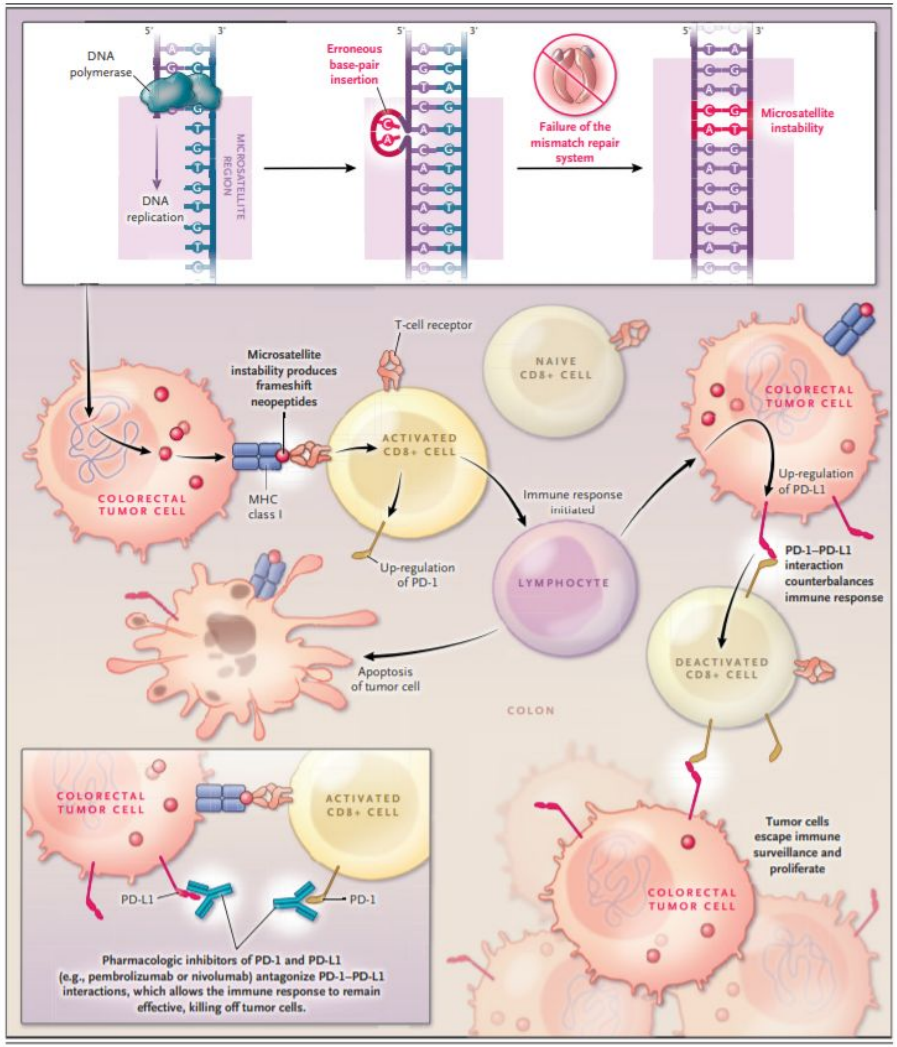


Figure 1. Algorithm for Lynch-Syndrome Testing in Patients with a New Diagnosis of Colorectal Cancer.

IHC denotes immunohistochemical analysis, and PCR polymerase-chain-reaction–based testing.


XP mutation
Ultra-hypermutated SNVs
Lynch/ CMMRD
Hypermutated SNVs
VHL-type alteration
Elevated frameshift indels
Pol E mutation
Ultra-hypermutated SNVs
BRCA1/2 mutation
Elevated frameshift indels
Transcription and translation
Mutated proteins
Proteasome
Peptides
TAP
MHC-1
β_2M
NeoAg
ER
Golgi
TCR
CD8+ T cell


DNA polymerase
DNA replication
MICROSATELLITE REGION
Erroneous base-pair insertion
Failure of the mismatch repair system
Microsatellite instability
T-cell receptor
NAIVE CD8+ CELL
Microsatellite instability produces frameshift neopeptides
ACTIVATED CD8+ CELL
COLORECTAL TUMOR CELL
MHC class I
Up-regulation of PD-1
Immune response initiated
LYMPHOCYTE
Apoptosis of tumor cell
COLORECTAL TUMOR CELL
Up-regulation of PD-L1
PD-1–PD-L1 interaction counterbalances immune response
DEACTIVATED CD8+ CELL
COLON
COLORECTAL TUMOR CELL
ACTIVATED CD8+ CELL
PD-L1
PD-1
Pharmacologic inhibitors of PD-1 and PD-L1 (e.g., pembrolizumab or nivolumab) antagonize PD-1–PD-L1 interactions, which allows the immune response to remain effective, killing off tumor cells.
Tumor cells escape immune surveillance and proliferate
COLORECTAL TUMOR CELL

KN-016: Study Design[1]

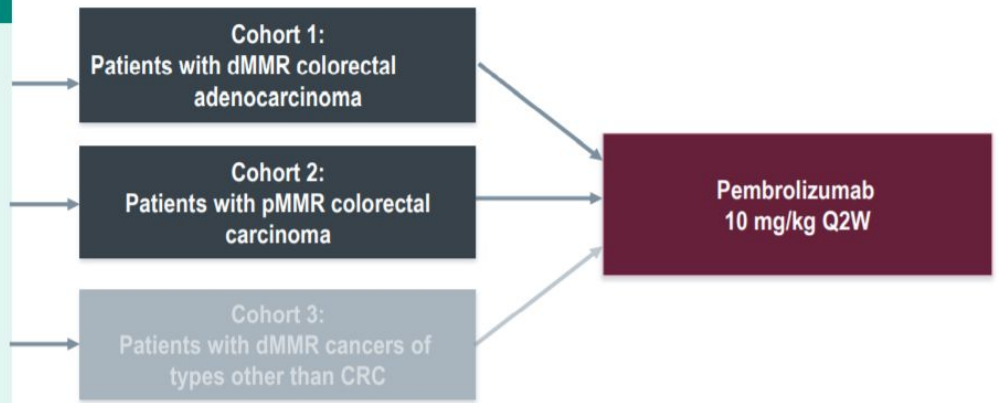
Phase 2 Study of Pembrolizumab in Patients With MSI Tumors

Patients (N=171)[1]:

For Cohorts 1 and 2[2]:

- Histologically proven metastatic or locally advanced dMMR colorectal solid tumor malignancy
  - IHC showing deficiency in MLH1, MSH2, MSH6, or PMS2
  - Or, MSI detected by PCR (instability in 2 or more loci); local testing acceptable
- Measurable disease
- Patients with colon cancer must have received at least 2 prior therapy regimens
- ECOG PS 0–1
- No prior anti–PD-1/PD-L1/PD-L2, anti-CD137, anti–OX-40, anti-CD40, anti–CTLA-4

Radiographic assessments were performed at 12 weeks and every 8 weeks thereafter[3]



Primary End Points[1]

irPFS and irORR rate, ORR

Secondary End Points[1]

OS, irPFS, PFS, BOR, DCR, irAEs

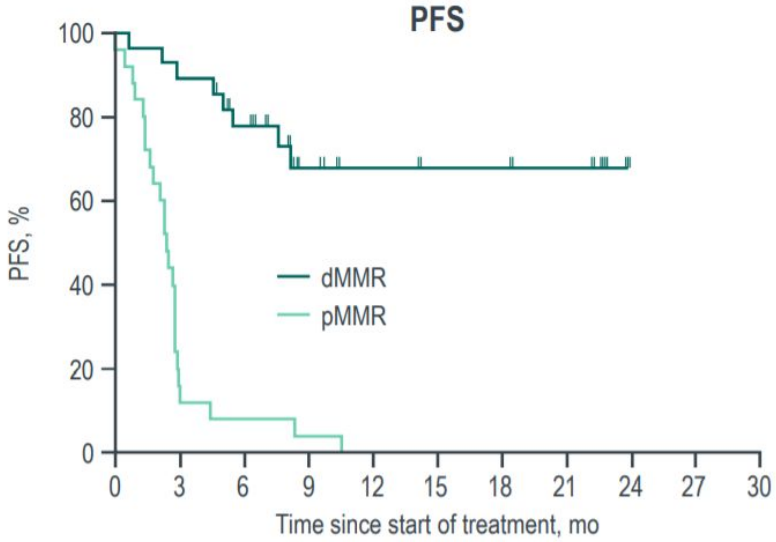
KN-016: Baseline Characteristics (Cohorts 1 and 2)[1]

Characteristic	dMMR CRC (n=28)		pMMR CRC (n=25)	
Age, y, median (range)	49 (26–75)		62 (32–79)	
	n	%	n	%
Female	13	46	9	36
ECOG PS 0	5	18	7	28
Liver metastases	14	50	15	60
Prior regimens, median	3		4	
Detected germline mutation/Lynch syndrome				
Yes	15	54	0	0
No	2	7	25	100
Unknown	11	39	0	0

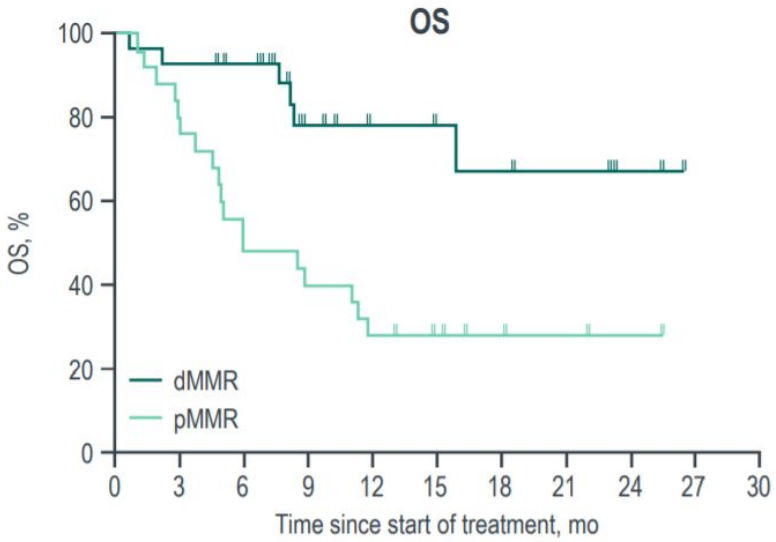
KN-016: Efficacy Results—Response Rate (Cohorts 1 and 2)[1]

	dMMR CRC (n=28)			pMMR CRC (n=25)		
Characteristic	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
CR	3	11		0	0	
PR	13	46		0	0	
SD (at 12 weeks)	9	32		4	16	
PD	1	4		11	44	
Not evaluable[a]	2	7		10	40	
ORR	16	57	39–73	0	0	0–13
DCR	25	89	73–96	4	16	6–35
Follow-up, mo, median		9.3			6	

KN-016: Efficacy Results—Survival (Cohorts 1 and 2)[1]



- mPFS was 2.3 months for pMMR
- mPFS was NR for dMMR



- mOS was 5.98 months for pMMR
- mOS was NR for dMMR

KN-016: Safety Summary (Cohorts 1 and 2)[1]

Event	All grades (N=53)		Grade 3 or 4 (N=53)	
	n	%	n	%
Generalized symptoms				
Fatigue	5	9	0	0
Arthralgia	8	15	0	0
Gastrointestinal				
Nausea/vomiting	4	8	0	0
Diarrhea/colitis	6	11	1	2
Endocrine disorders				
Thyroiditis/hypothyroidism	6	11	0	0
Hepatobiliary				
Pancreatitis	4	8	2	4
Hyperbilirubinemia	2	4	0	0

Event	All grades (N=53)		Grade 3 or 4 (N=53)	
	n	%	n	%
Rash/pruritus	13	25	1	2
Respiratory				
Pneumonitis	2	4	0	0
Other				
Anemia	2	4	1	2
Flu-like symptoms	2	4	0	0
Leukopenia	2	4	1	2
Thrombocytopenia	3	6	1	2

KN-158/164: Study Design

Pooled analysis of KEYNOTE-164 (MSI-H CRC) cohorts A and B and KEYNOTE-158 (MSI-H non-CRC) with ≥18 months of additional follow-up across 28 tumor types

Key Eligibility Criteria KEYNOTE-164[a]/158[a]

- Age ≥18 years
- dMMR/MSI-H locally confirmed by IHC/PCR, centrally by PCR
- Previously treated[c]
  - KEYNOTE-164
    - **Cohort A:** ≥2 prior lines of therapy (including fluoropyrimidine, oxaliplatin, and irinotecan)
    - **Cohort B :** ≥1 prior line of therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR)
  - KEYNOTE-158:
    - ≥1 prior therapy
- ECOG performance status 0/1
- Measurable disease RECIST v1.1

→ **Pembrolizumab 200 mg Q3W** →

Continue for/until:
- 35 cycles (~2 y)
- PD
- Unacceptable toxicity
- Study withdrawal

→ **Survival follow-up**

Primary End Points

ORR (RECIST v1.1) by central imaging vendor

Secondary End Points

DOR, PFS (RECIST v1.1) by central imaging vendor; OS, safety and tolerability

KN-158/164: Baseline Characteristics

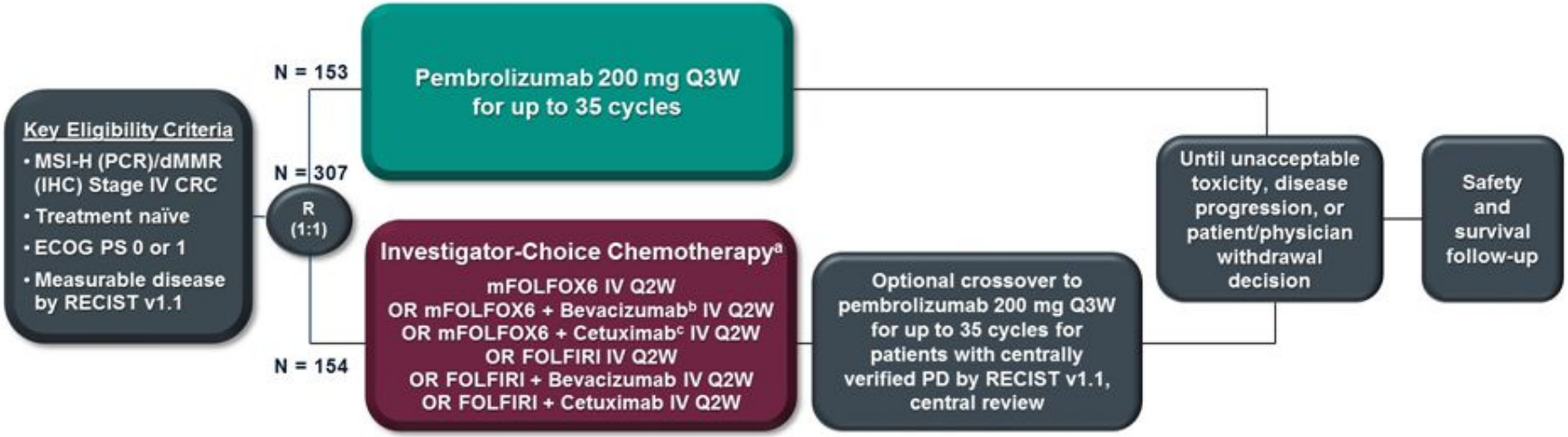
Characteristic, n (%)	KEYNOTE-164 N = 124	KEYNOTE-158 N = 233	Total N = 357
Age, median (range), years	55.5 (21 – 84)	60.0 (20 – 87)	59 (20 – 87)
≥65 years	44 (36)	87 (37)	131 (37)
Male	69 (56)	96 (41)	165 (46)
ECOG PS 1	73 (59)	120 (52)	193 (54)
Number of prior lines			
0	0	7 (3)[a]	7 (2)[a]
1	30 (24)	87 (37)	117 (33)
2	48 (39)	61 (26)	109 (31)
≥3	46 (37)	78 (33)	124 (35)

KN-158/164: Antitumor Response

Best Response	Pembrolizumab N=357	
	n	% (95% CI)
ORR	121	34 (29-39)
Complete response	30	8 (6-12)
Partial response	91	26 (21-30)
Stable disease	68	19 (15-24)
Progressive disease	145	41 (36-46)
Non-evaluable	6	2 (0-4)
No assessment	17	5 (3-8)
≧18 months, %	54	
Median DOR, month (range)	NR (2.9+ to 31.3+)	
Median PFS, month (95% CI)	4.0 (2.5-4.3)	
12-month PFS, %	35	
24-month PFS, %	31	
Median OS, month (95% CI)	27.8 (21.3-NR)	
12-month OS, %	65	
24-month OS, %	52	

Tumor type	N	CR, %	PR, %	ORR %	Median OS months, (95% CI)
Colorectal	124	6	27	33	NR (26.3–NR)
Endometrial	49	16	41	57	NR (27.2–NR)
Gastric	24	17	29	46	NR (7.2–NR)
Biliary	22	9	32	41	24.3 (6.5–NR)
Pancreatic	22	5	14	19	4.0 (2.1–9.8)
Small Intestine	19	16	26	42	NR (10.6–NR)
Ovarian	15	20	13	33	NR (3.8–NR)
Brain	13	0	0	0	5.6 (1.5–16.2)

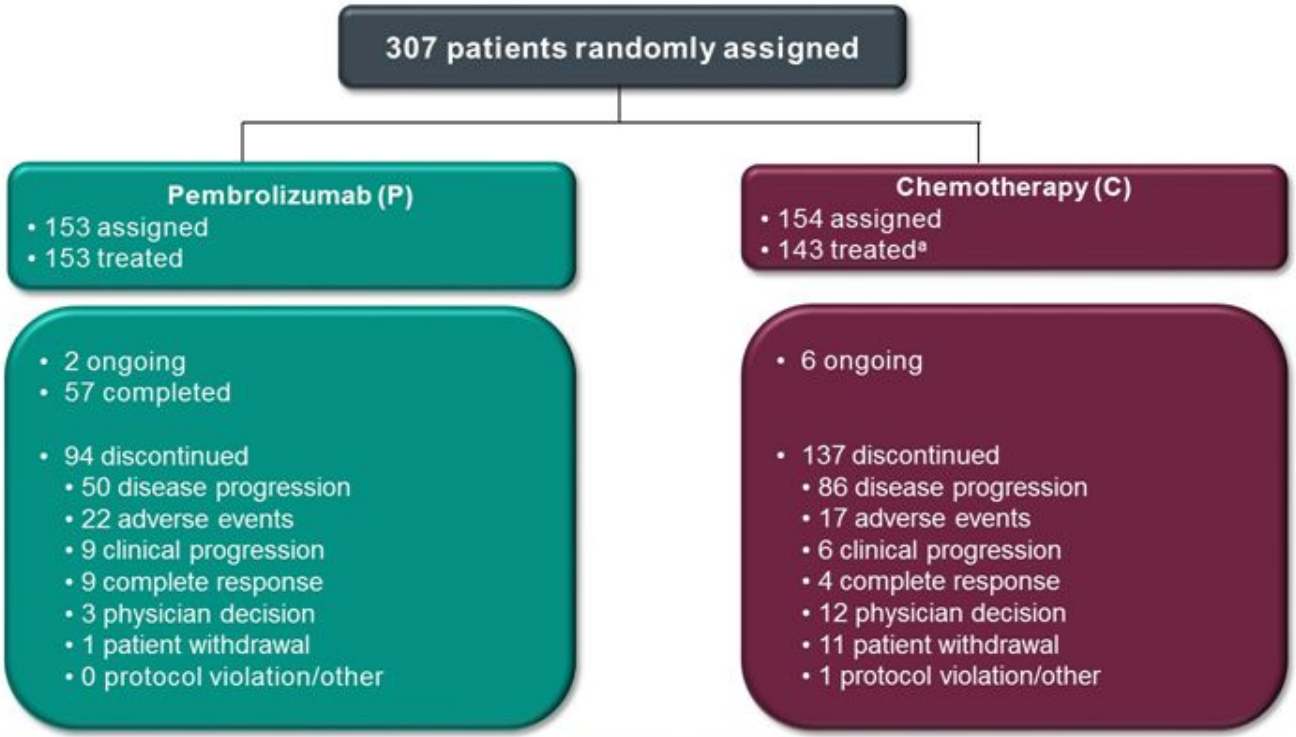
KEYNOTE-177 Study Design (NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Treatment Disposition



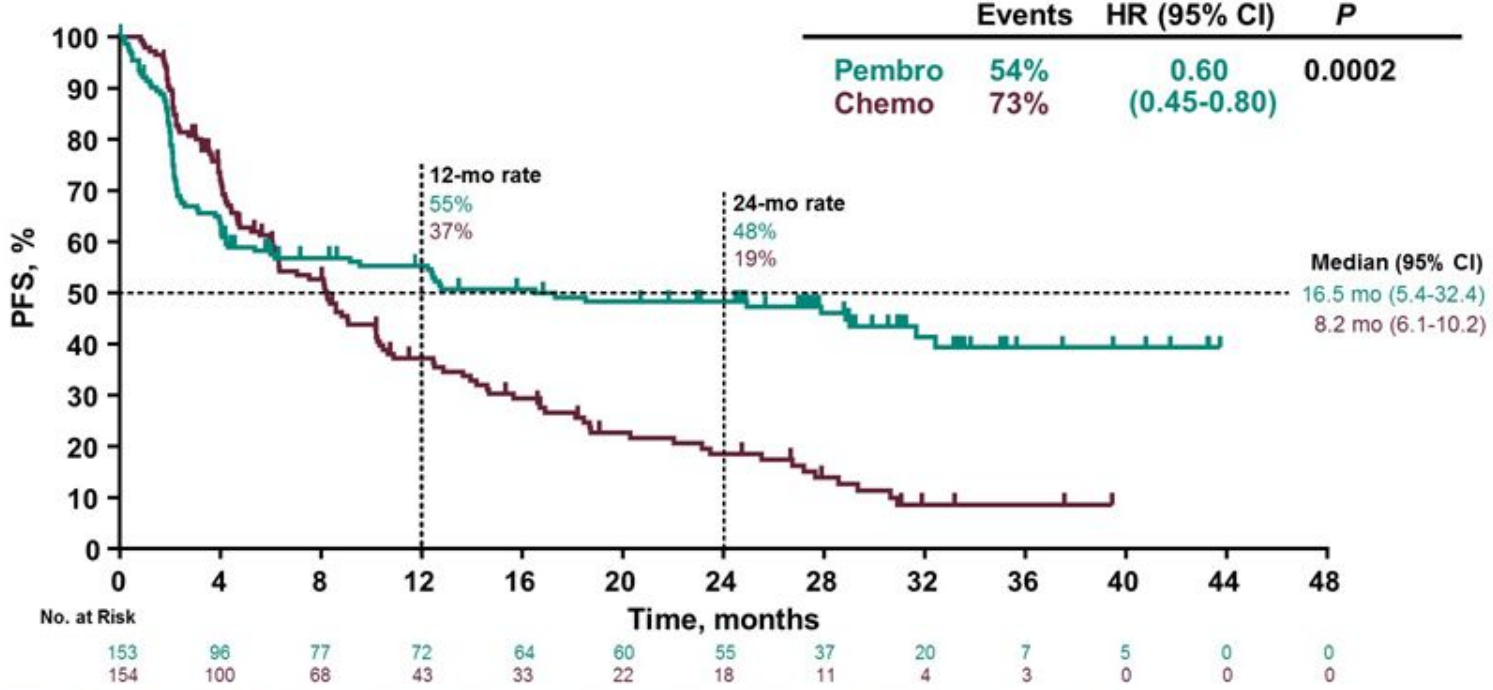
[a]11 patients received mFOLFOX6 only, 64 mFOLFOX6 plus bevacizumab, 5 FOLFOX6 plus cetuximab, 16 FOLFIRI alone, 36 FOLFIRI plus bevacizumab, and 11 FOLFIRI plus cetuximab.
Disease progression assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

Baseline Characteristics

	Pembrolizumab N = 153	Chemotherapy N = 154
Age, median (range), years	63.0 (24-93)	62.5 (26-90)
Male	71 (46)	82 (53)
ECOG PS 0	75 (49)	84 (55)
Metachronous disease	80 (52)	74 (48)
Hepatic metastases	71 (46)	54 (35)
Region		
Asia	22 (14)	26 (17)
Western Europe/North America	109 (71)	113 (73)
Rest of World	22 (14)	15 (10)
Primary tumor location		
Right	102 (67)	107 (70)
Left	46 (30)	42 (27)
Other/Missing	5 (3)	5 (3)
Prior systemic therapy		
Adjuvant	33 (22)	37 (24)
Neoadjuvant (peri-operative)	5 (3)	8 (5)
None	115 (75)	109 (71)
Mutation status		
BRAF, KRAS, NRAS all wildtype	34 (22)	35 (23)
BRAF V600E mutant	34 (22)	43 (28)
KRAS or *NRAS* mutant	33 (22)	41 (27)
Not evaluable[a]	52 (34)	38 (25)

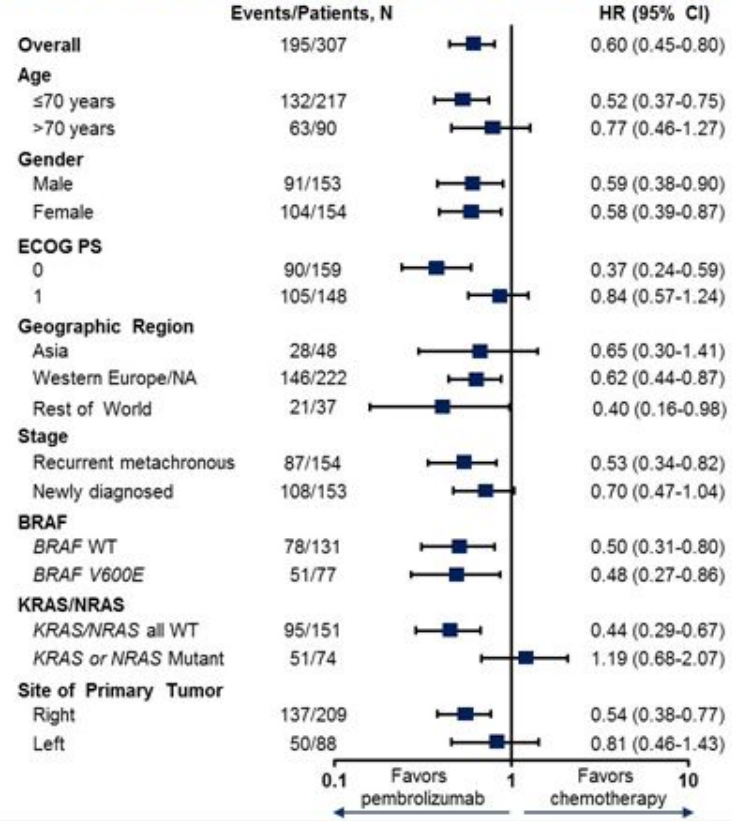
[a]Patients not evaluable for *BRAF, KRAS, NRAS* mutation if at least one of the mutation statuses was undetermined or missing, or the type of *BRAF* mutation was non V600E.Data cut-off: 19Feb2020.

Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Progression-Free Survival in Key Subgroups



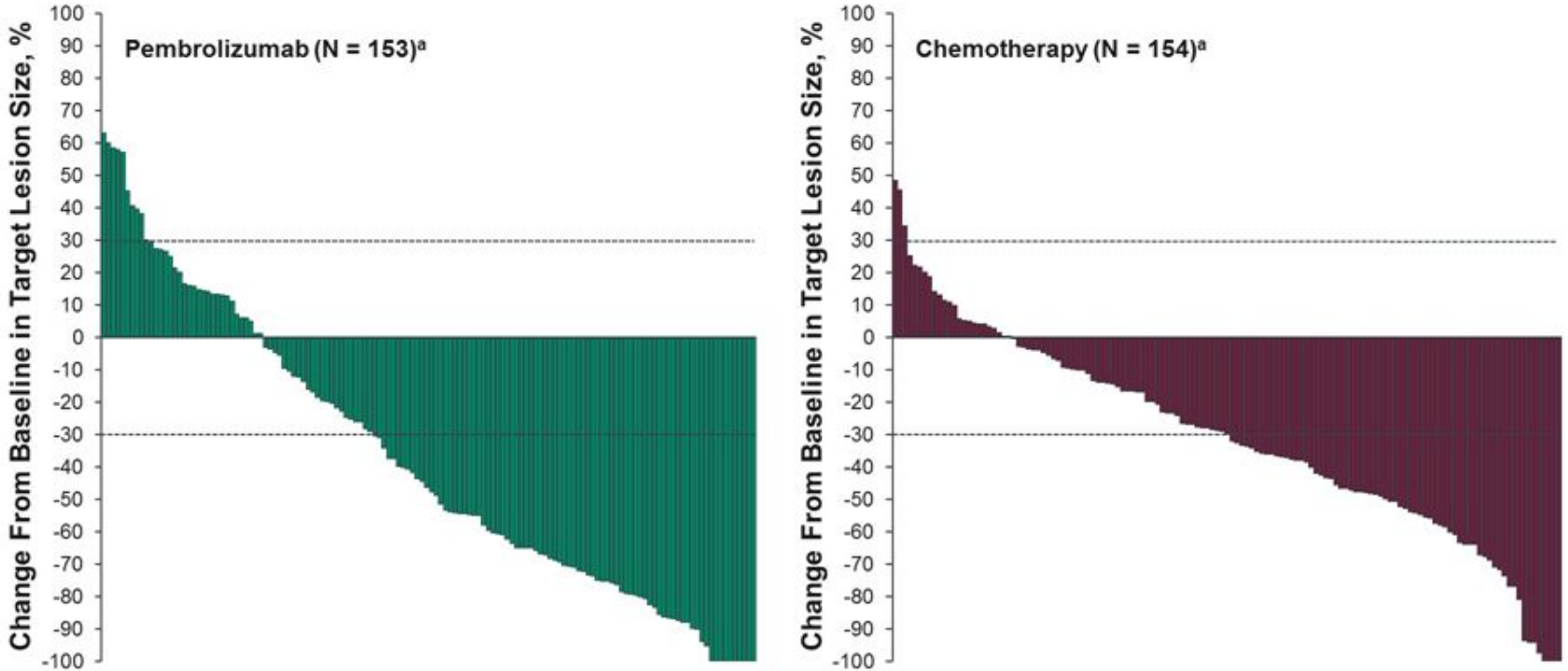
NA, North America; Data cut-off: 19Feb2020

Antitumor Response

	Pembrolizumab N = 153		Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**		**51 (33.1)**
Difference, estimate (95% CI) *P*-value		10.7 (-0.2-21.3) 0.0275	
Best Overall Response, n (%)			
Complete response	17 (11.1)		6 (3.9)
Partial response	50 (32.7)		45 (29.2)
Stable disease	32 (20.9)		65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)		116 (75.3)
Progressive disease	45 (29.4)		19 (12.3)
Not evaluable	3 (2.0)		2 (1.3)
No assessment	6 (3.9)		17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)		2.1 (1.7-24.9)

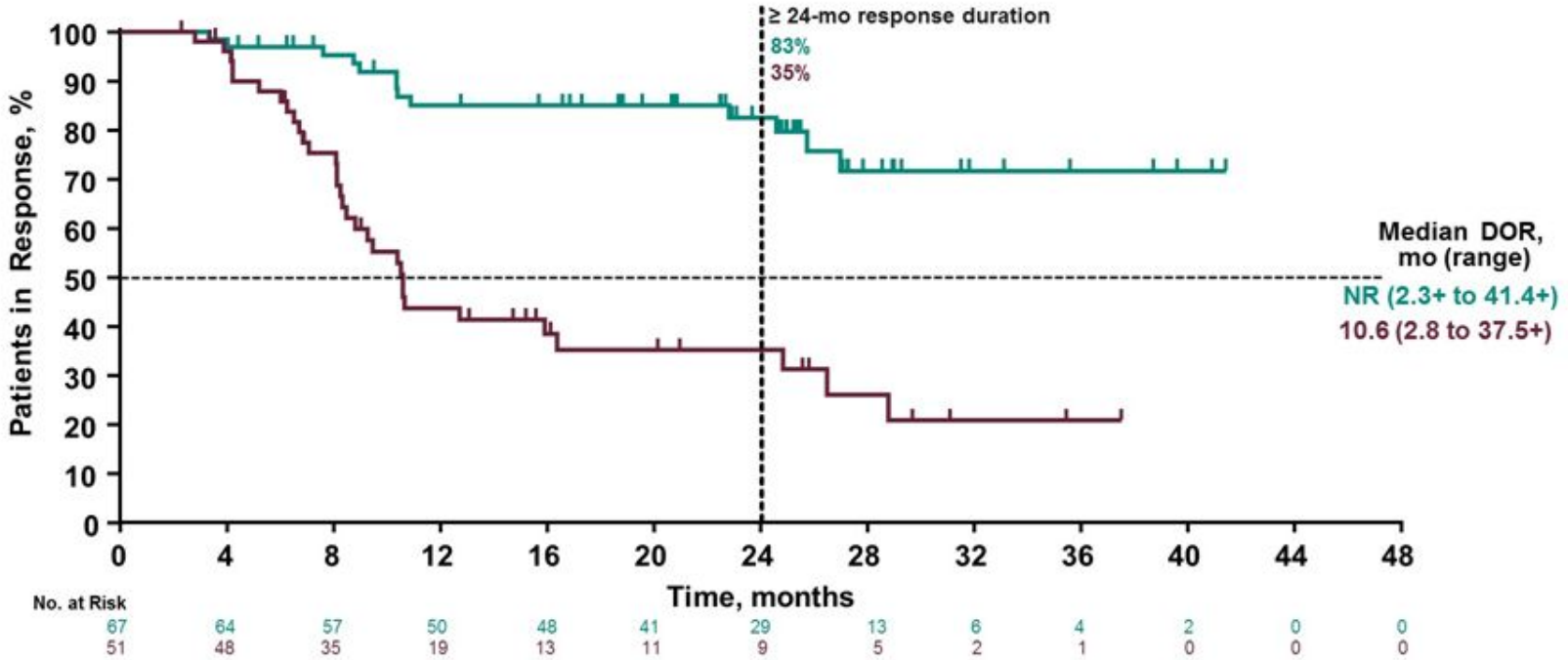
Data cut-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.

Radiographic Response in Target Lesions



[a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Duration of Response



Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

Adverse Events (AEs) in All Treated Patients

	Pembrolizumab N = 153		Chemotherapy N = 143	
All AEs	97%		99%	
Treatment-related	80%		99%	
Grade ≥3	22%		66%	
Death	0		1%[a]	
Discontinued	10%		6%	
Incidence ≥20%[b] in any group	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Diarrhea	25%	2%	52%	10%
Fatigue	21%	2%	44%	9%
Nausea	12%	0	55%	2%
Decreased appetite	8%	0	34%	2%
Stomatitis	5%	0	30%	4%
Alopecia	3%	0	20%	0
Vomiting	3%	0	28%	4%
Decreased neutrophil count	1%	0	23%	17%
Neutropenia	0	0	21%	15%
Peripheral sensory neuropathy	0	0	20%	2%

[a]One grade 5 event of intestinal perforation; [b]Treatment-related adverse events; Data cut-off: 19Feb2020.

Immune-Mediated AEs and Infusion Reactions

	Pembrolizumab N = 153		Chemotherapy N = 143	
All	31%		13%	
Grade ≥3	9%		2%	
Discontinued	7%		0	
Died	0		0	
Incidence >0%	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Hypothyroidism	12%	0	2%	0
Colitis	7%	3%	0	0
Hyperthyroidism	4%	0	0	0
Pneumonitis	4%	0	1%	0
Adrenal insufficiency	3%	1%	0	0
Hepatitis	3%	3%	0	0
Infusion reactions	2%	0	8%	1%
Hypophysitis	1%	0	0	0
Myocarditis	0	0	1%	0
Myositis	1%	0	0	0
Nephritis	1%	0	0	0
Pancreatitis	1%	1%	0	0
Severe skin reactions	1%	1%	1%	1%
Thyroiditis	1%	0	0	0
Type 1 Diabetes Mellitus	1%	1%	0	0

Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness; Data cutoff: 19Feb2020.

CONCLUSIONES:

Pembrolizumab proporcionó una mejoría clínicamente y una respuesta estadísticamente significativa en la SLP versus la quimioterapia en pacientes con mCRC MSI-H;

- PFS media 16,5 vs 8,2 meses (HR 0.60 - 95% CI 0.45 - 0.80; P = 0.0002)
- PFS a 24 meses; 48,3% vs 18,6%

La respuesta con Pembrolizumab versus quimioterapia proporcionó una respuesta más durable;

- ORR 43,8% vs 33,1% (P = 0.0275)
- Media de duración de respuesta: No alcanzada vs 10,6 meses

Mejor perfil de seguridad versus quimioterapia;

- Incidencia de efectos adversos grado 3 relacionados al tratamiento 22% vs 66%

PEMBROLIZUMAB debería ser un estándar de tratamiento en pacientes con mCRC MSI-H en primera línea